REVIEW ARTICLE

MEDICAL PROGRESS

Heart Failure

Mariell Jessup, M.D., and Susan Brozena, M.D.

THE CLINICAL SYNDROME OF HEART FAILURE IS THE FINAL PATHWAY for myriad diseases that affect the heart. Since the mid-1990s, when the last review of heart failure appeared in the *Journal*,[1] discoveries from basic research and findings from key clinical trials have resulted in considerable change in the scope of therapies available and the continuing advancement of our understanding of the pathophysiological mechanisms of heart failure. In this article, we highlight these new developments.

From the Heart Failure–Cardiac Transplantation Program, Cardiovascular Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia. Address reprint requests to Dr. Jessup at the Heart Failure–Cardiac Transplantation Program, 6 Penn Tower, 3400 Spruce St., Philadelphia, PA 19104, or at jessupm@uphs.upenn.edu.

N Engl J Med 2003;348:2007-18.

A COSTLY AND DEADLY DISORDER

Nearly 5 million Americans have heart failure today, with an incidence approaching 10 per 1000 population among persons older than 65 years of age. Heart failure is the reason for at least 20 percent of all hospital admissions among persons older than 65. Over the past decade, the rate of hospitalizations for heart failure has increased by 159 percent.[2] In 1997, an estimated $5,501 was spent for every hospital-discharge diagnosis of heart failure, and another $1,742 per month was required to care for each patient after discharge. Accordingly, substantial efforts have been made to identify and treat the factors that predict recurrent hospitalization. End points of large randomized trials now include the effect of the studied intervention on the rate of hospital admissions. For example, angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta-blockers, spironolactone, biventricular pacing, coronary bypass surgery, and the use of multidisciplinary teams to treat heart failure have all been shown to reduce the rate of hospitalizations substantially, as well as to reduce mortality or improve functional status.[3-5] Considerable debate has focused on the mechanisms that reduce the rate of admissions and on the type of physician who should care for patients with heart failure. In the United States, more than two thirds of patients with heart failure are cared for exclusively by primary care practitioners.

Multiple clinical trials completed during the past 15 years have unequivocally shown a substantial reduction in mortality for patients with systolic heart failure. Simultaneously, however, large epidemiologic surveys, such as the ongoing Framingham Study, have not documented any meaningful change in overall death rates. (Death seems to have been delayed, however, and occurs a longer time after major cardiac events such as a myocardial infarction.) Symptomatic heart failure continues to confer a worse prognosis than the majority of cancers in this country, with one-year mortality of approximately 45 percent.[6,7]

Why have the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure? It is important to recognize that heart failure is a clinical syndrome arising from diverse causes. Not all patients with the condition have poorly contracting ventricles and a low ejection fraction. Many have uncorrected valvular disease, such as aortic stenosis or mitral regurgitation, or abnormal filling, resulting in diastolic heart failure. A large majority of patients with heart failure are elderly, and 75

percent of patients have a history of hypertension. Many patients have at least one serious coexisting condition, in addition to advanced age. Such patients have not usually been subjects in investigational trials. Moreover, until recently, the majority of patients entered into trials of investigational drugs were middle-aged white men with heart failure due to ischemic cardiomyopathy. Fewer women and members of racial minorities have taken part in trials, and very few trials have included persons older than 75 years of age. Thus, despite the acknowledged successes of the therapies outlined below, there is much to be done in the prevention and management of heart failure in the large subgroups of patients who are not well represented in trials. Certainly, successful treatments have not been systematically applied to the majority of patients with heart failure, and for the reasons stated above, those that have been applied may not be efficacious.

Although heart failure is a major public health problem, there are no national screening efforts to detect the disease at its earlier stages, as there are for breast and prostate cancer or even osteoporosis. Heart failure is largely preventable, primarily through the control of blood pressure and other vascular risk factors. Yet, until recently, the factors that render a patient at high risk for heart failure had not been clearly defined or publicized. The guidelines for the evaluation and management of chronic heart failure that were published recently by the American College of Cardiology and the American Heart Association have corrected this deficit.[8] The writing committee developed a new approach to the classification of heart failure that emphasizes its evolution and progression and defined four stages of heart failure. Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. Patients with stage B heart failure have a structural abnormality of the heart but have never had symptoms of heart failure. Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Patients with stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment.

This staged classification underscores the fact that established risk factors and structural abnormalities are necessary for the development of heart failure, recognizes its progressive nature, and superimposes treatment strategies on the fundamentals of preventive efforts. The classification is a departure from the traditional New York Heart Association (NYHA) classification, which has primarily been used as shorthand to describe functional limitations.[9] Heart failure may progress from stage A to stage D in a given patient but cannot follow the path in reverse. In contrast, a patient with NYHA class IV symptoms might have quick improvement to class III with diuretic therapy alone. This staged heart-failure classification promotes a way of thinking about heart failure that is similar to our way of thinking about cancer — that is, the identification and screening of patients who are at risk, patients with in situ disease, and patients with established or widespread disease. The ensuing discussion about the treatment of heart failure is keyed toward this new staging classification.

THE SYNDROME OF HEART FAILURE

The traditional view that heart failure is a constellation of signs and symptoms caused by inadequate performance of the heart focuses on only one aspect of the pathophysiology involved in the syndrome. Currently, a complex blend of structural, functional, and biologic alterations are evoked to account for the progressive nature of heart failure and to explain the efficacy or failure of therapies used in clinical trials.[10] For example, the rationale for the use of beta-blockers in a patient with a poorly contracting heart is based on a conceptual framework broader than that which suggests the treatment of congestion with diuretics or digoxin. The rationale for using beta-blockers is predicated on an understanding of the role of the sympathetic nervous system in promoting the release of renin and other vasoactive substances that trigger vasoconstriction, tachycardia, and changes in myocytes that lead to disadvantageous ventricular dilatation.

Indeed, recent reviews have combined several models that had been used previously to understand heart failure in order to illustrate more fully the cascade of mechanisms, as well as the opportunities for intervention.[11] Thus, the hemodynamic model of heart failure emphasized the effect of an altered load on the failing ventricle and ushered in the era of vasodilators and inotropic agents. The neurohumoral model recognized the importance of activation of the renin–angiotensin–aldosterone axis and the sympathetic nervous system in the progression of cardiac dysfunction. More recently, efforts to antagonize the effects of circulating norepinephrine and angiotensin II have shifted with the

recognition that these and other vasoactive substances are also synthesized within the myocardium and therefore act in an autocrine and paracrine manner, in addition to their actions in the circulation. For example, brain natriuretic peptide is produced by the ventricular myocardium in response to stretch; its vasodilatory and natriuretic effects counteract the opposing actions of angiotensin II and aldosterone. Other studies have scrutinized myocytes from failing hearts in an attempt to detect abnormal signaling, gene expression, or contractile protein structure. Table 1 details many of the factors that contribute to the heart-failure syndrome as it is currently understood. Because no single pathophysiological model can account for the host of clinical expressions of heart failure, current therapy often targets more than one organ system, as outlined in Figure 1. Additional pathophysiological concepts that have become clinically meaningful areas for investigation or treatment are described below.

Table 1. Pathophysiological Mechanisms Important in the Syndrome of Heart Failure.

Cardiac abnormalities
Structural abnormalities
Myocardium or myocyte
Abnormal excitation–contraction coupling
β-Adrenergic desensitization
Hypertrophy
Necrosis
Fibrosis
Apoptosis
Left ventricular chamber
Remodeling
Dilatation
Increased sphericity
Aneurysmal dilatation or wall thinning
Coronary arteries
Obstruction
Inflammation
Functional abnormalities
Mitral regurgitation
Intermittent ischemia or hibernating myocardium
Induced atrial and ventricular arrhythmias
Altered ventricular interaction
Biologically active tissue and circulating substances
Renin–angiotensin–aldosterone system
Sympathetic nervous system (norepinephrine)
Vasodilators (bradykinin, nitric oxide, and prostaglandins)
Natriuretic peptides
Cytokines (endothelin, tumor necrosis factor, and interleukins)
Vasopressin
Matrix metalloproteinases
Other factors
Genetic background, including effects of sex
Age
Environmental factors, including use of alcohol, tobacco, and toxic drugs
Coexisting conditions
Diabetes mellitus
Hypertension
Renal disease
Coronary artery disease
Anemia
Obesity
Sleep apnea
Depression

REMODELING

Increased levels of circulating neurohormones are only part of the response seen after an initial insult to the myocardium. Left ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease; its hallmarks include hypertrophy, loss of myocytes, and increased interstitial fibrosis.[12,13]

For example, after a myocardial infarction, the acute loss of myocardial cells results in abnormal loading conditions that involve not only the border zone of the infarction, but also remote myocardium. These abnormal loading conditions induce dilatation and change the shape of the ventricle, rendering it more spherical, as well as causing hypertrophy. Remodeling continues for months after the initial insult, and the eventual change in the shape of the ventricle becomes deleterious to the overall function of the heart as a pump (Fig. 2A).[14] In cardiomyopathy, the process of progressive ventricular dilatation or hypertrophy occurs without the initial apparent myocardial injury observed after myocardial infarction (Fig. 2B).

Several trials involving patients who were studied after a myocardial infarction or who had dilated cardiomyopathy found a benefit from ACE inhibitors, beta-adrenergic antagonists, or cardiac resynchronization.[15-18] Such beneficial effects were associated with so-called reverse remodeling, in which the therapy promoted a return to a more normal ventricular size and shape.[15-18] The reverse-remodeling process is a mechanism through which a variety of treatments palliate the heart-failure syndrome.

MITRAL REGURGITATION

Another potential deleterious outcome of remodeling is the development of mitral regurgitation. As

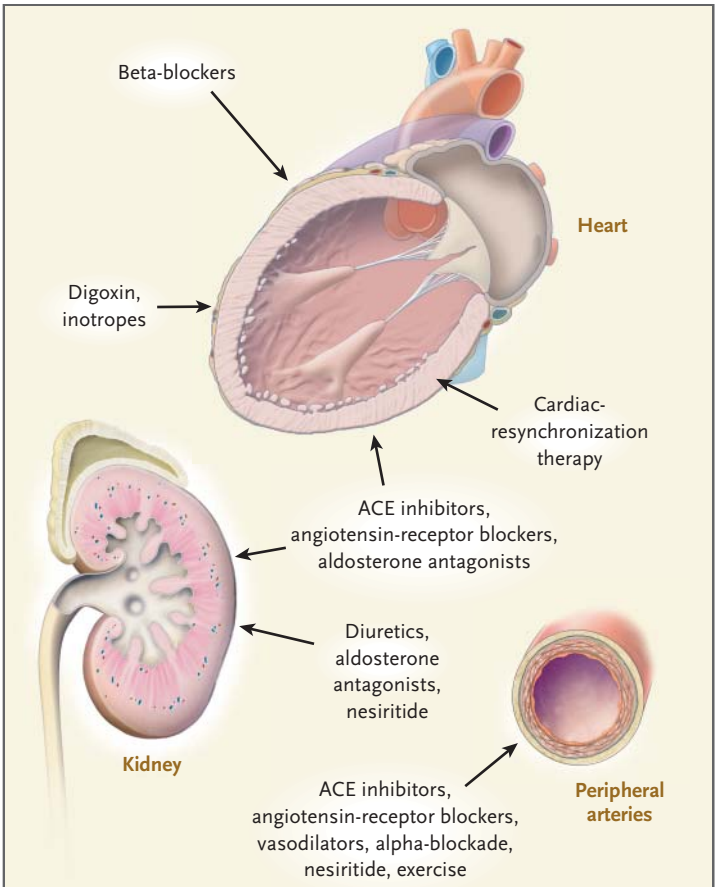

Figure 1. Primary Targets of Treatment in Heart Failure.

Treatment options for patients with heart failure affect the pathophysiological mechanisms that are stimulated in heart failure. Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers decrease afterload by interfering with the renin–angiotensin–aldosterone system, resulting in peripheral vasodilatation. They also affect left ventricular hypertrophy, remodeling, and renal blood flow. Aldosterone production by the adrenal glands is increased in heart failure. It stimulates renal sodium retention and potassium excretion and promotes ventricular and vascular hypertrophy. Aldosterone antagonists counteract the many effects of aldosterone. Diuretics decrease preload by stimulating natriuresis in the kidneys. Digoxin affects the Na^+/K^+–ATPase pump in the myocardial cell, increasing contractility. Inotropes such as dobutamine and milrinone increase myocardial contractility. Beta-blockers inhibit the sympathetic nervous system and adrenergic receptors. They slow the heart rate, decrease blood pressure, and have a direct beneficial effect on the myocardium, enhancing reverse remodeling. Selected agents that also block the alpha-adrenergic receptors can cause vasodilatation. Vasodilator therapy such as combination therapy with hydralazine and isosorbide dinitrate decreases afterload by counteracting peripheral vasoconstriction. Cardiac resynchronization therapy with biventricular pacing improves left ventricular function and favors reverse remodeling. Nesiritide (brain natriuretic peptide) decreases preload by stimulating diuresis and decreases afterload by vasodilatation. Exercise improves peripheral blood flow by eventually counteracting peripheral vasoconstriction. It also improves skeletal-muscle physiology.

the left ventricle dilates and the heart assumes a more globular shape, the geometric relation between the papillary muscles and the mitral leaflets changes, causing restricted opening and increased tethering of the leaflets and distortion of the mitral apparatus. Dilatation of the annulus occurs as a result of increasing left ventricular or atrial size or as a result of regional abnormalities caused by myocardial infarction.[19-21] The presence of mitral regurgitation results in an increasing volume overload on the overburdened left ventricle that further contributes to remodeling, the progression of disease, and symptoms. Correction of mitral regurgitation has been an appropriate focus of therapy.

ARRHYTHMIAS AND BUNDLE-BRANCH BLOCK

The myocardial conduction system is vulnerable to the same pathophysiological processes that occur in the myocytes and interstitium, with altered conduction properties observed in response to ischemia, inflammation, fibrosis, and aging. Supraventricular arrhythmias, particularly atrial fibrillation, are often the precipitating events that herald the onset of either systolic or diastolic heart failure.[22] Elevated ventricular end-diastolic pressure in a patient with hypertension or abnormal myocardial function leads to atrial stretch, which in turn incites electrical instability. Recognition of the presence of atrial fibrillation in a patient is critical, since several studies have now demonstrated the effectiveness of oral anticoagulant therapy for the prevention of stroke.[23]

Abnormal myocardial conduction can also lead to delays in ventricular conduction and bundle-branch block. Left bundle-branch block is a significant predictor of sudden death and a common finding in patients with myocardial failure.[24-26] Its presence also affects the mechanical events of the cardiac cycle by causing abnormal ventricular activation and contraction, ventricular dyssynchrony, delayed opening and closure of the mitral and aortic valves, and abnormal diastolic function. Hemodynamic sequelae include a reduced ejection fraction, decreased cardiac output and arterial pressure, paradoxical septal motion, increased left ventricular volume, and mitral regurgitation.[27-30] Ventricular arrhythmias are thought to be secondary to a dispersion of normal conduction through nonhomogeneous myocardial tissue, which promotes repetitive ventricular arrhythmias.

The rate of sudden cardiac death among persons with heart failure is six to nine times that seen in the

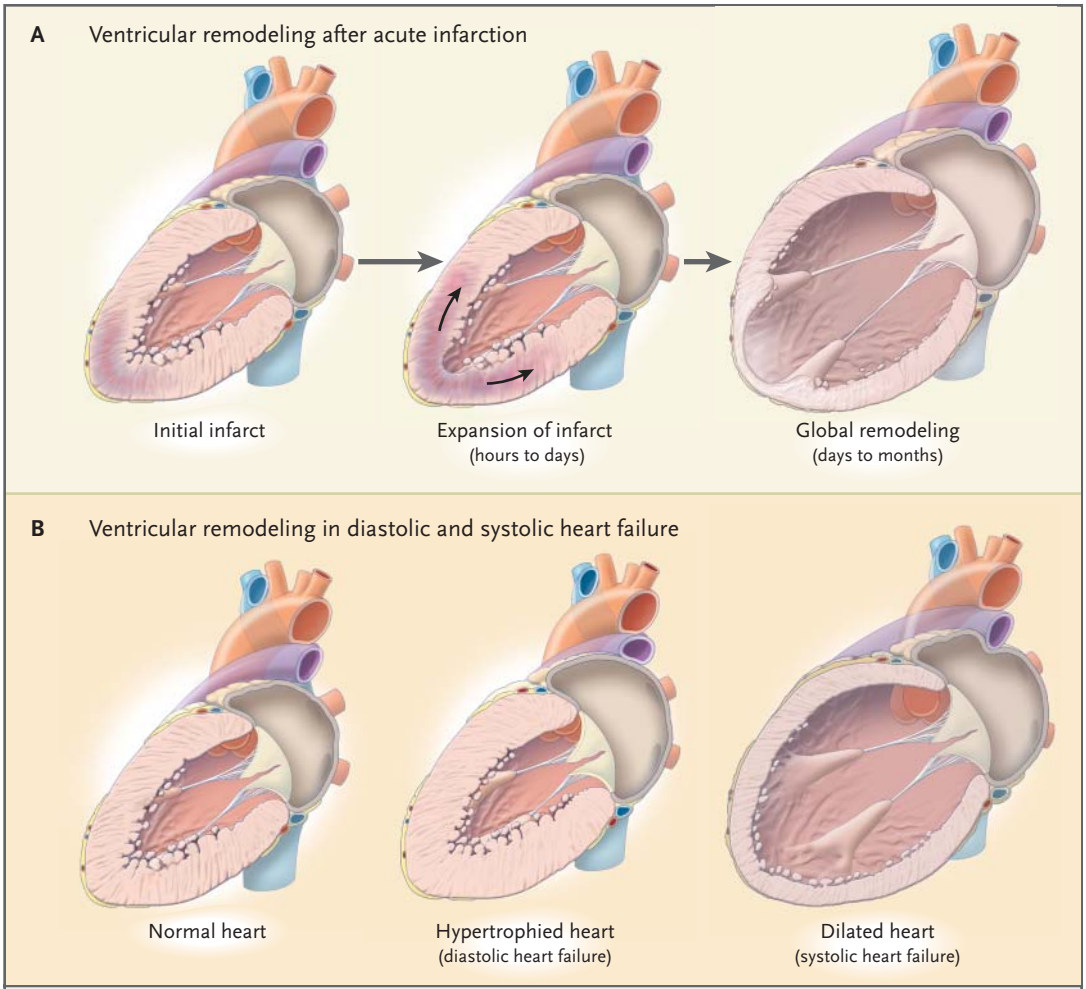

Figure 2. Ventricular Remodeling after Infarction (Panel A) and in Diastolic and Systolic Heart Failure (Panel B).
At the time of an acute myocardial infarction — in this case, an apical infarction — there is no clinically significant change in overall ventricular geometry (Panel A). Within hours to days, the area of myocardium affected by the infarction begins to expand and become thinner. Within days to months, global remodeling can occur, resulting in overall ventricular dilatation, decreased systolic function, mitral-valve dysfunction, and the formation of an aneurysm. The classic ventricular remodeling that occurs with hypertensive heart disease (middle of Panel B) results in a normal-sized left ventricular cavity with thickened ventricular walls (concentric left ventricular hypertrophy) and preserved systolic function. There may be some thickening of the mitral-valve apparatus. In contrast, the classic remodeling that occurs with dilated cardiomyopathy (right side of Panel B) results in a globular shape of the heart, a thinning of the left ventricular walls, an overall decrease in systolic function, and distortion of the mitral-valve apparatus, leading to mitral regurgitation.

general population.[31] Major innovations in medical and device-based therapy for the primary and secondary prevention of lethal ventricular arrhythmias have occurred during the past decade but are beyond the scope of this article. Increasing use of implantable cardioverter–defibrillators has unequivocally reduced mortality in a subgroup of patients with heart failure.

DIASTOLIC HEART FAILURE

It is estimated that 20 to 50 percent of patients with heart failure have preserved systolic function or a normal left ventricular ejection fraction. Although such hearts contract normally, relaxation (diastole) is abnormal. Cardiac output, especially during exercise, is limited by the abnormal filling characteristics of the ventricles. For a given ventricular volume,

ventricular pressures are elevated, leading to pulmonary congestion, dyspnea, and edema identical to those seen in patients with a dilated, poorly contracting heart.[32-35] Characteristics of patients with systolic heart failure and those with diastolic heart failure are compared in Table 2. Patients with diastolic heart failure are typically elderly, often female, and usually obese and frequently have hypertension and diabetes. Mortality among these patients may be as high as that among patients with systolic heart failure, and the rates of hospitalization in the two groups are equal.[36] The diagnosis of diastolic heart failure is usually made by a clinician who recognizes the typical signs and symptoms of heart failure and who is not deterred by the finding of normal systolic function (i.e., a normal ejection fraction) on echocardiography. Echocardiography may be useful in the detection of diastolic filling abnormalities.

Unfortunately, unlike heart failure due to systolic dysfunction, diastolic heart failure has been studied in few clinical trials, so there is little evidence to guide the care of patients with this condition. Physiological principles used in the treatment of such patients include the control of blood pressure, heart rate, myocardial ischemia, and blood volume.

Table 2. Characteristics of Patients with Diastolic Heart Failure and Patients with Systolic Heart Failure.*

Characteristic	Diastolic Heart Failure	Systolic Heart Failure
Age	Frequently elderly	All ages, typically 50–70 yr
Sex	Frequently female	More often male
Left ventricular ejection fraction	Preserved or normal, approximately 40% or higher	Depressed, approximately 40% or lower
Left ventricular cavity size	Usually normal, often with concentric left ventricular hypertrophy	Usually dilated
Left ventricular hypertrophy on electrocardiography	Usually present	Sometimes present
Chest radiography	Congestion with or without cardiomegaly	Congestion and cardiomegaly
Gallop rhythm present	Fourth heart sound	Third heart sound
Coexisting conditions		
Hypertension	+++	++
Diabetes mellitus	+++	++
Previous myocardial infarction	+	+++
Obesity	+++	+
Chronic lung disease	++	0
Sleep apnea	++	++
Long-term dialysis	++	0
Atrial fibrillation	+ (usually paroxysmal)	+ (usually persistent)

* A single plus sign denotes "occasionally associated with," two plus signs "often associated with," three plus signs "usually associated with," and a zero "not associated with."

MANAGEMENT OF HEART FAILURE

CLINICAL ASSESSMENT

Breathlessness, fatigue, and even edema may be due to a host of noncardiac conditions and do not necessarily indicate the presence of heart failure. Nevertheless, the clinician must have a high index of suspicion that the source of a patient's problems may be cardiac and must become adept at assessing patients for fluid overload and cardiac abnormalities. Measurement of serum brain natriuretic peptide may aid in the diagnosis of heart failure.[37] Serial measurements of weight at office visits, combined with instructions for daily weighing at home, help to alert the clinician and the patient to the possibility of fluid retention. The patient should be evaluated regularly in an appropriate position (45-degree elevation), with notation of the jugular venous pressure. Hepatojugular reflux, presence of a gallop rhythm, and peripheral edema are key findings on physical examination that may indicate a need for additional diuretic therapy and may be prognostically important.[38]

TREATMENT OF PATIENTS WITH STAGE A HEART FAILURE

Control of risk factors in stage A (e.g., hypertension, coronary artery disease, and diabetes mellitus) has a favorable effect on the incidence of later cardiovascular events (Fig. 3). Results from trials have shown that the effective treatment of hypertension decreases the occurrence of left ventricular hypertrophy and cardiovascular mortality, as well as reducing the incidence of heart failure by 30 to 50 percent.[39,40] Guidelines have recommended that the target for diastolic blood pressure in patients considered to be at high risk, particularly those with diabetes, be below 80 mm Hg, with the goal of further reducing morbidity and mortality.[41] Patients with diabetes have a high incidence of heart disease, with multiple

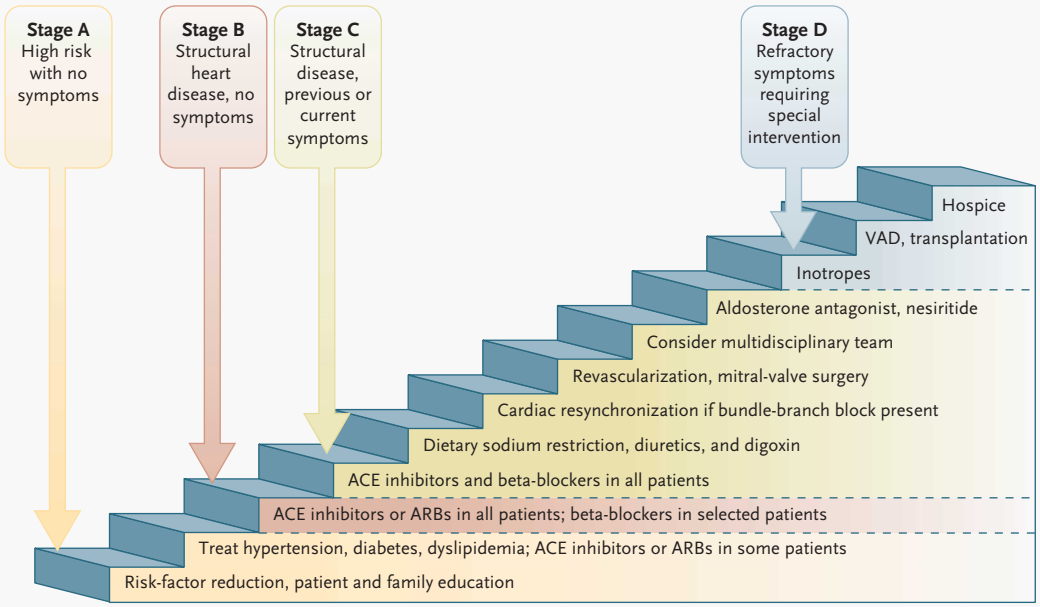

Figure 3. Stages of Heart Failure and Treatment Options for Systolic Heart Failure.

Patients with stage A heart failure are at high risk for heart failure but do not have structural heart disease or symptoms of heart failure. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy. Patients with stage B heart failure have structural heart disease but have no symptoms of heart failure. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction, or valvular heart disease, all of whom would be considered to have New York Heart Association (NYHA) class I symptoms. Patients with stage C heart failure have known structural heart disease and current or previous symptoms of heart failure. Their symptoms may be classified as NYHA class I, II, III, or IV. Patients with stage D heart failure have refractory symptoms of heart failure at rest despite maximal medical therapy, are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA class IV symptoms. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and VAD ventricular assist device.

adaptive and maladaptive biochemical and functional cardiac abnormalities.[42] ACE-inhibitor treatment of asymptomatic high-risk patients with diabetes or vascular disease and no history of heart failure has yielded significant reductions in the rates of death, myocardial infarction, and stroke.[43-45] The use of the angiotensin-receptor blocker losartan has been shown to delay the first hospitalization for heart failure in patients with diabetes mellitus and nephropathy.[46] In short, the goal of treatment in stage A is to prevent remodeling.

TREATMENT OF STAGE B, C, OR D HEART FAILURE WITH OR WITHOUT SYMPTOMS

The goals of therapy for patients with heart failure and a low ejection fraction are to improve survival, slow the progression of disease, alleviate symptoms, and minimize risk factors. Modifications of lifestyle can be helpful in controlling the symptoms of heart failure. For example, basic habits of moderate sodium restriction, weight monitoring, and adherence to medication schedules may aid in avoiding fluid retention or alerting the patient to its presence. Moderation of alcohol intake is advised; avoidance of nonsteroidal antiinflammatory drugs (NSAIDs) is also important.[47] NSAIDs have been associated with an increase in the incidence of new heart failure, decompensated chronic heart failure, and hospitalizations for heart failure. For selected patients, a regularly scheduled exercise program may have beneficial effects on symptoms.[48,49] ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, thereby minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium and

causes natriuresis in the kidney. The beneficial effects of ACE inhibitors in heart failure and after a myocardial infarction include improvements in survival, the rate of hospitalization, symptoms, cardiac performance, neurohormonal levels, and reverse remodeling.[50-52]

ACE inhibitors have not been unequivocally shown to reduce the incidence of sudden death. They are recommended for many patients with stage A heart failure and all patients with stage B, stage C, or stage D heart failure. But unresolved issues persist. First, underuse of ACE inhibitors by physicians for fear of potential side effects has been a concern. Yet side effects are fairly predictable and reversible and can usually be successfully managed. Second, the optimal dose of an ACE inhibitor is uncertain. Most randomized trials have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors.[53-56] Finally, it is uncertain whether there are any meaningful differences among the many ACE inhibitors available today. Table 3 details some common clinical problems with recommended approaches.

Beta-blockers have long been used for the treatment of hypertension, angina, and arrhythmias and for prophylaxis in patients who have had a myocardial infarction. This class of medication has had a

Table 3. Common Clinical Problems in Patients with Heart Failure and Recommended Solutions.*

Clinical Problem	Recommended Solutions
The patient has classic symptoms of heart failure with a normal left ventricular ejection fraction.	Consider diastolic heart failure, valvular heart disease, hypertensive heart disease, and ischemia.
The patient has hypotension: when is the systolic blood pressure too low?	Asymptomatic patients with dilated cardiomyopathy often tolerate a systolic blood pressure of 90 mm Hg. If the patient has no lightheadedness or undue fatigue, peripheral perfusion is adequate, and blood urea nitrogen and creatinine are unchanged, continue the same doses of medications. In symptomatic patients, decrease the dose of diuretic. If symptoms persist, adjustment of the timing of concomitant medications may be helpful. Decreasing the dose of the ACE inhibitor, beta-blocker, ARB, or vasodilator is indicated.
The patient has hyperkalemia.	Ensure that the patient is taking no exogenous potassium supplement or potassium-containing salt substitute. Avoid hypovolemia. Consider decreasing the dose of a potassium-sparing diuretic. Concomitant use of an ACE inhibitor or ARB and spironolactone may increase the risk of hyperkalemia. Avoid high doses of ACE inhibitors and ARBs in patients receiving spironolactone. Avoid use of spironolactone in patients with renal failure, and use low doses of ACE inhibitors and ARBs.
The patient has increasing azotemia while taking ACE inhibitors.	Decrease the dose of diuretic. Consider renal-artery stenosis if azotemia persists.
The patient has a cough while taking ACE inhibitors.	Rule out worsening congestive heart failure. Change to ARB if severe cough persists.
Should the dose of the ACE inhibitor be increased or should beta-blocker therapy be initiated in a symptomatic patient?	Start beta-blocker therapy if there are no contraindications.
Should an ARB be added to ACE-inhibitor therapy or should a beta-blocker be added in a symptomatic patient?	Start beta-blocker therapy if there are no contraindications.
The patient has worsening symptoms of congestive heart failure after starting beta-blocker therapy.	Increase the dose of diuretic and slow the titration of the beta-blocker.
The patient has worsening bronchospasm after starting beta-blocker therapy.	Decrease the dose of the beta-blocker. Consider a beta-selective agent. Discontinue treatment with the drug if the problem persists.
Persistent paroxysmal nocturnal dyspnea or orthopnea or daytime fatigue despite absence of fluid retention on physical examination.	Evaluate the patient for central or obstructive sleep apnea.
The patient requires repeated hospitalizations.	A multidisciplinary approach should be initiated, with a visiting nurse in the home. Referral for heart failure is indicated.

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

remarkable effect on chronic heart failure. The primary action of beta-blockers is to counteract the harmful effects of the sympathetic nervous system that are activated during heart failure. The beneficial effects of these drugs have been demonstrated in trials involving patients with heart failure from various causes and of all stages. These effects include improvements in survival, morbidity, ejection fraction, remodeling, quality of life, the rate of hospitalization, and the incidence of sudden death.[3,57] Beta-blockers should be used in all patients in stable condition without substantial fluid retention and without recent exacerbations of heart failure requiring inotropic therapy. There are a few populations of patients in whom beta-blockers should not be used or should be used only with extreme caution. Such patients include those with reactive airway disease, those with diabetes in association with frequent episodes of hypoglycemia, and those with bradyarrhythmias or heart block who do not have a pacemaker.

Although the short-term effects of beta-blockers may result in a temporary exacerbation of symptoms, their long-term effects are uniformly beneficial. Placebo-controlled trials involving long-term treatment have shown improved systolic function after three months of treatment and reverse remodeling after four months.[18,58,59] In the United States, two beta-blockers are specifically approved for the treatment of heart failure: carvedilol and long-acting metoprolol. Currently, neither drug has proved to be consistently superior; both have shown significant clinical efficacy. Carvedilol is a nonselective β-adrenergic antagonist with alpha-blocking effects; metoprolol is a selective β_1-adrenergic antagonist with no alpha-blocking effects. A large trial comparing these drugs is nearing completion. However, the most frequently prescribed beta-blocker in the United States is atenolol; there have been no studies to date on the use of atenolol in patients with heart failure. Drugs that antagonize the sympathetic nervous system through alternative pathways, such as clonidine or moxonidine, have been less clinically useful in patients with heart failure.

Available angiotensin-receptor antagonists block the effects of angiotensin II at the angiotensin II subtype 1 receptor. The recently published guidelines recommend that these drugs should not be used as first-line therapy for heart failure of any stage but should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.[8] Several trials involving patients with heart failure have shown that angiotensin-receptor antagonists have efficacy similar to that of ACE inhibitors but are not superior.[60-62] On the other hand, in a randomized trial of patients with symptomatic left ventricular systolic dysfunction, the addition of valsartan to ACE-inhibitor treatment reduced the rate of the combined end point of death or cardiovascular events and improved clinical signs and symptoms of heart failure.[63] However, patients who were receiving beta-blockers, an ACE inhibitor, and the angiotensin-receptor blocker valsartan had more adverse events and increased mortality. More recently, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial was completed in patients with stage B heart failure — specifically, asymptomatic patients with hypertension and left ventricular hypertrophy on electrocardiography. Treatment with the angiotensin-receptor blocker losartan yielded improvements in cardiovascular morbidity and survival, as well as a decrease in the incidence of new-onset diabetes, as compared with treatment with the beta-blocker atenolol.[64] Thus, accumulating data lend support to the contention that angiotensin-receptor antagonists are a reasonable alternative to ACE inhibitors.

ADDITIONAL THERAPY FOR SYMPTOMATIC PATIENTS WITH STAGE C OR STAGE D HEART FAILURE

There is evidence to support the use of spironolactone, an aldosterone antagonist, in patients with advanced symptoms of heart failure — specifically, NYHA class III or IV symptoms.[65] In patients with advanced heart failure, circulating levels of aldosterone become elevated in response to stimulation by angiotensin II, and there is a decrease in the hepatic clearance of aldosterone due to hepatic congestion. Aldosterone stimulates the retention of salt, myocardial hypertrophy, and potassium excretion; spironolactone counteracts these responses.[66] The beneficial effects of spironolactone in heart failure may also include a decrease in collagen synthesis that promotes organ fibrosis.

Since heart failure is a salt-avid syndrome resulting in intravascular volume overload, diuretics are a mainstay for controlling symptoms of congestion. Thiazide or loop diuretics are often prescribed, and combination therapy may be used to promote effective diuresis in advanced cases.[67,68]

It is only within the past five years that a large, randomized, placebo-controlled study of digoxin for symptomatic patients with a low ejection frac-

tion has been completed. There was no difference in mortality between patients receiving digoxin and patients receiving placebo, but there were decreases in the digoxin group in the rates of worsening heart failure and hospitalization.[69] Recent data suggest that the maintenance of a low serum digoxin concentration (<0.09 ng per milliliter) is as effective in reducing the rate of cardiovascular events as the maintenance of a higher concentration and is associated with a lower rate of toxic effects.[70] Elderly patients and those with renal insufficiency are more prone to toxic effects. There is a commonly observed and clinically important interaction between digoxin and amiodarone: digoxin levels can become markedly elevated after the introduction of amiodarone.

There are some patients who cannot tolerate either ACE inhibitors or angiotensin-receptor blockers, usually because of hyperkalemia or renal insufficiency. In such patients who remain symptomatic despite diuretic and beta-blocker therapy, treatment with the vasodilator combination of hydralazine and isosorbide dinitrate may be an option.[71]

NONPHARMACOLOGIC THERAPY

Cardiac resynchronization therapy is an innovative, pacemaker-based approach to the treatment of patients with heart failure who have a wide QRS complex on 12-lead electrocardiography. The purpose of resynchronization is to provide electromechanical coordination and improved ventricular synchrony in symptomatic patients who have severe systolic dysfunction and clinically significant intraventricular conduction defects, particularly left bundle-branch block.

A percutaneous, three-lead, biventricular pacemaker system is used; one lead is placed in the right atrium, one is placed in the right ventricle, and a third is passed through the right atrium, through the coronary sinus, and into a cardiac vein on the lateral wall of the left ventricle. This left ventricular lead constitutes the key difference between resynchronization therapy and standard dual-chamber pacing. Beneficial effects include reverse remodeling, resulting in decreased heart size and ventricular volumes, improved ejection fraction, and decreased mitral regurgitation. Clinical improvements in exercise tolerance, quality of life, and the rate of hospitalization have been documented.[72-78] To date, however, resynchronization therapy has not been shown to enhance survival.

REVASCULARIZATION AND SURGICAL THERAPY

Patients with heart failure of any stage who are at risk for coronary artery disease should be screened for myocardial ischemia. Revascularization, through either a catheter-based or a surgical approach, often improves ischemic symptoms, improves cardiac performance, and reduces the risk of sudden death.[79,80] Patients with stage C or stage D heart failure, who have heretofore been considered unacceptable candidates for surgery, may in fact derive substantial benefit from bypass surgery and additional techniques designed to reduce myocardial wall stress. Procedures to eliminate or exclude areas of infarction, repair mitral regurgitation, or support the failing myocardium are undergoing clinical trials.[81-83] Similarly, the role of mechanical devices that serve to support patients who are awaiting heart transplantation or are definitive therapy for end-stage (stage D) heart failure continues to evolve, and such devices offer great hope to many patients who are not eligible for cardiac transplantation.[84]

THE FUTURE

Many common clinical problems encountered in patients with heart failure remain unresolved. The role of anticoagulant therapy in patients with systolic dysfunction and sinus rhythm is unclear; neither the type of therapy needed nor the appropriate duration of treatment is known. There may be an important adverse interaction between aspirin and ACE inhibitors that will be clarified in upcoming trials.[85] The optimal care for patients with heart failure and preserved systolic function (diastolic heart failure) awaits further research. The value of revascularization in patients with symptoms of heart failure but without angina will be explored in an important trial that is slated to begin soon.[86] How will we identify patients with familial cardiomyopathy at an earlier stage?[87-89] How do we identify patients with the greatest risk of sudden death? What is the best way to prevent sudden death in a cost-effective manner? Who will be best served by mechanical cardiac-support devices? Can we afford optimal care for the growing number of patients with heart failure? These questions and many others will undoubtedly be answered in the years to come. Perhaps our most intensive investigations, however, should be reserved for efforts that have been shown to prevent this cardiac plague — the control of hypertension and vascular risk factors.

Dr. Jessup reports having received consulting fees from Acorn, Medtronic, Guidant, and GlaxoSmithKline, lecture fees from GlaxoSmithKline, AstraZeneca, Scios, Guidant, and Medtronic, and grant support from Guidant. Dr. Brozena reports having received grant support from Abbott, Icon, and Medtronic and lecture fees from Merck and GlaxoSmithKline.

REFERENCES

1. Cohn JN. The management of chronic heart failure. N Engl J Med 1996;335:490-8.
2. 2001 Heart and stroke statistical update. Dallas: American Heart Association, 2000.
3. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: scientific review. JAMA 2002;287:883-9.
4. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. Am J Med 2001;110:378-84.
5. Shah NB, Der E, Ruggerio C, Heidenreich PA, Massie BM. Prevention of hospitalizations for heart failure with an interactive home monitoring program. Am Heart J 1998;135:373-8.
6. Konstam MA. Progress in heart failure management? Lessons from the real world. Circulation 2000;102:1076-8.
7. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? J Am Coll Cardiol 2000;36:2284-6.
8. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101-13.
9. Gibelin P. An evaluation of symptom classification systems used for the assessment of patients with heart failure in France. Eur J Heart Fail 2001;3:739-46.
10. McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure. Circulation 2002;105:2099-106, 2223-8.
11. Mann D. Mechanisms and models in heart failure: a combinatorial approach. Circulation 1999;100:999-1008.
12. Sutton MGSJ, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101:2981-8.
13. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart: a new era in the treatment of heart failure. Circulation 1996; 94:2285-96.
14. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990;81:1161-72.
15. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807-16.
16. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. Circulation 1995;91:2573-81.
17. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995;25: 1154-61.
18. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 2002;105:1304-10.
19. Otsuji Y, Gilon D, Jiang L, et al. Restricted diastolic opening of the mitral leaflets in patients with left ventricular dysfunction: evidence for increased valve tethering. J Am Coll Cardiol 1998;32:398-404.
20. He S, Fontaine AA, Schwammenthal E, Yoganathan AP, Levine RA. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. Circulation 1997;96:1826-34.
21. Van Dantzig JM, Delemarre BJ, Koster RW, Bot H, Visser CA. Pathogenesis of mitral regurgitation in acute myocardial infarction: importance of changes in left ventricular shape and regional function. Am Heart J 1996;131:865-71.
22. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98:946-52.
23. Wenger NK. Oral anticoagulant therapy at elderly age: heart failure and nonvalvular atrial fibrillation. Am J Geriatr Cardiol 1996; 5:78-83.
24. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660-7.
25. Rabkin SW, Mathewson FL, Tate RB. The electrocardiogram in apparently healthy men and the risk of sudden death. Br Heart J 1982;47:546-52.
26. Schneider JF, Thomas HE Jr, McNamara PM, Kannel WB. Clinical-electrocardiographic correlates of newly acquired left bundle branch block: the Framingham study. Am J Cardiol 1985;55:1332-8.
27. Gerber TC, Nishimura RA, Holmes DR Jr, et al. Left ventricular and biventricular pacing in congestive heart failure. Mayo Clin Proc 2001;76:803-12.
28. Hultgren HN, Craige E, Fujii J, Nakamura T, Bilisoly J. Left bundle branch block and mechanical events of the cardiac cycle. Am J Cardiol 1983;52:755-62.
29. Sadaniantz A, Saint Laurent L. Left ventricular Doppler diastolic filling patterns in patients with isolated left bundle branch block. Am J Cardiol 1998;81:643-5.
30. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991;66:443-7.
31. Stevenson WG, Stevenson LW. Prevention of sudden death in heart failure. J Cardiovasc Electrophysiol 2001;12:112-4.
32. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol 2002;39:138-41.
33. Brutsaert DL, Sys SU. Diastolic dysfunction in heart failure. J Card Fail 1997;3:225-42.
34. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118-21.
35. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. II. Causal mechanisms and treatment. Circulation 2002;105:1503-8.
36. Senni M, Redfield MM. Heart failure with preserved systolic function: a different natural history? J Am Coll Cardiol 2001;38: 1277-82.
37. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002;39:202-9.
38. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 2001;345:574-81.
39. Mosterd A, D'Agostino RB, Silbershatz H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. N Engl J Med 1999;340:1221-7.
40. Deedwania PC. Hypertension and diabetes: new therapeutic options. Arch Intern Med 2000;160:1585-94.
41. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46. [Erratum, Arch Intern Med 1998;158:573.]
42. Taegtmeyer H, McNulty P, Young ME. Adaptation and maladaptation of the heart in diabetes. I. General concepts. Circulation 2002;105:1727-33.
43. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13. [Erratum, BMJ 1999;318: 29.]
44. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk

patients. N Engl J Med 2000;342:145-53. [Errata, N Engl J Med 2000;342:748, 1376.]
45. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9. [Erratum, Lancet 2000;356:860.]
46. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345:861-9.
47. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000;160:777-84.
48. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. JAMA 2000;283:3095-101.
49. Coats AJ. Exercise training for heart failure: coming of age. Circulation 1999; 99:1138-40.
50. Munzel T, Keaney JF Jr. Are ACE inhibitors a "magic bullet" against oxidative stress? Circulation 2001;104:1571-4.
51. Khalil ME, Basher AW, Brown EJ Jr, Alhaddad IA. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. J Am Coll Cardiol 2001;37:1757-64.
52. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273: 1450-6. [Erratum, JAMA 1995;274:462.]
53. Gullestad L, Aukrust P, Ueland T, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol 1999;34:2061-7.
54. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. J Am Coll Cardiol 2000;36:2090-5.
55. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312-8.
56. Tang WH, Vagelos RH, Yee YG, et al. Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. J Am Coll Cardiol 2002; 39:70-8. [Erratum, J Am Coll Cardiol 2002; 39:746.]
57. Farrell MH, Foody JM, Krumholz HM. Beta-blockers in heart failure: clinical applications. JAMA 2002;287:890-7.
58. Bristow M. Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000;101:558-69.
59. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. J Am Coll Cardiol 2000;36:2072-80.
60. Havranek EP, Thomas I, Smith WB, et al. Dose-related beneficial long-term hemodynamic and clinical efficacy of irbesartan in heart failure. J Am Coll Cardiol 1999;33: 1174-81.
61. Pitt B, Poole-Wilson PA, Segal R, et al. Effects of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial — the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582-7.
62. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747-52.
63. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
64. Dahlof B, Devereux RB, Kjeldsen SE, et al. 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.
65. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
66. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689-97.
67. Ellison D. Diuretic drugs and the treatment of edema: from clinic to bench and back again. Am J Kidney Dis 1994;23:623-43.
68. Brater DC. Diuretic therapy. N Engl J Med 1998;339:387-95.
69. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-33.
70. Adams KF, 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;39:946-53.
71. Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001;161:342-52.
72. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001; 344:873-80.
73. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. Circulation 1999;99:2993-3001.
74. Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. J Am Coll Cardiol 2000;35: 1221-7.
75. Saxon LA, De Marco T. Cardiac resynchronization: a cornerstone in the foundation of device therapy for heart failure. J Am Coll Cardiol 2001;38:1971-3.
76. Stellbrink C, Breithardt O-A, Franke A, et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 2001;38:1957-65.
77. Touiza A, Etienne Y, Gilard M, Fatemi M, Mansourati J, Blanc JJ. Long-term left ventricular pacing: assessment and comparison with biventricular pacing in patients with severe congestive heart failure. J Am Coll Cardiol 2001;38:1966-70.
78. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
79. Bitran D, Merin O, Klutstein MW, Od-Allah S, Shapira N, Silberman S. Mitral valve repair in severe ischemic cardiomyopathy. J Card Surg 2001;16:79-82.
80. Baumgartner WA. What's new in cardiac surgery. J Am Coll Surg 2001;192:345-55.
81. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. Eur J Cardiothorac Surg 2000;17:213-21.
82. Raman JS, Hata M, Storer M, et al. The mid-term results of ventricular containment (ACORN WRAP) for end-stage ischemic cardiomyopathy. Ann Thorac Cardiovasc Surg 2001;7:278-81.
83. Starling RC, McCarthy PM, Buda T, et al. Results of partial left ventriculectomy for dilated cardiomyopathy: hemodynamic, clinical and echocardiographic observations. J Am Coll Cardiol 2000;36:2098-103.
84. Jessup M. Mechanical cardiac-support devices — dreams and devilish details. N Engl J Med 2001;345:1490-3.
85. Massie BM, Teerlink JR. Interaction between aspirin and angiotensin-converting enzyme inhibitors: real or imagined. Am J Med 2000;109:431-3.
86. Bouchart F, Tabley A, Litzler PY, Haas-Hubscher C, Bessou JP, Soyer R. Myocardial revascularization in patients with severe ischemic left ventricular dysfunction: long term follow-up in 141 patients. Eur J Cardiothorac Surg 2001;20:1157-62.
87. Keeling PJ, McKenna WJ. Clinical genetics of dilated cardiomyopathy. Herz 1994; 19:91-6.
88. Mestroni L, Giacca M. Molecular genetics of dilated cardiomyopathy. Curr Opin Cardiol 1997;12:303-9.
89. Roberts R, Brugada R. Genetic aspects of arrhythmias. Am J Med Genet 2000;97: 310-8.