Medical Advances in the Treatment of Congestive Heart Failure

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The increased incidence and prevalence of congestive heart failure place a high priority on novel treatment strategies. Left ventricular ejection fraction remains the single most valuable measurement providing both diagnostic and prognostic insights. The most systematic approach to heart failure involves an objective assessment of functional disability, to include exercise tests such as a 6-minute walk under standardized conditions. Left ventricular dysfunction incites a host of neurohumoral compensations that are of fundamental importance in the heart failure syndrome expression. Both vasodilator neurohormones and vasodilator neurohormones are stimulated and provide new therapeutic opportunities. The therapeutic approach to heart failure begins with a strong emphasis on prevention, patient education, and self-participation in therapy with respect to both its monitoring and adjustment. Diuretics remain a mainstay of therapy but, in the face of severe heart failure, may become ineffectual, requiring constant infusion of loop-acting diuretics, combination diuretics, or diuretics in association with concomitant low-dose dopamine infusion. Vasodilator therapy has been an important advance: combination hydralazine and nitrate therapy was initially shown to be efficacious in improving survival, and more recently, angiotensin-converting enzyme (ACE) inhibitors, in the form of enalapril, have shown incremental benefit on survival over this combination. Interestingly, there is now evidence from both SOLVD and SAVE to demonstrate an unexpected and, as yet, unexplained reduction in the frequency of both unstable angina and myocardial infarction. Although, on balance, the weight of evidence concerning the long-term efficacy of inotropic agents has been disappointing, especially as it relates to their unfavorable effects on survival, recent information on vesnarinone, an agent with a complex and diversified mechanism of action, suggests that with appropriate doses, improved symptoms and survival are possible. A substantial amount of new information from randomized placebo-controlled trials attests to the symptomatic relief, hemodynamic improvement, and gain in exercise performance achieved by digoxin. A long-term survival study is ongoing to assess its effects on mortality. β-Blockers, especially metoprolol, appear beneficial in some patients with heart failure, possibly related to their reduction in sympathetic nerve activity and restoration of β-receptor population, with resultant improved contractile performance, enhanced myocardial relaxation, and overall increase in cardiac efficiency. Based on available evidence, the best contemporary approach to treatment involves the use of ACE inhibitors coupled with diuretic therapy, either continuous or intermittent, to relieve central or peripheral congestion. The addition of digoxin or a hydralazine nitrate combination is a logical next step, with commencement of low-dose β-blocker a reasonable option. The residual mortality in the treatment groups of large-scale, contemporary, randomized clinical trials of novel therapy suggests substantial continuing need for the development of novel treatment strategies. (Circulation. 1994;88:2941-2952.)

KEY WORDS • heart failure, congestive • diuretics • vasodilation • inotropic agents

Medicines are nothing in themselves, if not properly used, but the very hands of the gods, if employed with reason and prudence.
Herophilus (floru in 300 BC)

Background

There can be no doubt that therapeutic advances in heart failure must constitute a central health care priority, given the increasing incidence and prevalence of the disorder and the enormous associated socioeconomic implications. Framingham data indicate that the prevalence among those aged 50 to 59 years is 1% of the US population and that this doubles with each decade of age increment thereafter. It is conservatively estimated that more than 2 million Americans are affected with heart failure, with more than 400,000 new cases occurring annually and a resultant 900,000 hospitalizations, which translates into an annual estimated cost of nearly $9 billion. When these data are placed in the context of a 5-year mortality of ≈50% and the current shift toward an aging population, the challenge looms large. This is further emphasized by new survival data from patients with overt congestive heart failure in the Framingham Heart Study that indicate persisting high lethality (age adjusted) without significant temporal prognostic improvement during the 40-year period 1948 through 1988.

The extraordinary growth in our understanding of the pathophysiology, natural history, and epidemiology of
heart failure within the past decade has spawned, on the one hand, a stunning array of novel treatment strategies and on the other, a sober reevaluation of therapeutic objectives. During this period, a precise definition of heart failure has remained elusive. Physicians have relied on the time-honored general and all-inclusive portrait of heart failure as characterized by an inadequacy of the heart, usually in association with elevated central cardiac filling pressures, to meet the metabolic demands of peripheral organs and tissues either at rest or during stress. Although left ventricular dysfunction remains the center of attention, it is now recognized that heart failure concepts are modeled, it evokes a dramatic heterogeneity of compensatory responses that involve the heart, other vital organs, the peripheral vasculature, and skeletal muscle: each of these may be variably modulated by a complex and still incompletely understood neurohormonal system. Moreover, it is these compensatory responses that appear to govern modes of clinical presentation, response to therapy, and prognosis. The single most valuable measurement in heart failure remains the left ventricular ejection fraction.\(^{3,4}\) Despite its importance in providing both diagnostic and prognostic insights, ejection fraction bears an imperfect relation to symptoms, exercise tolerance, and response to therapy. This dissociation may relate in part to (1) coexistent diastolic dysfunction that rises in prevalence with increasing age and may escape conventional noninvasive assessment; (2) peripheral circulatory and skeletal muscle adaptations; and (3) neurohormonal profile.\(^{5-9}\) A substantial proportion, ie, between one third and one half of heart failure patients, die suddenly, and this appears especially true if they have underlying coronary artery disease. Whereas there is an important relation between baseline left ventricular ejection fraction and ultimate survival, the proportion of patients dying suddenly tends to be greater in patients with less severe manifestations of heart failure; moreover, the presence of ventricular arrhythmia is associated with reduced survival and an increased propensity for sudden death.\(^{10,11}\) Male sex, advanced age, and diabetes in women all portend worsened survival.\(^{4}\) Heart failure also imposes an enormous burden of morbidity, with frequent exacerbations requiring hospitalization, increased risk of acute myocardial infarction and unstable angina, pulmonary embolism, and a fourfold increase in the risk of cerebrovascular accident.\(^{1}\) Prevention of these and other complications is a fundamental component of effective therapy. For purposes of addressing contemporary management of heart failure, this review of therapeutic advances will be limited to patients with systolic dysfunction as defined by a left ventricular ejection fraction <45%. The lack of a uniformly accepted definition of heart failure and the myriad of patient subsets within this heterogeneous diagnosis present a considerable challenge to the practicing physician selecting therapy.\(^{12}\) Symptomatic questioning of patients on quality-of-life issues is notoriously imprecise, and many efforts have been undertaken to classify patients in a manner that extends the traditional New York Heart Association functional classification. A variety of comprehensive quality-of-life assessment techniques using interviews and questionnaires are now available to enhance the validity of clinical assessment.\(^{13,14}\) Feinstein and colleagues\(^{15}\) recently devised a dyspnea fatigue index for patients with heart failure that is user-friendly and incorporates not only functional impairment associated with various everyday activities but also, and importantly, the pace at which they are performed. On initial testing the index appears reproducible, reliable, and capable of distinguishing changes induced by therapy. A more systematic and objective assessment of functional disability involves exercise testing. Submaximal as opposed to maximal testing appears to more closely simulate activities of daily living, and concomitant measurement of respiratory gas exchange allows for the determination of maximal VO\(_2\) and the anaerobic threshold.\(^{16}\) A commonly used standardized exercise test is that designed by Guyatt and coworkers\(^{17}\) involving a 6-minute walk under standardized conditions with uniform encouragement that has been demonstrated to be a reproducible and valid measurement of exercise capacity in heart failure. Lipkin and coworkers\(^{18}\) have determined that fast (change in exercise stage every 2 minutes) versus slow (change in exercise stage every 6 minutes) exercise tests are more likely to be limited by breathlessness in the former and fatigue in the latter. The sensation of breathlessness was associated with a rapid rise in plasma lactate and fall in arterial pH stimulating a hyperventilatory response and had no correlation with resting or maximal pulmonary capillary wedge pressure. The traditional goal of heart failure therapy has been to enhance exercise tolerance and reduce symptoms in those patients with functional disability. In 1986, the VHeFT-I study extended this goal by demonstrating improved survival with vasodilator therapy using a combination of hydralazine and isosorbide dinitrate.\(^{19}\) Whereas subsequent studies\(^{20-22}\) have persuasively indicated that pharmacologic therapy can improve survival in heart failure, others have cogently and unhappily demonstrated the capacity for treatment to increase morbidity and shorten survival, thereby highlighting the potential for therapeutic misadventure.\(^{23-25}\) Ironically, it is now evident that in patients with advanced symptoms, treatment strategies exist that may produce symptomatic benefit on the one hand yet impair survival on the other. Left ventricular dysfunction stimulates a host of neurohormonal compensations that appear fundamentally important in the expression of the heart failure syndrome. Experimentally and clinically, it appears that activation of the sympathetic nervous system with elevation in plasma norepinephrine occurs before activation of the renin-angiotensin-aldosterone axis.\(^{26,27}\) Vasopressin and, more recently, endothelin are known to be potent endogenous vasoconstrictors: endothelin appears to increase early in heart failure, paralleling plasma norepinephrine response, and correlates well with pulmonary vasoconstriction.\(^{28,29}\) The sodium- and water-retaining capabilities of angiotensin, aldosterone, and vasopressin all exacerbate the circulatory congestion of the heart failure syndrome. Counterregulatory vasodilator and natriuretic systems exist, and although there is evidence of their early activation in heart failure, escape from the protective influence of these neurohormons can ultimately occur.\(^{30}\) Atrial natriuretic peptide, in addition to its physiological effects, inhibits noradrenaline, renin, aldosterone, and vasopressin and
antagonizes their effects on peripheral blood vessels.\textsuperscript{9} Although endothelium-derived relaxing factor (EDRF) antagonizes the effects of endothelin, clear evidence exists concerning the attenuation of EDRF-dependent vasodilation in patients with heart failure.\textsuperscript{31} The salutary effects of endogenous vasodilator prostaglandins in heart failure can be unmasked by the administration of indomethacin, with resultant hemodynamic deterioration presumed secondary to unopposed accentuation of vasoconstrictor neurohormones.\textsuperscript{32} Recently, an endogenous digitalis-like factor in human plasma has been identified as ouabain or an isomer of ouabain.\textsuperscript{33} This substance has a potentially important homeostatic regulatory role in heart failure; initial studies indicate that it is elevated and bears an inverse relation with cardiac index and mean arterial pressure in heart failure.\textsuperscript{34} Interestingly, its elevation is also associated with lower-than-expected plasma angiotensin II levels.\textsuperscript{35} In addition to the evidence from plasma data for the existence of neurohumoral regulatory mechanisms, there is now an indication of a separate cardiac tissue renin-angiotensin system, in which angiotensin II formation is not blocked by the use of angiotensin-converting enzyme (ACE) inhibitors, that provides new insights into potential factors that regulate cardiac cellular growth, injury, and repair.\textsuperscript{36} In response to the increase in wall stress and both pressure and volume overloads, there is initial cardiac hypertrophy, which gives way in the face of progressive heart failure to progressive dilatation and, ultimately, left ventricular thinning. Concurrent with this is a transformation from the original elliptical to a more globular cardiac shape that is less efficient and associated with higher end-systolic wall stress and reduced inotropic reserve.\textsuperscript{37} Assumption of a more globular shape is also associated with the development of functional mitral regurgitation and impaired prognosis.\textsuperscript{38,39} In this regard, it is appreciated that the interstitial collagen network of the heart is not only a key determinant of force delivery and relaxation but also plays a major role in resisting the tendency toward cardiac dilatation and shape change.\textsuperscript{40} Sparked by these insights, novel research pathways have led to a new agenda of therapeutic targets aimed at modifying the cardiac and vascular remodeling induced by heart failure, with the resultant overall goal of halting or even reversing disease progression through repair.\textsuperscript{41}

**General Approaches**

Advances in the management of heart failure must begin with prevention and possible health measures. Attention to the correctable risk factors for coronary artery disease, the major cause of heart failure, includes an assertive approach to hypercholesterolemia, hypertension, obesity, and cigarette intake. Education, with emphasis on simple preventive strategies, and nonpharmacologic approaches to heart failure treatment are powerful and often neglected measures. As a beginning, this involves ensuring patients’ understanding of their disease and how they can participate meaningfully in their own treatment strategy, ie, sensible nutrition with attention to the potential harm of excess sodium and alcohol intake and the use of nonsteroidal anti-inflammatory agents. Whereas strenuous physical activity may overtax the circulation of the patient with compensated heart failure, regular aerobic exercise can enhance the efficiency of the cardiovascular system, with resultant increase in exercise tolerance.\textsuperscript{42} Such a program may also improve mental well-being and help to circumvent some of the psychological factors known to aggravate the heart failure state. Compliance with medical therapy is facilitated by written instructions and educational pamphlets, with reinforcement during alert outpatient monitoring.

A comprehensive search for systemic diseases that might be responsible for heart failure development or at least influential in exacerbating the syndrome is a cornerstone of the general approach. Given the prevalence of coronary disease and its etiologic importance as the major cause of congestive heart failure in North America, evaluation for active myocardial ischemia and the potential for enhancing ventricular function through revascularization should be undertaken. The potential for subendocardial ischemia alone to induce transmural abnormalities in left ventricular function, the appreciation of a metabolically downregulated hibernating state, and the capacity to reverse akinetic and even dyskinetic left ventricular segments through revascularization mandates a comprehensive search for ischemia.\textsuperscript{43-45}

In approaching optimal therapy for patients with heart failure, it is desirable to preserve or restore normal sinus rhythm so that atrioventricular synchrony exists with optimal atrioventricular delay.\textsuperscript{46} Optimal electrical/mechanical performance and heart rate control may ultimately require placement of a cardiac pacemaker.\textsuperscript{47} Despite the relatively high incidence of ventricular arrhythmia and sudden unexpected death in heart failure, antiarrhythmic agents cannot be recommended in the post-CAST era.\textsuperscript{11,48} Although there are some grounds for optimism regarding the ability of \( \beta \)-blockers and amiodarone to reduce the incidence of sudden death in patients with heart failure, no prospective, randomized data are currently available to justify broad application of this strategy, although a survival trial on amiodarone in heart failure is in progress\textsuperscript{49,50} (Table 1). This has led to the suggestion that the automatic implantable cardioverter-defibrillator may provide a better alternative. However, a recent single-institution report of 68 consecutive patients treated with the automatic defibrillator for ventricular tachycardia or fibrillation provided sobering information for patients with ejection fractions <30%.\textsuperscript{51} Surgical mortality in this group was 11%, and they had a 57% survival during a 31-month follow-up period. The majority of the deaths were nonsudden, raising the concern that device therapy may simply convert the mode of exit of patients with advanced left ventricular dysfunction rather than alter the final result. The incidence of embolic complications in heart failure is known to be increased, and systemic anticoagulation has traditionally been advised. Conflicting impressions have emerged from nonrandomized retrospective observations in two survival trials regarding the frequency of emboli and the role of systemic anticoagulants, indicating that this area is ripe for future investigation.\textsuperscript{52,53} In patients with cardiomegaly, well-established heart failure, and particularly atrial fibrillation, the indications for anticoagulation seem reasonably clear.

A potentially important new factor has recently been identified, ie, obstructive sleep apnea in patients with dilated cardiomyopathy.\textsuperscript{54} Given that estimates of this
problem suggest that as many as 2% of women and 4% of middle-aged men have clinically important sleep apnea and that heart failure affects at least 1% of the population, coexistence of these two entities is likely in a significant proportion of individuals. Nasal continuous positive airway pressure not only is effective in curing the sleep apnea but in preliminary studies appears to result in improved functional class and ejection fraction in patients with symptomatic cardiomyopathy. The mechanisms whereby improvement in cardiac function occurs in this context may be reduction of left ventricular afterload, attenuation of sympathetic surges during sleep, and improvement in hypoxemia.

**Pharmacologic Therapy**

Treatment objectives associated with drug therapy for heart failure include the reduction of central circulatory congestion and/or edema and the improvement of systemic perfusion. Other desirable aims include the reduction of myocardial oxygen consumption, enhancement of coronary perfusion, slowing of rapid heart rate, restoration of baroreceptor function, reversal of neurohumoral activation, restoration of cardiac size and shape, promotion of cardiac and vascular repair, and enhancement of survival.

### Diuretics

Diuretics remain a mainstay of heart failure treatment when fluid retention or central circulatory congestion is present. These agents are usefully classified according to their predominant site of action, i.e., proximal tubule, loop of Henle, distal convoluted tubule, or collecting duct, and a further refinement of this classification can be undertaken based on their mode of action at each site. The loop-active diuretics, consisting of furosemide, bumetanide, and ethacrynic acid, block the majority of active sodium chloride transport and are effective even when glomerular filtration rate is low. Diuretics acting at the distal tubule, such as hydrochlorothiazide and metolazone, are longer acting but less powerful than loop-active diuretics and more dependent on glomerular filtration rate for their effectiveness. Agents acting on the collecting duct tend to be relatively weak diuretics, but their potassium-conserving properties through either direct inhibition of Na-H exchange (thereby reducing potassium secretion) or direct antagonism of the effects of aldosterone, i.e., spironolactone, can be usefully exploited in combination with other agents. When hyperaldosteronism is present, however, the diuretic potential of spironolactone may be substantially enhanced. Renewed interest in the use of this agent has arisen because of its impressive ability to inhibit aldosterone-mediated myocardial fibrosis in experimental animals. A pilot study to evaluate the safety of aldactone in patients with class III or IV heart failure receiving an ACE inhibitor and diuretics is currently in progress with a view to a subsequent large-scale study of aldactone on mortality in heart failure (Table 1) (B. Pitt, personal communication, July 1993).

When heart failure is severe and large doses of diuretics in isolation become ineffective, additional strategies may be useful: (1) constant infusion of loop-active diuretics providing large doses at relatively low infusion rates may increase efficacy and reduce side effects; (2) combination of diuretics acting at different sites may provide synergism; this is especially true with the addition of loop-active diuretics to thiazides, which appears to increase thiazide-sensitive NaCl transport in the distal convoluted tubule; and (3) the use of diuretics may be potentiated by the infusion of renal doses of dopamine to increase renal blood flow.

Diuretics carry with them certain untoward effects that require clinical wariness. These include electrolyte imbalance in the form of hypokalemia and hypomagnesemia, both of which may potentiate digitalis intoxication and other ventricular arrhythmias. Hyponatremia with attendant activation of the renin-angiotensin system may develop. Overzealous use of diuretics and failure to respond to changing clinical circumstances may result in dehydration and prerenal azotemia. Vigilant clinical and laboratory monitoring, reduction of the dose when concomitant vasodilators are added, self-adjustment of diuretics, and intermittent dosing based on body weight changes monitored at home coupled with informed outpatient surveillance may be rewarded by avoidance of frequent hospitalizations for heart failure exacerbations. The use of diuretics for central and peripheral circulatory congestion remains a cornerstone of heart failure therapy, and evidence now exists to support their concomitant use with ACE inhibitor therapy. Potentiation of the effects of endogenous atrial natriuretic factor through the use of an endopeptidase inhibitor in nine class III and IV heart failure patients has recently been shown to produce impressive natriuresis and diuresis, decline in left ventricular filling pressure, and plasma norepinephrine, offering potential promise for novel therapy.
Vasodilator Therapy

The introduction of vasodilator therapy for patients with congestive heart failure was a therapeutic milestone. Remarkable hemodynamic benefit was evident in advanced heart failure with initial use of intravenous infusions of phentolamine, nitroprusside, and nitroglycerine.62-64 The demonstration of drugs with purely peripheral mechanisms of action rapidly led to the introduction and testing of a host of such agents administered orally to patients with heart failure, and sublingual nitroglycerin emerged as useful emergent therapy for acute pulmonary edema.65 Controversy has marked the role of long-acting nitrate therapy in heart failure because of a relative paucity of adequately sized double-blind placebo-controlled studies and because of concerns of nitrate tolerance.66-68 The most convincing study for efficacy of monotherapy with nitrates in chronic heart failure was that of Leier and coworkers,69 who used isosorbide dinitrate administered orally. After 3 months of therapy, clinical status was improved, treadmill exercise time increased, cardiac dimensions were reduced, and a sustained effect was evident on left ventricular filling pressure; however, tolerance was evident to the systemic arterial dilator effects of isosorbide dinitrate. Investigation of the problem of nitrate tolerance has revealed that it appears to be mediated by depletion of sulfhydryl groups at the cellular level and is associated with reflex unfavorable neurohumoral stimulation in humans, associated with fluid retention.66,67 A variety of strategies have been developed to combat nitrate tolerance, including concomitant administration of sulfhydryl-containing compounds, ACE inhibitors, and diuretics; these have met with mixed results.70-73 Intermittent TID dosing of nitrates appears to be most successful in circumventing tolerance, and given the recent discovery of nitric oxide as an endogenous vasodilator, the long history of nitrate use appears to have met with renewed physiological validation.70

Combination therapy with hydralazine and nitrates was thought to simulate the balanced arterial and venodilator effects of nitroprusside, and this combination was the first vasodilator regimen to demonstrate mortality reduction among symptomatic patients with ejection fractions <45%.74 This improvement in mortality was associated with an increase in left ventricular ejection fraction not seen in the placebo or prazosin group, and prazosin therapy was not associated with enhanced survival.

An impressive body of evidence exists attesting to the efficacy of ACE inhibitors and their ability to improve symptoms, hemodynamics, and exercise performance in patients with heart failure. In 1987, the CONSENSUS investigators reported a landmark study of ACE inhibitors that revealed a 31% reduction in mortality in patients with functional class IV heart failure treated with enalapril.75 The benefit in mortality was related to a reduction in death from progressive heart failure and was associated with a reduction in heart size and in requirement for other heart failure medications and with a significantly greater increase in the serum sodium level. Within 5 years of the CONSENSUS study, a remarkable series of publications reporting on the efficacy of ACE inhibitors in large-scale clinical trials emerged. The Veterans Administration Study Group undertook a second study using the hydralazine nitrate combination that had been the best therapy in VHeFT-I as a reference standard to compare enalapril 20 mg daily in patients with mild to moderate heart failure.22 In this study, VHeFT-II, enalapril resulted in a 28% lower mortality at 2 years, which was largely attributable to a reduction in sudden death among those patients who were least severely symptomatic: it is of particular interest that enalapril was able to decrease both the persistence of baseline ventricular tachycardia after 3 months of therapy and the emergence of new ventricular tachycardia at 1 and 2 years of follow-up, thereby paralleling the reduction in sudden death observed in the overall study.76 Although the hydralazine nitrate combination was superior to enalapril in increasing oxygen consumption at peak exercise and providing a greater increment in ejection fraction, this did not translate into a survival advantage. This finding has particularly important mechanistic implications in that it suggests that the survival advantage achieved by enalapril was secondary to a nonperipheral vasodilator mechanism perhaps mediated by antagonism of vasoconstrictor neurohormones, metabolic effects, and direct cardiac and/or coronary vascular protection. One disadvantage of the hydralazine nitrate combination, ie, 300 mg per day hydralazine and 160 mg isosorbide dinitrate, is patient compliance, with approximately one half of patients discontinuing or reducing the dose of one or the other of the medications. The SOLVD investigators, in a placebo-controlled trial of symptomatic heart failure patients, also demonstrated a survival benefit with enalapril treatment of 16% risk reduction, although approximately one third of patients in the active treatment arm had stopped enalapril by the end of the study.71 Importantly, these investigators demonstrated a parallel benefit on frequency of hospitalization for worsening heart failure and a survival benefit largely attributable to a reduction in progressive heart failure in patients with low ejection fractions. Approximately 1 year later, the SOLVD investigators reported on the prevention arm of their study, which examined in a placebo-controlled fashion the effects of enalapril on patients with functional class I or II heart failure and left ventricular ejection fractions of ≤35% who were not receiving drug treatment for heart failure.72 Although no significant reduction in mortality was seen over the average follow-up of 37 months, there was a 20% reduction in hospitalization for new or worsening heart failure in enalapril-treated patients that was most pronounced among patients with the lowest ejection fractions. An unexpected and interesting finding from the SOLVD study was that on composite analysis of both treatment and prevention arms, enalapril reduced the frequency of both myocardial infarction (23%) and unstable angina (20%).76

The unfavorable survival rates evident in symptomatic patients with heart failure also prompted examination of the benefits of ACE inhibitor therapy early after myocardial infarction in patients without symptoms. This initiative arose from both experimental work and clinical studies that revealed attenuation of the progressive ventricular dilatation after large myocardial infarction.77-79 Pfeffer and colleagues,80 in the Survival and Ventricular Enlargement (SAVE) trial, demonstrated that captopril 150 mg in divided doses daily given to
asymptomatic patients 3 to 16 days after myocardial infarction with ejection fractions of ≤40% resulted in a 19% reduction in mortality at 42 months. Captopril also reduced the frequency of hospitalization for heart failure, and importantly, these investigators confirmed the findings in SOLVD, namely a 25% reduction in recurrent myocardial infarction.

Thus, there is now clear evidence and compelling indication for the incorporation of ACE inhibitor therapy into the management of all symptomatic patients with heart failure as well as those patients with left ventricular dysfunction after myocardial infarction, irrespective of their symptomatic status. Given the side effects associated with ACE inhibitor therapy and an excess unexplained and possibly unrelated increase in gastrointestinal cancer frequency in the SOLVD study, caution should be exercised before the application of this therapy to all asymptomatic patients with left ventricular dysfunction.75 Those patients with most marked left ventricular dysfunction and/or evidence of advancing left ventricular enlargement or dysfunction would be reasonable candidates for early therapy, irrespective of symptoms. The divergence between the doses of ACE inhibitors used in clinical practice and those necessary to suppress neurohumoral activation, ie, the doses used in the survival trials, underscores the need for attention to compliance and adequate dosing. It remains unclear whether the survival benefit seen in the trials to date is a class effect of ACE inhibitors. In this regard, the retrospective post hoc evaluation by Pouleur and colleagues84 in the enalapril and captopril subsets of the xamoterol heart failure mortality study is of interest. In patients with similar baseline characteristics, these investigators found an excess mortality in the captopril compared with the enalapril group. This difference may be spurious but could reflect the shorter half-life of captopril and requirement for more frequent dosing, with a potential compliance problem associated with captopril rather than a true pharmacologic difference between the agents.82 A recent comparison of equipotent doses of lisinopril and captopril in heart failure has revealed suggestive evidence of an advantage in symptomatic benefit and ejection fraction but not exercise time with lisinopril as opposed to captopril.83 The issue of dose response is currently under examination in a large-scale survival study comparing low-versus high-dose lisinopril (ATLAS) (Table 1).

Although calcium antagonists were initially demonstrated to produce short-term favorable hemodynamic effects in congestive heart failure, their sustained administration has failed to show consistent benefit. Rather, there is good evidence that patients deteriorate, with worsening congestive heart failure.84 These observations appear to be related more to the neurohumoral antagonism with increased plasma renin, vasopressin, and norepinephrine than to their negative inotropic effects.85,86 Newer, more vascular-selective dihydropyridine calcium antagonists hypothesized to diminish vascular compliance more significantly, thereby inducing more ventricular unloading than first-generation agents, have been shown to improve both symptoms and exercise tolerance.87,88 Whether these agents are able to circumvent the problems associated with their predecessors remains uncertain and is the subject of ongoing clinical trials (Table 1).

The newest vasodilator available for clinical use is flosequinan, the first of a new class of fluoroquinolones, which has relatively balanced direct-acting arteriodilator and venodilator properties. This agent derives its clinical effect from the combined action of the parent compound and its similarly active sulfone hepatic metabolite and appears to act via attenuation of the second messenger inositol triphosphate, thereby reducing intracellular calcium availability for contraction of vascular smooth muscle.89 Initial trials demonstrated benefit in hemodynamic performance and exercise tolerance.90,91 Flosequinan also compared favorably to both enalapril and captopril in clinical trials, as well as demonstrating additional improvement when added for symptom control in patients receiving diuretics and ACE inhibitors.92-94 Interestingly, however, dose-response relations with flosequinan revealed no evidence of additional benefit at the peak dose of 150 mg compared with 75 and 100 mg.94,95 A large-scale survival trial of 100 mg flosequinan daily has recently been terminated earlier than planned because of the finding of excess mortality in the flosequinan group (M. Packer, personal communication, July 1993). The direct chronotropic action of this agent, which is independent of its blood pressure-lowering effect; its potential for accumulation in congestive heart failure; and its nonspecific phosphodies- terase inhibitor action may have been influential factors on this result.89

Recent interest in the investigation of novel vasodilators in heart failure has focused on the endogenous substance prostacyclin, which is known to produce vasodilatation of both pulmonary and systemic arterial as well as peripheral venous beds, with commensurate reduction in both preload and afterload of both ventricles. Its additional favorable cardiovascular profile, ie, inhibition of platelet aggregation, direct cytoprotection, and smooth muscle cell proliferation inhibition, coupled with preliminary favorable short-term hemodynamic studies in humans, stimulated the development of a large-scale survival trial to investigate prolonged infusion of prostacyclin in patients with refractory severe congestive heart failure.96-98 This trial has been terminated earlier than planned because of excess mortality in the treatment group (R. Califf, personal communication, July 1993). Noteworthy in this regard is an initial clinical study of prostacyclin in heart failure was the finding of an increase in plasma epinephrine and heart rate.98

Inotropic Therapy

Perhaps the most distinguishing feature of inotropic therapy for heart failure is the chasm that has developed between expectations and achievement. If the failing heart cannot meet the demands of the peripheral circulation because contractile performance is impaired and its cyclic AMP (cAMP) depleted, what more logical approach is first apparent than to enhance the inotropic state with an agent that increases cAMP, the second messenger responsible for transmitting catecholamine-induced increases in cytosolic calcium?99,100 Two basic pharmacologic strategies exist for increasing cAMP, ie, either increasing its synthesis or reducing its degradation. Increasing cAMP synthesis through the use of catecholamines in oral forms such as prenalterol, pirbuterol, salbutamol, or L-dopa, although providing
short term benefit, has been plagued by the development of an unfavorable side-effect profile, including acceleration of heart rate, accentuation of cardiac rhythm disturbances, and attenuation of efficacy.\textsuperscript{96-103} Although intravenous dobutamine can produce dramatic short-term clinical and hemodynamic benefit, attempts to translate this into an outpatient strategy for sustained management with intermittent infusions were met with increased ventricular arrhythmias and mortality.\textsuperscript{104,105} A similar legacy of problems has greeted attempts to reduce degradation of cAMP through the use of phosphodiesterase inhibitors such as enoxamine and, most recently, milrinone.\textsuperscript{23,25} The excess mortality associated with milrinone in a large survival study, which was primarily sudden and probably mediated by proarrhythmia, coupled with smaller previous studies of similar inotropic agents, helped close the door on this approach to the long-term therapy of heart failure.\textsuperscript{106,107} Given the suggestion that advanced heart failure should be perceived as a state of energy starvation or a cardiomyopathy of overload on the one hand and that excessive endogenous catecholamine activity is associated with downregulation of \(\beta\)-receptors on the other, it is perhaps not surprising on reflection that further sustained inotropic stimulation seems harmful.\textsuperscript{108} Our knowledge here is incomplete, however, and confounded by the fact that a number of inotropic agents have peripheral vasodilating effects that are beneficial and that dose-response relations of their diverse effects across heterogeneous subsets of patients with heart failure are poorly characterized, with the result that the balance between benefit and harm in individual patients of studies is difficult to discern. Moreover, in facing the challenge of advanced refractory heart failure, the practicing physician, after discussion with the patient, may be justified in using a therapy that achieves symptomatic relief despite an unfavorable impact on survival.

Additional inotropic agents with distinctive mechanisms of action are undergoing active investigation. Vesnarinone (OPC-8212) has a complex and diversified mechanism of action that both affects ion channels and increases the inward calcium current through mild inhibition of phosphodiesterase.\textsuperscript{109} Initial studies by Feldman and coworkers\textsuperscript{109} indicated clinical benefit in a small randomized trial, which stimulated the conduct of a larger study in patients with advanced class III or IV heart failure. The investigators then examined two doses of vesnarinone, ie, 60 mg and 120 mg, against placebo in a randomized permuted-block design for 6 months in class III heart failure patients with ejection fraction \(\leq 30\%\) (mean, 20\(\pm\)6\%), of whom 90\% were on digoxin and ACE inhibitors. Although the 120-mg arm of the study was terminated earlier than planned because of a twofold increase in mortality, paradoxically, patients in the 60-mg arm showed a 50\% (95\% CI, 20\% to 69\%) reduction in the risk of worsening heart failure or death compared with the placebo arm (15\% mortality at 28 weeks), emphasizing both the narrow therapeutic range of this agent and the peril of judging drug efficacy at a single dose.\textsuperscript{110} Although there was an overall 62\% (95\% CI, 28\% to 80\%) reduction in all-cause mortality, this was coupled with an important side effect of reversible neutropenia, which occurred in 2.5\% of vesnarinone-treated patients. Because the 60-mg vesnarinone dose has little hemodynamic effect, the mechanism of benefit is unclear but may relate to its effects as an antiarrhythmic or cytokine inhibitor.\textsuperscript{111} Further studies of this and related agents are warranted. Pimobendan is another new inotropic agent that has some phosphodiesterase inhibitory and vasodilator activity but is also known to sensitize the contractile apparatus to intracellular calcium.\textsuperscript{112} Kubo et al.\textsuperscript{112} in a randomized blinded study of three doses of pimobendan in heart failure patients who were symptomatic despite digitalis, diuretics, and vasodilators, found significant increases in exercise duration and peak \(V_{O_2}\) as well as an improvement in quality of life and reduction in hospitalization rates. This agent was well tolerated and did not increase plasma norepinephrine or show evidence of proarrhythmia. Interestingly, the intermediate 5-mg dose achieved better results than the peak dose, which had previously shown the largest hemodynamic improvement, highlighting once again the difficulty in establishing the optimal dose of a new drug in heart failure with multiple effects. Additional safety and efficacy studies on this agent are required before its ultimate role is clear.

Ironically, digitalis, the longest-surviving inotropic agent, a \(\text{Na}^+\),\(\text{K}^+\)-ATPase inhibitor that increases calcium availability to contractile elements, is only now undergoing an assessment of its effects on survival in patients with heart failure.\textsuperscript{113,114} Acute hemodynamic and neurohumoral studies of intravenous digoxin in heart failure patients have demonstrated significant decrements in plasma norepinephrine, renin, and aldosterone; increments in cardiac index have correlated with a decline in norepinephrine, leading to the speculation that the neurohumoral alterations were secondary to hemodynamically modulated sympathoinhibitory withdrawal.\textsuperscript{115} This issue was more directly addressed by Ferguson and colleagues,\textsuperscript{116} who used direct microneurographic peroneal recordings; they documented a profound and sustained decrease in efferent sympathetic nerve activity. Interestingly, these workers also demonstrated that a comparable increase in cardiac index achieved with dobutamine was not associated with alteration in sympathetic activity and suggested that the effects resulted from afferent activation of low- or high-pressure barore-
TABLE 2. Natural History and Treatment of Heart Failure as Defined by Large, Contemporary Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Drug</th>
<th>Patient Population</th>
<th>Entry EF, %</th>
<th>No. of Patients</th>
<th>Mean Follow-up, mo</th>
<th>Placebo Mortality, %</th>
<th>Relative Risk ±95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHeFT-I</td>
<td>Hydralazine/nitrate</td>
<td>Class II-III CHF</td>
<td>30</td>
<td>642</td>
<td>27</td>
<td>34.3</td>
<td>0.64</td>
</tr>
<tr>
<td>CONSENSUS-I</td>
<td>Enalapril</td>
<td>Class IV CHF</td>
<td>. . .</td>
<td>253</td>
<td>6</td>
<td>44</td>
<td>0.56</td>
</tr>
<tr>
<td>SOLVD, treatment</td>
<td>Enalapril</td>
<td>CHF, EF ≤35%</td>
<td>25</td>
<td>2569</td>
<td>41.4</td>
<td>39.7</td>
<td>0.84</td>
</tr>
<tr>
<td>SOLVD, prevention</td>
<td>Enalapril</td>
<td>Asymptomatic, EF ≤35%</td>
<td>28</td>
<td>4228</td>
<td>37.4</td>
<td>15.8</td>
<td>0.82</td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>Post-MI, EF ≤40%</td>
<td>31</td>
<td>2231</td>
<td>42</td>
<td>25</td>
<td>0.81</td>
</tr>
<tr>
<td>Xamoterol</td>
<td>Xamoterol</td>
<td>Class III/IV CHF</td>
<td>. . .</td>
<td>516</td>
<td>3</td>
<td>3.7</td>
<td>2.54</td>
</tr>
<tr>
<td>PROMISE</td>
<td>Milrinone</td>
<td>Class III/IV CHF</td>
<td>21</td>
<td>1088</td>
<td>6.1*</td>
<td>24</td>
<td>1.27</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; CI, confidence interval; CHF, congestive heart failure; and MI, myocardial infarction.

*Median.

Receptor mechanisms. A renaissance of interest in evaluation of digoxin's efficacy has occurred in the past decade, resulting in conclusive evidence for benefit in randomized placebo-controlled trials assessing symptomatic relief, hemodynamics, and exercise performance.137-140 Furthermore, a withdrawal trial of 178 patients with class II or III heart failure and ejection fractions of ≤35% who were clinically stable on triple therapy with digoxin, diuretics, and ACE inhibitors has convincingly demonstrated a greater than fivefold increase in the risk of recurrent symptoms and morbidity after digoxin withdrawal.121 Those who appear to benefit most from digitals are heart failure patients with left ventricular systolic dysfunction and cardiomegaly. New understanding of the metabolic and drug/drug interactions that potentiating digoxin toxicity has contributed to safer use of digoxin.138 Taken together, these developments have helped to secure a revitalized and more secure position for digoxin in the long-term management of patients with heart failure that will undergo reevaluation when survival data are available (Table 1).144

β-Blockers

Nearly 20 years ago, Waagstein et al122 first reported on the effects of chronic β-receptor blockade in heart failure secondary to congestive cardiomyopathy. This therapy has since undergone multiple small-scale examinations and refinements and continued to withstand initial skepticism. The largest general clinical experience to date is with metoprolol, a β1-selective antagonist that has been shown in small randomized studies to improve functional classification, hemodynamic performance, left ventricular ejection fraction, and exercise capacity.139,140 Withdrawal of therapy has been met with recurrence of symptoms.124,125 The Metoprolol in Dilated Cardiomyopathy (MDC) Trial evaluated 383 functional class II and III heart failure patients with idiopathic dilated cardiomyopathy. This study has recently been completed after a follow-up time of 12 to 18 months and revealed a significant decrease in the frequency of metoprolol-treated patients deteriorating to the point of achieving heart transplantation criteria (19 placebo and 2 metoprolol patients, P = .0001). In addition, there was a marginally significant 34% reduction in the composite end point of death or need for transplantation (ie, 25 events in metoprolol versus 38 in placebo, P = .058; 95% CI, 6% to 62%) (K. Swedberg, personal communication, August 1993).126 Some evidence exists to suggest that preferential benefit accrues to patients with idiopathic dilated cardiomyopathy as opposed to those with heart failure secondary to coronary artery disease.126 Proposed mechanisms for benefit of β-blocker therapy include reduction in sympathetic nervous activity, restoration of the β1-cardiac receptor population with improved contractile performance, enhanced myocardial relaxation, and improved cardiac efficiency associated with a reduction in heart rate.127 Newer β-blockers undergoing intensive study currently include bucindolol, a nonselective β-blocker with vasodilator properties that has been shown to reduce both plasma norepinephrine and renin, and carvedilol, an agent with mild β1-selective antagonism and α1-blocking properties.127,128

Large-scale survival studies on β-blockers in heart failure have not been performed. Notably, however, xamoterol, a β-blocker with partial β-agonist activity, has been demonstrated to have a deleterious effect on survival in patients with class III or IV heart failure, possibly associated with its inability to reduce resting heart rate and potentially unfavorable effects on neurohumoral activation.124 Xamoterol has also been classified as a β-agonist because of its tendency to increase resting heart rate, especially during sleep; during exercise, however, its β-receptor antagonism is more prominent.128 Interestingly, a post hoc analysis of the Beta-blocker Heart Attack Trial (BHAT) demonstrated that the mode of survival benefit in convalescent myocardial infarction patients with heart failure appeared to be related to a reduction in sudden death presumed sec-
TABLE 3. Heart Failure Agenda for 2000

| Elucidate cellular and molecular causative mechanisms |
| Identify full spectrum of compensations, their triggers, controls, and interactions at both circulatory and tissue levels |
| Characterize growth factors and modulators of myocyte and nonmyocyte response to injury |
| Develop animal models that address the spectrum of human therapeutic objectives and authentically reflect outcome measures, including survival |
| Develop an early, preclinical detection strategy and treatment for heart failure |
| Sharpen useful and objective diagnostic criteria for heart failure that accurately track the disease |
| Develop comprehensive and reliable methods for stratifying patients into prognostic subsets |
| Develop noninvasive measures to identify and quantify both myocardial ischemia and diastolic dysfunction so as to permit accurate evaluation of their role in the heart failure syndrome, whether as a dominant or significant partner |
| Implement therapy that antagonizes neurohumoral activation, halts or reverses the disease progression, and enhances survival; ensure that symptomatic treatment does not compromise these objectives |
| Capitalize on new neurohumoral knowledge to develop agents that promote endogenous support of contractile function, vasodilatation, and diuresis |
| Explore gene therapy for repair of ventricular (myocyte and nonmyocyte) and vascular remodeling |
| Investigate novel surgical and mechanical solutions for heart failure |
| Enhance donor heart availability to facilitate cardiac transplantation |

secondary to an antiarrhythmic effect. Eichhorn, in a recent comprehensive review, estimates that approximately 1 in 10 patients with heart failure will initially have symptom aggravation with commencement of metoprolol and suggests a regimen commencing with 6.25 mg BID with gradual increments to 50 mg BID.

Based on available evidence, the best contemporary pharmacologic approach to heart failure should involve ACE inhibitors in doses known to prolong survival coupled with diuretic therapy, either continuous or intermittent, to relieve central or peripheral congestion. The addition of digoxin to the medication of patients with symptoms persisting on combined ACE inhibitor and diuretic therapy is a logical next step, although the addition of nitrates and/or hydralazine is another alternative. Patients unable to tolerate ACE inhibitor therapy should be offered the option of combined hydralazine nitrate therapy. In refractory heart failure, the addition of (initially) low-dose metoprolol therapy, especially in those patients with congestive cardiomyopathy and resting tachycardia, may be useful. A contemporary heart failure paradigm is illustrated in the Figure and undertakes to define therapeutic goals according to symptomatic status. Importantly, this demonstrates that there is a quartet of therapeutic goals, the relative importance of which depends on the symptomatic status of the patient and expectations concerning the natural history. As patients become progressively more somatic, with declining life expectancy, therapeutic priorities focus more on relief of symptoms and prevention of complications. The threshold for accepting greater risk to achieve benefit under such circumstances is diagonally depicted as rising, indicating a willingness to accept more risk to achieve benefit in patients with advanced symptoms. By contrast, in patients who are asymptomatic with minimal impact on survival, choice of therapy should be directed toward improvement in survival and halting progression of or reversing the disease. At this point in the evolution of the disease, one is not willing to tolerate substantial risk to achieve benefit.

In Table 2, a summary of recently published placebo-controlled survival trials aimed at reducing morbidity and mortality from heart failure is shown. The study drug, patient characteristics at entry, average ejection fraction at baseline, mean follow-up time, and placebo mortality are shown. As is evident from the relative risk in the right column, although the vasodilator trials show a survival benefit, substantial residual mortality exists in the treatment group, which indicates the need for future progress in the treatment of heart failure. Importantly, four trials that have had negative effects on survival used agents that increased resting heart rate, i.e., the Xamoterol and Promise trials, and the recently concluded survival trials with flosequinan and prostacyclin. This tendency for an increase in heart rate, with a propensity for accentuation of ventricular arrhythmias and unfavorable neurohumoral activation, is reminiscent of the negative clinical experience with other phosphodiesterase inhibitors and β-agonists.

A discussion of mechanical assist devices, cardiomyoplasty, and cardiac transplantation as approaches to the heart failure syndrome is beyond the scope of this review. Although important gains in survival have been achieved by cardiac transplantation, continuing problems with rejection, heart failure, sepsis, accelerated atherosclerosis, and psychosocial adjustment remain a concern and pose opportunities for creative solutions.

Despite the enormous explosion in our knowledge concerning treatment opportunities in heart failure, we remain ignorant about many aspects of the syndrome and the agents that modify it. Heterogeneity of patients and etiologies and differing mechanisms of action of the same drugs with different dose-response relations for each remain important components of the problem. Fresh approaches rigorously tested and derived from the basic laboratory will be required to meet the enormous challenges ahead. Table 3 depicts a proposed future agenda for advances in heart failure.

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