ACE Inhibitors in Congestive Heart Failure

Theodore R. Kantner, MD
Lubbock, Texas

Despite improved understanding of both disease mechanisms and the quality of care, congestive heart failure (CHF) remains a serious clinical problem. The traditional treatments, diuretics and digitalis, continue to play a major role in the management of many patients with CHF; however, in the last decade, angiotensin-converting enzyme (ACE) inhibitors have been added as an important treatment option. These agents counteract the overstimulation effects of diuretics on the renin-angiotensin-aldosterone system. In addition, some studies indicate that ACE inhibitors may improve symptoms and survival. Recent evidence suggests that in patients with mild to moderate CHF, ACE inhibitor and a diuretic should be administered with or without digitalis to achieve the maximum clinical benefit.

Key words. Angiotensin-converting enzyme inhibitors; heart failure, congestive.
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Congestive heart failure (CHF) is a serious and growing clinical problem. Although our understanding of the disease process has improved over the last several decades, the incidence of CHF has increased, while the survival rate has not substantially improved. There are approximately 3 million existing cases and 400,000 new cases of CHF each year in the United States.[1,2] The 5-year survival rate of patients treated with the traditional regimen of diuretics and digitalis glycosides remains less than 50%.[3,4] Development of new, more effective treatments for CHF has therefore been a medical priority.

The purpose of this review is to briefly summarize the pathophysiology of CHF and to discuss the major therapeutic interventions, addressing especially the emerging evidence for the utility of the angiotensin-converting enzyme (ACE) inhibitors in this difficult treatment situation. This review focuses on the most common cause of heart failure, which results from systolic left ventricular dysfunction.

Overview of Pathophysiology

In congestive heart failure due to systolic dysfunction, myocardial contractility, left ventricular performance, and cardiac output are reduced. The decline in cardiac output, in turn, triggers a number of interrelated hormonal and neurohormonal responses designed to increase blood volume and systemic vascular resistance to maintain perfusion of major organ systems. However, hormonal and neurohormonal overstimulation contributes to decompensation, perpetuating the downward spiral of heart failure.

One of the most important of these responses is activation of the renin-angiotensin-aldosterone (RAA) system, which is primarily stimulated by reduced perfusion of the kidney.[5–7] As a result, renin is released, and angiotensinogen is converted to the physiologically inactive peptide angiotensin I. The angiotensin-converting enzyme then transforms angiotensin I into the potent vasoconstrictor angiotensin II. In addition to increasing vascular resistance, angiotensin II also stimulates the secretion of aldosterone from the adrenal glands.[5] The release of aldosterone causes an increase in blood volume due to the retention of sodium and water and excretion of potassium.[1,6]

The resulting arterial vasoconstriction increases impedance to left ventricular ejection, further impairing cardiac performance, and also limits blood flow to skeletal muscles, leading to fatigue.[8] The sodium-retentive effects of aldosterone result in increases in blood volume and left ventricular filling pressure, contributing to pulmonary edema.[5,8] This increase in blood volume also raises atrial filling pressures and contributes to peripheral edema.

Other biochemical and metabolic changes observed in heart failure include increases in the levels of circulating catecholamines[1,9] and plasma vasopressin,[1,10] and

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From the Department of Family Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas. Requests for reprints should be addressed to Theodore R. Kantner, MD, Department of Family Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

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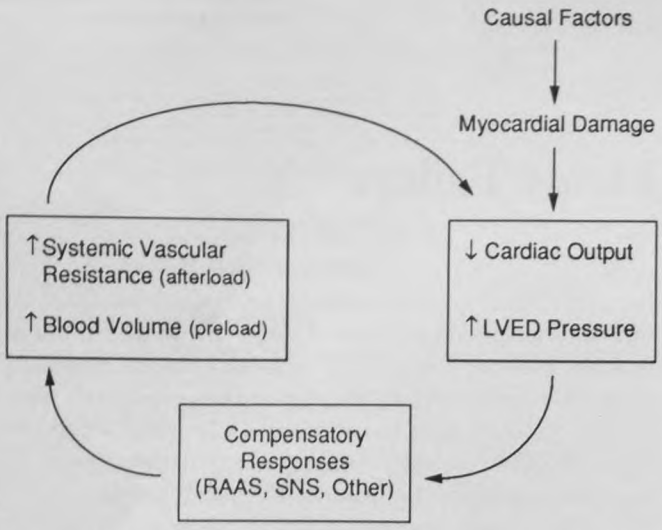

Figure 1. Vicious circle of heart failure. Decreased cardiac output causes stimulation of the renin-angiotensin-aldosterone system and aldosterone release. The resultant vasoconstriction and increased systemic vascular resistance eventually act to perpetuate heart failure. LVED denotes left ventricular end-diastolic pressure; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. (From Faxon.[1] Reprinted with permission from the *American Heart Journal*.)

decreases in plasma levels of bradykinin and vasodilatory prostaglandins.[1] All of these responses may be useful to compensate for acute heart failure; however, they are deleterious in chronic heart failure, leading to progressively declining myocardial function and organ perfusion (Figure 1).[1] The degree of activation of the neurohormonal system has been shown to be inversely related to prognosis in patients with CHF.[5,11]

Principal Treatments

Diuretics

Diuretic therapy remains a key component of treatment for all classes of heart failure. These agents stimulate excretion of sodium and water, thereby reducing pulmonary congestion and improving dyspnea and edema. Potent loop diuretics, such as furosemide and bumetanide, are preferred in patients with severe heart failure, whereas oral thiazides may suffice for patients with milder conditions.[5] A loop diuretic can also be used in combination with a thiazide or metolazone (a quinazoline) to achieve an added effect.[5,12]

Despite their considerable value in CHF, there are a number of serious considerations regarding the use of diuretic therapy. Diuretics may deplete electrolytes and increase the risk of ventricular arrhythmias in susceptible patients.[13,14] In addition, diuretics can stimulate the RAA system, producing markedly increased plasma renin and angiotensin II activity, with concurrently raised plasma aldosterone levels.[15,16] Diuretic therapy may also stimulate the sympathetic nervous system, causing an increase in circulating norepinephrine levels.[15,16] These stimulatory effects can further increase systemic vascular resistance and reduce cardiac output, thereby exacerbating the vicious circle of heart failure.[5] A large percentage of patients who are adequately controlled initially begin to experience clinical deterioration within months when managed on diuretic monotherapy.[13] These limitations indicate that although diuretics continue to be highly useful in CHF, they may not represent optimal treatment when used alone.

Digitalis

After more than 200 years of clinical use, the efficacy and safety of digitalis glycosides in all degrees of CHF remain controversial.[5,17] The usefulness of digitalis has been demonstrated in severe heart failure and in cases where atrial fibrillation is a complication of CHF.[5,18] Conflicting data have been reported concerning the use of digitalis in the treatment of patients with mild to moderate CHF and normal sinus rhythm. Several controlled trials have found the drug to be effective in the treatment of some patients with chronic heart failure in normal sinus rhythm.[19,20] In contrast, placebo-controlled, double-blind investigations by Fleg et al[21,22] did not demonstrate any noticeable effect of digoxin on symptoms in patients with mild CHF. Further, whether discontinuation of digoxin in mild CHF leads to clinical deterioration has not been established.[21,23,24] An additional consideration in the decision to institute treatment with digitalis glycosides in CHF is their potential for arrhythmic effects.[25–27] Sudden cardiac death, presumably due to ventricular arrhythmias, is the terminal event in approximately 40% of patients with CHF.[26] Digitalis sensitizes the heart to low concentrations of potassium, a risk factor for the development of arrhythmias.[26] The assessment of digitalis may be complicated because digitalis toxicity can occur in some patients at drug levels generally regarded as safe, whereas in other patients even elevated levels of digitalis may not produce symptoms of toxicity or ECG abnormalities.[5,28] Finally, an association between digitalis and increased mortality in patients who have had a myocardial infarction has been reported.[29,30] Despite these conflicting studies, in general the data suggest that digitalis remains a valuable therapeutic agent for relieving symptoms and improving exercise performance and left ventricular function in patients with congestive heart failure.[31] It has been suggested, however,

continued on page 309

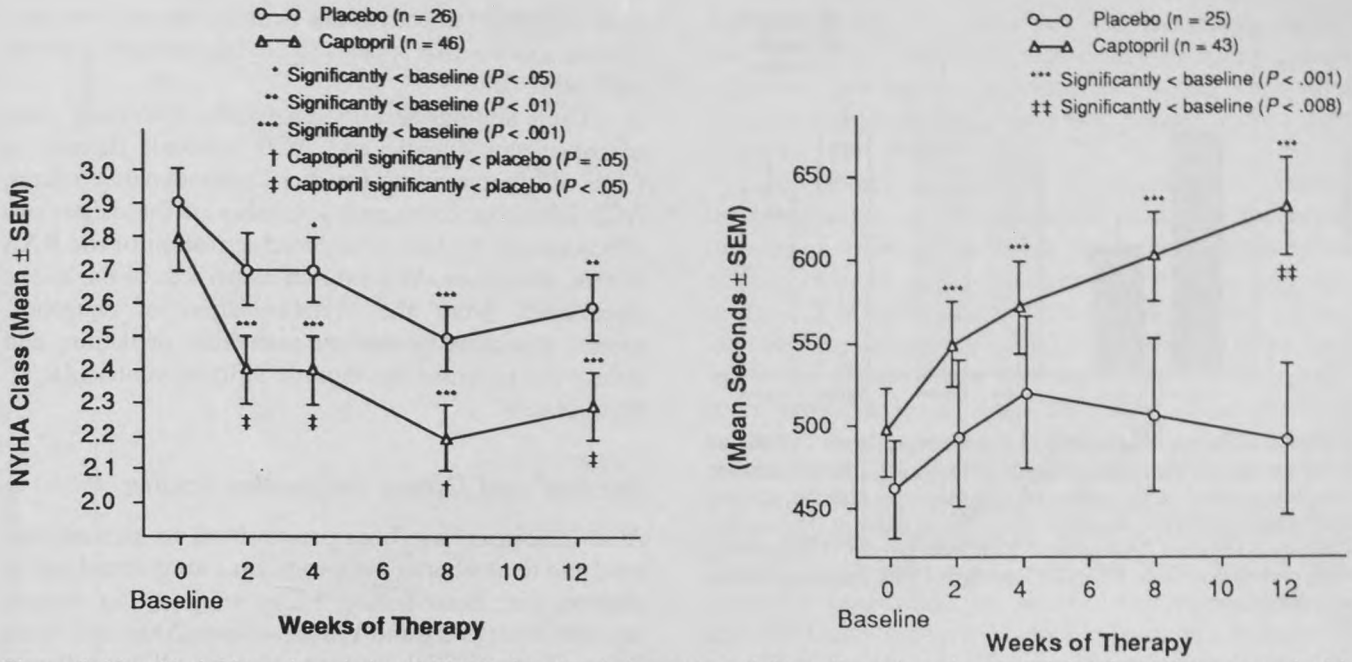

Figure 2. New York Heart Association (NYHA) functional class ratings (left) and exercise tolerance (right) for patients treated with captopril or placebo in addition to digoxin and diuretics. (From Captopril Multicenter Research Group.[34] Reprinted with permission from the *Journal of the American College of Cardiology*.)

that digitalis should be co-administered with an agent that has been shown to improve survival in this patient population, such as an ACE inhibitor.[13]

ACE Inhibitors

In the United States, the ACE inhibitors captopril and enalapril have been approved by the Food and Drug Administration (FDA) for the treatment of CHF when added to digitalis and diuretics. Captopril can also be added to diuretics alone when administration of digoxin is not feasible. A number of other drugs of this class are currently under study. The bulk of the current information concerning the efficacy and safety of ACE inhibitors in CHF is drawn from studies of the prototype agent, captopril. Although the usefulness of ACE inhibitors in severe heart failure is well documented,[32,33] data concerning their value in mild to moderate heart failure have only recently become available.

Captopril Added to Diuretic-Digoxin Therapy

In a placebo-controlled multicenter study of patients with heart failure refractory to diuretic and digitalis therapy,[34] 50 patients had captopril (75 to 300 mg per day) added to their baseline therapy of digitalis and diuretics, while 42 patients (control group) received placebo in addition to their existing regimen. Of the patients treated with captopril, 54% were in the New York Heart Association (NYHA) functional class III, 44% were in class II, and 2% were in class IV.[35] Clinical improvement was noted in 80% of patients treated with captopril, compared with only 27% of patients given placebo ($P < .05$).[34] Mean improvement in NYHA class, exercise tolerance, and ejection fraction was significantly better among patients who received captopril (Figure 2). Improvements in specific symptoms of CHF, such as dyspnea, orthopnea, fatigue, and edema, were also significantly greater in the captopril group ($P < .05$ to $P < .001$). This study demonstrated that patients with mild to moderate heart failure who are already receiving a diuretic with digitalis may benefit substantially from the addition of an ACE inhibitor to their therapeutic regimen.

Captopril Compared with Digoxin in Patients Receiving a Diuretic

An important comparison of benefits with an ACE inhibitor vs digitalis in the treatment of patients with mild to moderate CHF was undertaken in a large 6-month trial conducted by the Captopril-Digoxin Multicenter Research Group.[17] In this study, 300 patients with mild CHF (mainly NYHA class II) receiving stable diuretic therapy were assigned on a double-blind basis to additional treatment with captopril, digoxin, or placebo.

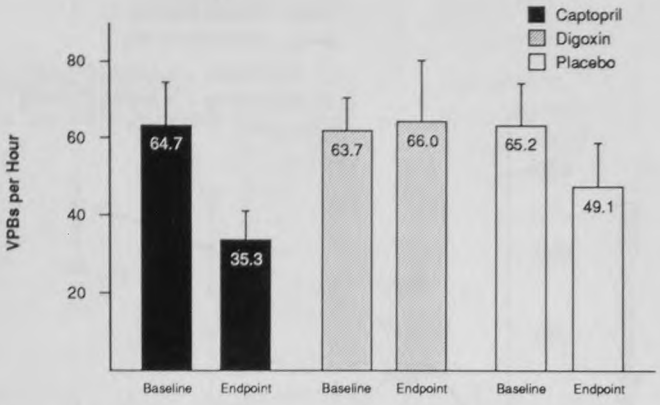

Figure 3. Numbers of ventricular premature beats (VPBs) at baseline and endpoint for patients with >10 VPBs per hour at baseline treated with captopril, digoxin, or placebo during maintenance diuretic therapy. P < .05 vs digoxin. (From the Captopril-Digoxin Multicenter Research Group.[17] Reprinted with permission from *JAMA*. Copyright 1988, American Medical Association.)

Compared with the placebo group (ie, those on diuretics alone), captopril (75 to 150 mg/d) significantly improved both exercise time ($P < .05$) and NYHA functional class ($P < .01$), whereas digoxin did not. Digoxin increased ejection fraction significantly compared with captopril and placebo ($P < .05$). The number of ventricular premature beats (VPBs), however, decreased by 45% in the captopril group but did not change significantly in the digoxin group among patients with more than 10 VPBs per hour at baseline (Figure 3). Patients receiving placebo (ie, only diuretic therapy) had a greater incidence of treatment failure and a significantly ($P < .05$) greater number of hospitalizations and emergency department visits compared with those in either the captopril or digoxin groups. Patients in the placebo group also required increased dosages of diuretics to control their heart failure symptoms, compared with patients receiving captopril or digoxin.

In another large study among 116 patients with NYHA class II or III heart failure, Heck et al[36] administered either captopril, 25 mg twice daily, or digoxin, 0.1 mg twice daily. All patients also received hydrochlorothiazide, 50 mg/d. Over 12 months of therapy, the group treated with captopril demonstrated statistically significant improvements in echocardiographically determined diameters, exercise tolerance, and NYHA class, compared with patients treated with digoxin.

These results support previous reports of an incremental benefit with the addition of low doses of captopril to diuretic therapy. They also indicate that captopril can be an effective and safe alternative to digoxin in patients with mild to moderate CHF who are taking diuretics. ACE inhibitors directly blunt neurohormonal overstimulation, a factor that appears to be deleterious in patients with heart failure.

These findings also underscore the synergistic value of concurrent diuretic and ACE inhibitor therapy in CHF. While providing beneficial hemodynamic effects, ACE inhibitors counteract a number of the deleterious effects caused by diuretic-induced activation of the RAA system. Moreover, ACE inhibitors can reduce the loss of electrolytes, blunt the overstimulation of neurohormones, minimize or prevent potassium depletion, and reduce the potential for diuretic-induced ventricular arrhythmias.[13]

Survival and Disease Progression Studies

ACE inhibitors have been proven both to increase survival and to ameliorate symptoms on a long-term basis in patients with heart failure.[13] The results of an analysis reported by Furberg and Yusuf[37] of over 2000 cases from 24 randomized trials indicate that of all vasodilators tested, patients treated with ACE inhibitors have the lowest associated mortality rate. In the CONSENSUS trial,[38] 253 patients with severe CHF (class IV) received their regular therapy—diuretics, digitalis, and vasodilators (eg, nitrates, prazosin, hydralazine)—to which either enalapril or placebo was added. At the end of 20 months of treatment, the mortality rate in the enalapril group was significantly ($P = .003$) reduced by 27% as compared with the placebo group[38,39] (Figure 4). A report on the follow-up data obtained 8 ½ months after the end of the CONSENSUS trial strongly supported the original data on reduction of mortality and also showed enalapril to have a longer duration of effect than previously reported.[40]

In another prospective trial,[41] addition of captopril or an isosorbide dinitrate–hydralazine combination was compared in 106 patients being evaluated for heart transplant. Although both drug regimens were titrated to achieve comparable hemodynamic effects, the addition of captopril therapy improved survival compared with the isosorbide dinitrate–hydralazine combination. In this study, ACE inhibitor therapy was shown to be an independent predictor of survival ($P = .015$). Similarly, the recent second Veterans Administration Cooperative Vasodilator–Heart Failure Trial (V–HeFT II) compared a regimen of enalapril added to digoxin and diuretic therapy with the addition of hydralazine and isosorbide dinitrate in patients with chronic congestive heart failure.[42] Two-year mortality was significantly ($P = .016$) lower with enalapril (18%) than in the hydralazine–isosorbide dinitrate group (25%). Lower mortality was primarily the result of a reduced incidence of sudden

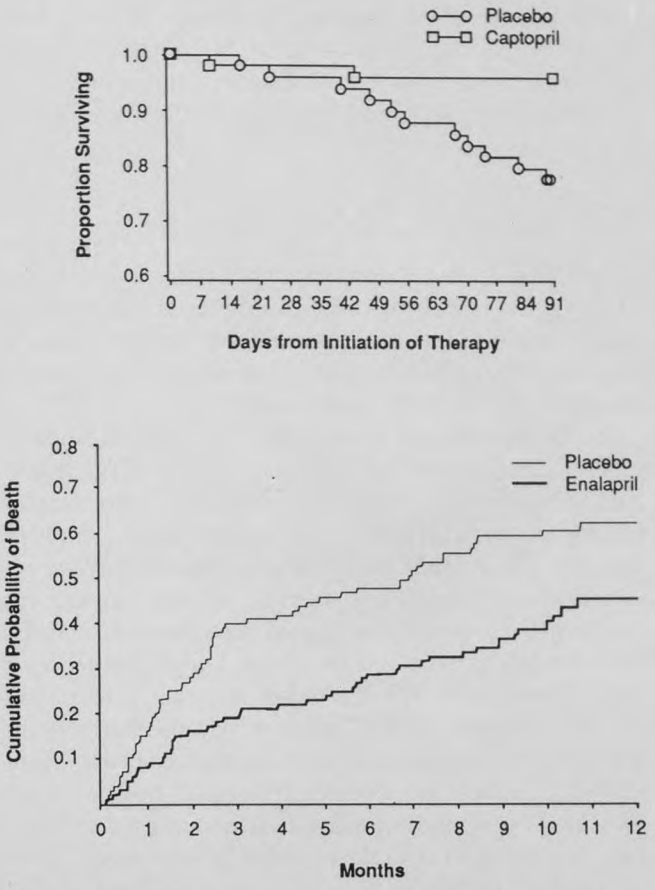

Figure 4. Survival over time in patients with moderate to severe heart failure treated with an ACE inhibitor—captopril[39] or enalapril[38]—or placebo added to digoxin and diuretics. (Adapted from Newman, et al,[39] with permission from the *American Journal of Medicine*, and from the CONSENSUS Trial Study Group[38] with permission from *The New England Journal of Medicine*.)

death, an effect that had not been previously demonstrated.

A retrospective review of clinical trials involving patients with CHF, including patients with NYHA classes II, III, and IV, indicates that captopril added to digoxin and diuretics has a favorable effect on survival. In a report by Kleber et al,[43] 170 patients with mild CHF (NYHA class II) received either captopril or placebo twice daily over diuretic-digoxin background therapy for a mean observation period of 2 ½ years (range 3 months to 5 years). Although there was no statistical difference in overall mortality between groups, there was a marked reduction in progression of CHF to class IV or death (14.0% vs 32.4%), and a significantly ($P < .12$) higher event-free survival rate (1547 vs 1308 days) with captopril than with placebo. In another trial among 105 patients treated with captopril or placebo,[39] the mortality rate was 21% in the placebo group and only 4% in the captopril group. The difference was statistically significant ($P < .1$). Sudden cardiac death was the terminal event in eight patients assigned to placebo, compared with the sudden death of only one patient treated with captopril ($P < .05$).

The efficacy of captopril in preventing or slowing the progression of left ventricular dilatation following myocardial infarction (MI) has also been investigated in clinical trials. In a placebo-controlled study among patients with an initial anterior MI,[44] end-diastolic volume increased significantly ($P < .2$) in the placebo group but not in the group treated with captopril. Moreover, captopril attenuated additional ventricular dilatation in a subgroup of patients with a greater risk of this adverse process. (Patients with ventricular dilatation in the first year after MI had a significantly worse prognosis than other post-MI patients.) In another study,[45] patients who had experienced a Q-wave MI were treated with captopril, furosemide, or placebo. Captopril decreased left ventricular end-systolic volume index significantly ($P < .05$) compared with furosemide, whereas ventricular volume was significantly increased during treatment with the diuretic or placebo over the 12-month study period.

The potential for improved survival in post-MI patients with left ventricular dysfunction is being further examined in large, multicenter, controlled trials of both captopril[46] and enalapril.[47] The Survival and Ventricular Enlargement (SAVE) study evaluated the efficacy of captopril in improving survival and in reducing cardiovascular mortality and the incidence of major deterioration in ejection fraction in post-MI patients.[46] Results of this trial are forthcoming. The Studies of Left Ventricular Dysfunction (SOLVD) trial[47] involved a randomized, double-blind, placebo-controlled protocol designed to assess whether the addition of enalapril to conventional therapy would reduce mortality in patients with congestive heart failure and a low ejection fraction (≤ 0.35). Most patients (90%) were in NYHA classes II and III. After an average follow-up of 41.4 months, the difference in survival significantly ($P = .0036$) favored enalapril.

Few studies have carefully examined quality-of-life indicators while studying ACE inhibition in patients with CHF. In a small group of refractory patients placed on captopril therapy, Dzau and associates[48] reported improvement in NYHA functional class in all patients, along with significant decreases in both hospital admissions ($P < .005$) and hospital days ($P < .02$) during the period of study (Figure 5).

Practical Considerations with ACE Inhibitors

Of all the ACE inhibitors available, captopril has been the most widely studied to date. Studies with other ACE

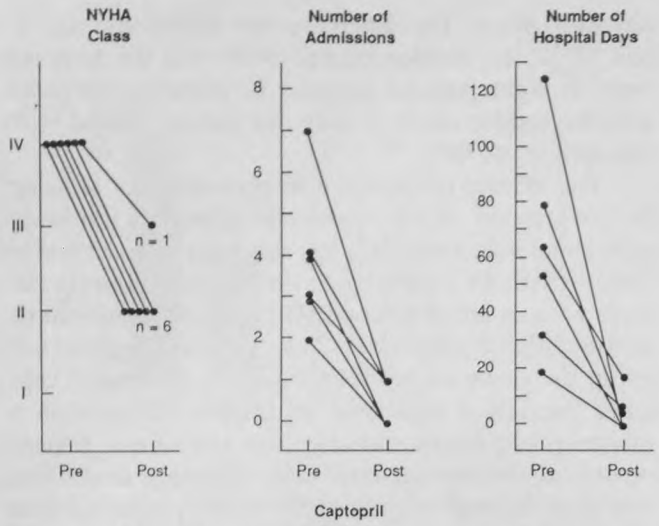

Figure 5. Effects of captopril added to digoxin, diuretics, and vasodilators on New York Heart Association (NYHA) class, number of hospital admissions, and number of hospital days in patients with congestive heart failure refractory to conventional therapy. Patients were followed for longer than 3 months. (From Dzau et al.[48] Reprinted with permission from *The New England Journal of Medicine*.)

inhibitors,[49] however, show effects similar to those observed with captopril in CHF, and a favorable effect on survival has also been demonstrated with enalapril.[38,42,47]

Because orally administered enalapril must be converted in vivo to its active metabolite enalaprilat, peak hemodynamic effects of enalapril are not seen until approximately 6 hours after dosing.[50,51] In a study of patients with severe chronic heart failure treated with large fixed doses of either captopril or enalapril, clinically important symptomatic hypotension was noted more often in the enalapril group.[52] Hypotension associated with enalapril treatment was the most common cause of withdrawal in the CONSENSUS study.[38] For this reason, it was recommended that patients should be observed for at least 2 hours after administration of the initial dose of enalapril.[53] A significant ($P < .05$) decline in creatinine clearance was also observed with enalapril, but not with captopril, confirming earlier findings that the risk of reducing glomerular filtration rate may be minimized with captopril but may increase with enalapril in susceptible patients.[54]

Other clinical studies of patients with heart failure have also reported adverse changes in renal function associated with long-acting ACE inhibitors.[38,49,55] Because increased incidence of side effects, such as hypotension and renal function changes, may be associated with the longer-acting ACE inhibitors, treatment with shorter-acting agents such as captopril may be more beneficial in certain patients. It has therefore been suggested that longer-acting agents should be used cautiously in patients with severe CHF.[56] Nevertheless, these concerns must be balanced against convenience and the potential for increased compliance offered by longer-acting agents.

Other Agents for Congestive Heart Failure

In addition to the agents specifically approved by the FDA for the treatment of CHF, numerous other drugs may be useful. Many new agents from various chemical classes are being studied as well, but none is considered a first-line drug for CHF at this time.

Oral nitrates and α-adrenergic antagonists, such as prazosin, produce initial beneficial effects in CHF; however, development of tolerance and consequent loss of efficacy has been reported with both of these groups of agents.[57] Hydralazine and related vasodilators dilate resistance blood vessels and increase cardiac output, but they may fail to produce sustained hemodynamic benefits on a long-term basis and they have a high incidence of troublesome side effects, such as tachycardia and edema.[57] Calcium channel blockers may also have potentially beneficial dilating effects on resistance vessels. Their inhibitory effects on calcium transport, however, can concurrently produce significant cardiodepressant effects, and they are not currently regarded as important future drugs for CHF.[57]

Another group of drugs with which there is some experience in CHF is the phosphodiesterase inhibitors. Amrinone is the prototype drug of the class, and numerous related compounds have been investigated. Although these agents have demonstrated both short- and long-term hemodynamic benefits in CHF, there are concerns that they can provoke ventricular arrhythmias, adversely affect oxygen consumption, accelerate progression of the underlying disease, and increase overall mortality.[57] Milrinone, the second of the class of agents, has been associated with a higher mortality rate than digoxin in a comparative trial.[58] In the recent Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial, mortality increased by 30% in patients treated with milrinone compared with those in the placebo group.[59] Patients in both areas of the study received concomitant digoxin, diuretics, and ACE inhibitor therapy. Whether these problems can be overcome with the newer phosphodiesterase inhibitors now entering development remains to be evaluated.

Several investigators have suggested that low doses of β-blockers may provide improvement in symptoms of chronic heart failure owing to their potential for reversing the downregulation of myocardial β-receptors and by blocking the potentially harmful effects of circulating

catecholamines. The use of β-blockers in heart failure is being investigated in multicenter trials, but these agents must be used with extreme caution because of their risk of worsening heart failure.

Summary

Historically, the principal pharmacological treatments for CHF have been diuretics and digitalis glycosides. Both of these groups of agents have proven useful in patients with CHF, but they may also have limitations. Diuretics improve symptoms but stimulate the RAA system and are associated with a number of adverse biochemical effects. Digitalis has an important inotropic action but may be arrhythmogenic in some patients at risk. Digitalis may be most beneficial in the more severe grades of CHF or in those CHF patients with atrial arrhythmias.

In recent years, ACE inhibitors have been shown to be extremely useful agents in the management of CHF. Studies have shown that ACE inhibition can (1) provide long-term hemodynamic benefits, (2) blunt both the overstimulation of neurohormones associated with CHF and the stimulating effects of diuretics on the RAA system, and (3) reduce the potential for ventricular arrhythmias in some patients by offsetting potassium loss. Studies to date indicate that ACE inhibition is associated with reduction of symptoms and increased survival in patients with CHF. In mild to moderate CHF, ACE inhibitors are most clinically beneficial when used in conjunction with diuretic therapy, with or without digitalis. The early addition of an ACE inhibitor to heart failure therapy may improve both the quality of life and survival in a significant proportion of patients with CHF.

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