The prevalence of congestive heart failure (CHF), a debilitating condition associated with impaired quality of life and markedly shortened life expectancy, is increasing. The goals of therapy for CHF are reducing symptoms, improving functional capacity, and slowing the progression of the condition. In most cases, this is best achieved with a combination of diuretic and vasodilator therapy. Angiotensin-converting enzyme (ACE) inhibitors have several advantages over other vasodilatory agents and are becoming widely used for treating CHF. The most recently introduced ACE inhibitor, fosinopril, is at least as effective as enalapril, and its dual and compensatory route of excretion is particularly advantageous in patients with renal insufficiency. Fosinopril may also have particular benefits in the prevention of CHF, as it has beneficial effects on cardiac function that may help delay the onset of overt cardiac failure. Am J Hypertens 1997;10:289S–298S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Fosinopril, angiotensin-converting enzyme inhibitors, congestive heart failure.

Congestive heart failure (CHF) is a pathological syndrome resulting from chronically inadequate cardiac output. One consequence of the decreased cardiac output is reflex activation of neurohormonal systems, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The resultant peripheral vasoconstriction, sodium and water retention, and tachycardia initially maintain organ perfusion. However, these compensatory mechanisms increase ventricular afterload, end-diastolic volume, cardiac wall tension and myocardial oxygen consumption. The increase in blood volume results in edema and pulmonary congestion and places an increased load on the already compromised myocardium, furthering the deterioration in cardiac function. Thus, a maladaptive cycle is established that results in the progression of CHF.

CHF causes a constellation of symptoms, including fatigue, reduced exercise tolerance, dyspnea on exertion, and paroxysmal nocturnal dyspnea (PND). Decreased vasodilative capacity and physical deconditioning on the part of the subject may also be responsible for metabolic changes in the peripheral muscles and thus the fatigue. These symptoms can severely limit the functional capacity of the patient. Progression of CHF is associated with the need for increased diuretic use, more frequent hospitalizations or emergency room visits, and eventually death. The prognosis of the condition is poor; the 1-year mortality ranges from approximately 15% among relatively unselected patients to 50% among those in New York Heart Association (NYHA) functional class IV. Approximately 35% of all patients with the diagnosis of CHF are hospitalized every year. Therefore, CHF is not only a great personal burden for patients and their families, but also places considerable demands on health care resources. A major advance in the treatment of CHF was the introduction of ACE inhibitors.
of angiotensin-converting enzyme (ACE) inhibitors, initially for the treatment of hypertension, about 15 years ago. This article reviews experience with fosinopril, the first of a new class of ACE inhibitors, in patients with CHF, and discusses the possible advantages of fosinopril over other ACE inhibitors.

**PATHOGENESIS OF CHF**

The principal general causes of CHF are excessive cardiac workload or myocardial damage, with hypertension and myocardial infarction (MI) as the most common risk factors for the development of CHF. Pressure and volume overload result in left ventricular hypertrophy (LVH), which has been shown to be associated with the appearance of symptomatic cardiac failure and sudden cardiac death, both in the general population and more specifically in hypertensive patients. Myocardial damage, such as that caused by MI, also initiates a series of structural and functional changes in the myocardium leading to LVH and fibrosis (ventricular remodeling).

In addition to the changes in the heart, other organs are also affected by the hemodynamic abnormalities associated with the development and progression of CHF. In particular, increased vascular resistance and related neurohormonal compensatory changes often lead to reductions in renal blood flow, with consequent deleterious effects on renal function, especially in older patients.

**TREATMENT OF CHF**

The goals of treatment for CHF are to improve symptoms and functional capacity by normalizing cardiac loading conditions and to prevent or reduce the progression of the disease, particularly the deterioration of cardiac and other end-organ functions.

Three broad therapeutic groups form the usual basis of therapy for CHF: digitalis, diuretics, and vasodilators. Digitalis glycosides improve hemodynamics and symptomatology by increasing ionotropy and slowing resting heart rate. Digitalis slows deterioration of CHF and, although it improves filling pressures and cardiac output, it does not decrease peripheral resistance. To date, however, important prognostic benefits have not been demonstrated. The recently reported Digitalis Investigation Group (DIG) study showed no effect of digoxin on overall mortality, although it reduced hospitalizations for worsening CHF. Diuretics were introduced in the 1930s for the treatment of CHF. The diuresis caused by these agents reduces blood volume, which is initially beneficial; however, diuretics also stimulate the RAAS, which ultimately contributes to the progression of CHF.

The next important advance in the pharmacological treatment of patients with CHF was the introduction of the first vasodilators in the 1950s. However, only in recent years, with the supplementation of the traditional regimen of diuretics and digitalis with newer vasodilators, has it been possible to show an improved prognosis in CHF. The work of Cohn and Franciosa first introduced the concept of “unloading” the impaired ventricle to improve hemodynamic status and led to an effective strategy for treating patients with symptomatic CHF. In a landmark study, Cohn, in collaboration with the investigators of the Veterans Administration Vasodilator Heart Failure Trial (V-HeFT), showed that vasodilator therapy with hydralazine and nitrates improved survival in CHF patients whose activities were limited despite the use of digitalis or diuretics.

Shortly after this study, the results of the first trial with the ACE inhibitor enalapril appeared, following several mechanistic studies that showed that ACE inhibitors had beneficial hemodynamic effects in patients with severe CHF. Several other important clinical studies followed, showing that ACE inhibitors slow clinical deterioration, improve clinical signs and symptoms, enhance quality of life, and prolong survival in CHF patients. During the past decade ACE inhibitors have emerged as the cornerstone of the pharmacological management of CHF and they also appear to have a role in the prevention of this condition in some patients.

**ACTION OF ACE INHIBITORS**

Angiotensin converting enzymes are responsible for the conversion of angiotensin I to angiotensin II. Inhibition of these enzymes by ACE inhibitors reduces the levels of the vasoconstrictor angiotensin II and indirectly reduces the production of aldosterone. The result is peripheral vasodilatation, natriuresis and diuresis, and an improvement in left ventricular performance. The reduction in peripheral resistance reduces both preload and afterload, with an associated increase in cardiac output. Natriuresis and diuresis reduce blood volume, further reducing preload. This is often accompanied by reversal of tachycardia, and as a result better perfusion of the myocardium leads to a further increase in the capacity for cardiac work.

Angiotensin II also has trophic influences on cardiac tissue, leading to cardiovascular hypertrophy and hyperplasia, and cardiac remodeling after MI. These responses are blunted by ACE inhibition.

Fosinopril is the first of a new group of phosphinic acid-containing ACE inhibitors. It is a prodrug, which is converted to the active diacid moiety (fosinoprilat) in the gastrointestinal mucosa and liver. Fosinoprilat inhibits the angiotensin I pressor response and serum ACE activity in a dose-dependent manner.

**PHARMACOKINETICS OF FOSINOPRIL**

Unlike other ACE inhibitors, which are excreted via the kidney, fosinoprilat uniquely is eliminated in ap-
proximately equal amounts by the liver and the kidneys in subjects with normal renal and hepatic function. More importantly, in the presence of renal or hepatic impairment, compensatory increases occur in the elimination of the drug via the alternative route. The pharmacokinetics and pharmacodynamics of this inhibitor have been reviewed extensively. Following oral dosing the Tmax ranges from approximately 2.5 to 4 h, with Cmax and AUC values for fosinoprilat demonstrating dose-proportionality. Fosinopril is 95% to 99% protein bound and the average plasma elimination half-life (T1/2) is 11.5 to 12 h.

Recently, the pharmacokinetics and pharmacodynamics of fosinopril have been studied in healthy Chinese male volunteers (Data on file, Bristol-Myers Squibb) after a single oral 10 mg tablet (n = 12) or a single 7.5 mg intravenous dose of fosinopril (n = 12). The pharmacokinetic parameters are similar to values obtained previously in non-Chinese subjects (Data on file, Bristol-Myers Squibb) (Table 1). The mean half-life (T1/2) of the 10 mg oral dose was slightly longer in Chinese subjects and the area under the curve (AUC) and T1/2 of the 7.5 mg intravenous dose was slightly greater. The pharmacodynamic results showed that ACE inhibition approached 100% after 1 h, and ACE activity remained markedly reduced (>80%) throughout 24 h. Forty-eight hours following the IV dose, ACE activity was still appreciably lower than at baseline (>50% inhibition). This study suggests that fosinopril has similar pharmacokinetics in different ethnic populations.

In CHF, the impaired cardiac function results in reduced perfusion of the organs involved in drug clearance, notably the liver and kidneys. Renal function deteriorates in CHF, particularly in the elderly, which may affect the pharmacokinetics of drugs eliminated by renal excretion. Therefore, CHF can be associated with reduced drug clearance, increasing the elimination half-lives and the potential for accumulation of chronically administered drugs. The unique dual and compensatory mechanism of elimination of fosinopril is important because there is a compensatory increase in hepatic excretion when renal function is impaired. Thus, there is usually no need for dose reduction in renally impaired patients.

Another recent study compared the pharmacokinetic parameters of fosinopril and enalapril in patients with concomitant CHF (NYHA functional class II to IV) and chronic renal insufficiency (creatinine clearance ≤30 mL/min) after 10 days of once-daily dosing. Both ACE inhibitors exhibited a significant increase in area under the serum concentration–time curve (AUC) between the first and last days of treatment. However, fosinopril exhibited significantly less accumulation than enalapril in patients with concomitant CHF and renal insufficiency (P = .024). The accumulation index, defined as the ratio of the AUCs on days 1 and 10, was 1.41 for fosinopril and 1.96 for enalapril. In a similar study of patients with concomitant CHF and chronic renal insufficiency (creatinine clearance ≤30 mL/min), the accumulation of fosinopril and lisinopril were compared. This study also showed fosinopril to have a significantly lower accumulation index compared with lisinopril (1.21 v 2.76; P < .001). The accumulation indices in patients with renal insufficiency in the presence or absence of CHF are shown in Table 2.

These data support and extend the findings of Sica et al, who compared the multiple-dose pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. The percentage increases in AUC from day 1 to day 10 for fosinopril, enalapril, and

### Table 1. Pharmacokinetic Parameters of Fosinopril

<table>
<thead>
<tr>
<th></th>
<th>Chinese Subjects</th>
<th>White Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>183 ± 59</td>
<td>—</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>4.0</td>
<td>—</td>
</tr>
<tr>
<td>AUC0–T</td>
<td>1556 ± 586</td>
<td>7727 ± 2638</td>
</tr>
<tr>
<td>AUC0–`1</td>
<td>1636 ± 620</td>
<td>7816 ± 2693</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>17.4 ± 11.4</td>
<td>13.0 ± 5.2</td>
</tr>
<tr>
<td>CLR</td>
<td>549 ± 158</td>
<td>472 ± 213</td>
</tr>
</tbody>
</table>

Data taken from Bristol-Myers Squibb data on file and Hui et al.

### Table 2. Accumulation Indices of ACE Inhibitors in Patients with Renal Dysfunction in the Presence or Absence of Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Renal Impairment</th>
<th>CHF + Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosinopril</td>
<td>1.27</td>
<td>1.41</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.77</td>
<td>1.96</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.62</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data taken from Greenbaum et al and Zuchelli et al.
lisinopril were 26.8% ± 9.9%, 76.6% ± 16.6%, and 161.7% ± 31.8%, respectively. Accumulation indices of 1.27 for fosinopril, 1.77 for enalapril, and 2.62 for lisinopril demonstrate significantly less accumulation with fosinopril, relative to both enalapril (P < .05) and lisinopril (P < .001) (Figure 1). A survey of the literature has also shown low accumulation indices for fosinopril in patients with mild, moderate, or severe renal impairment (1.4, 1.3, and 1.6, respectively) and very high indices for a variety of other ACE inhibitors in patients with severe renal failure (Table 3).

It has been recommended that doses of enalapril be reduced in patients with severe renal insufficiency to avoid an increase in the incidence of clinically significant adverse events. Van Schaik et al demonstrated that adverse events associated with lisinopril were more common in renally impaired subjects and suggested dose reduction in patients with renal insufficiency. By contrast, the multiple-dose studies of Greenbaum et al, Zuchelli et al, and Sica et al and the single-dose study of Hui and colleagues suggest that the compensatory increase in hepatic clearance of fosinopril obviates the need for dose adjustment of fosinopril in the renally impaired patient. In addition, CHF is common in the elderly, who have a “natural” decline in renal function. The presence of renal impairment in this patient group is underestimated in general practice due to the lack of sensitivity of usual indices such as serum creatinine. Therefore, more CHF patients have concomitant renal impairment than is currently thought, and in such patients the ease of use of fosinopril in relation to dose titration and drug-related side effects associated with drug accumulation would be a particular advantage.

CLINICAL TRIALS WITH FOSINOPRIL IN HEART FAILURE

Progression of heart failure is characterized by a decline in functional capacity, episodes of acute deterioration requiring hospitalization, and by excessive mortality, often as sudden death. Exercise tolerance is an important measure of functional status in patients with CHF. Decreased exercise tolerance, in addition to reflecting reduced functional status, is correlated with an adverse prognosis in patients with heart failure. Clinical evaluations of drug interventions, therefore, often focus on early improvement in parameters such as exercise tolerance that denote improved functional capacity. Studies have also evaluated clinical parameters that indicate a worsening of the disease, or decompensation, such as the need for supplemental diuretics, hospitalization for worsening heart failure, emergency room visits, or death.

EFFECTS OF FOSINOPRIL ON EXERCISE TOLERANCE AND CLINICAL DETERIORATION IN PATIENTS WITH HEART FAILURE

Fosinopril has been shown to significantly improve exercise tolerance in comparative studies versus pla-
A 12-week double-blind study evaluated 308 patients with mild-to-moderate heart failure (NYHA functional class II or III) and LV ejection fraction ≤35%. Patients were given fosinopril 10 mg or placebo initially, which was then titrated, as tolerated, to 40 mg once-daily (more than 80% of patients received 40 mg). Patient demography in the two groups was similar. All patients received diuretic therapy, although digoxin was optional. At the end of the study, bicycle exercise time compared with baseline had increased more in the fosinopril group than in the placebo group (38.1 sec vs. 23.5 sec; \( P < .01 \) by prospectively defined dropout-adjusted end-point analysis). In addition, more patients remained free of clinical events indicative of worsening heart failure when receiving fosinopril (89%) than when receiving placebo (75%). Analysis of the occurrence of individual clinical events showed that the need for a supplemental diuretic was markedly reduced with fosinopril (8% vs. 20% of patients; \( P = .002 \), as were the number of hospital admittance (3% vs. 12% of patients; \( P = .002 \)) and study discontinuations (2% vs. 12% of patients; \( P < .001 \)). Symptoms of dyspnea (\( P = .017 \)) and fatigue (\( P = .019 \)) and NYHA functional class (\( P = .008 \)) also improved with fosinopril treatment relative to placebo. There were no significant differences between the number of deaths in the two groups.

Another trial, carried out over a 24-week period, also showed improved exercise tolerance with fosinopril (Table 4). A total of 241 male or female patients with mild-to-moderate heart failure (NYHA functional class II or III) and LV ejection fraction ≤35% were entered into this double-blind, placebo-controlled trial. Patients received 10 mg fosinopril or placebo initially, and were then titrated, as tolerated, to 20 mg once-daily (95% of patients received 20 mg) with concomitant diuretic therapy, but the use of digoxin was prohibited. At the end of the study, bicycle exercise time compared with baseline had increased more in the fosinopril group than in the placebo group (28.4 sec vs. 13.5 sec with placebo; \( P < .01 \) by prospectively defined dropout-adjusted end-point analysis). In addition, more patients remained free of clinical events indicative of worsening heart failure when receiving fosinopril (66%) than when receiving placebo (50%). Analysis of the occurrence of individual clinical events showed that the need for a supplemental diuretic was markedly reduced with fosinopril (8% vs. 20% of patients; \( P = .003 \)), as were the number of hospital admittance (3% vs. 12% of patients; \( P < .002 \)) and NYHA functional class (\( P = .008 \)).

### TABLE 4. EFFECT OF FOSINOPRIL ON EXERCISE TOLERANCE AND CLINICAL DETERIORATION IN PATIENTS WITH HF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Erhardt et al(^4^2)</th>
<th>Brown et al(^4^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>308</td>
<td>241</td>
</tr>
<tr>
<td>Length of study (weeks)</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>NYHA class at baseline</td>
<td>II–III</td>
<td>II–III</td>
</tr>
<tr>
<td>Fosinopril dose (Initial/maximum [mg/day])</td>
<td>10/40</td>
<td>10/20</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>Diuretics (digoxin optional)</td>
<td>Diuretics (digoxin prohibited)</td>
</tr>
<tr>
<td>Change in exercise time from baseline with fosinopril (sec)</td>
<td>38.1 (vs 23.5 with placebo)</td>
<td>28.4 (vs 13.5 with placebo)</td>
</tr>
<tr>
<td>Patients free of clinical events associated with disease progression (%)</td>
<td>89 (vs 75 with placebo)</td>
<td>66 (vs 50 with placebo)</td>
</tr>
<tr>
<td>Effect of fosinopril on NYHA class</td>
<td>Improved relative to placebo ( (P = .008) )</td>
<td>Improved more often and decreased less often relative to placebo ( (P = .003) )</td>
</tr>
<tr>
<td>Effect of fosinopril on symptomatology</td>
<td>Dyspnea and fatigue improved relative to placebo ( (P = .017 ) and ( P = .019 ), respectively)</td>
<td>Dyspnea, fatigue, and paroxysmal nocturnal dyspnea improved more frequently and worsened less frequently relative to placebo ( (P = .002) )</td>
</tr>
</tbody>
</table>

### TABLE 5. EFFECT OF DOUBLE-BLIND TREATMENT ON COMPOSITE ENDPOINT OF THERAPEUTIC COINTERVENTION OR WITHDRAWAL FOR WORSENING HF: MOST SEVERE EVENT FOR EACH PATIENT

<table>
<thead>
<tr>
<th>Event</th>
<th>Fosinopril ( n = 122 )</th>
<th>Enalapril ( n = 132 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (1.6)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>Withdrawal for worsening HF</td>
<td>6 (4.9)</td>
<td>10 (7.6)</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>1 (0.8)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Supplementary furosemide or emergency room treatment for worsening HF</td>
<td>6 (4.9)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>None of the above</td>
<td>107 (87.7)</td>
<td>105 (79.6)</td>
</tr>
</tbody>
</table>

\(^4^2\) Bristol-Myers Squibb data on file.
\(^4^3\) HF, heart failure.
italis was prohibited. Concurrent therapy with inotropes or other vasodilators was also prohibited.

At the end-point of the study, the mean treadmill exercise time, adjusted for baseline effects, had improved in the fosinopril group by 28.4 sec, compared with a decline in the placebo group of 13.5 sec (P < .047). NYHA functional class improved in 24% of the fosinopril group and in 13% of the placebo group and deteriorated in only 18% of the fosinopril-treated group compared with 32% of the placebo-treated group (P < .003). The study also found that more patients in the fosinopril group (66%) remained free of clinical events associated with disease progression compared with the placebo group (50%), and the fosinopril-treated group had significantly less severe clinical events (P = .004). Dyspnea, fatigue, and paroxysmal nocturnal dyspnea (PND) improved more frequently and worsened less frequently in the fosinopril group compared with placebo (P = .002), and edema also showed a trend towards improvement (P = .088) with fosinopril therapy.

EFFECTS ON CLINICAL EVENTS

Data from three studies that measured the effects of fosinopril on clinical events indicative of worsening heart failure have been analyzed in a pooled analysis. The parameters evaluated were: death from any cause, study discontinuation due to worsening heart failure, and hospitalization due to worsening heart failure. As shown in Figure 2, 95 (25%) of the events occurred in the placebo group; 40 (11%) occurred in the fosinopril-treated group (risk reduction 56% [95% confidence intervals (CI), 40% to 60%]). Analyses of the individual events also showed significant differences in favor of fosinopril, including hospitalizations due to worsening heart failure (P < .001; risk reduction 70% [95% CI, 48% to 83%]) and study discontinuations due to worsening heart failure (P < .001, risk reduction 68% [95% CI, 52% to 79%]). There were only 20 deaths in the three trials and these were evenly distributed between the groups; almost all were attributed to underlying cardiovascular disease.

COMPARATIVE STUDIES OF FOSINOPRIL AND ENALAPRIL

The effects of fosinopril and enalapril in patients with heart failure have been compared in a double-blind, randomized study of patients with moderate-to-severe chronic heart failure (NYHA functional class III or IV) over a 24-week period (Data on file, Bristol-Myers Squibb). Forty-three patients received fosinopril and 47 received enalapril. Starting doses were 5 mg fosinopril once daily or 2.5 mg enalapril once daily, and both were then titrated over 3 weeks to doses of up to 20 mg daily. Doses of diuretic were decreased as appropriate. Exercise tolerance was assessed using an upright bicycle ergometer. The results showed that patients receiving fosinopril showed a greater increase from baseline in exercise duration compared with those on enalapril at all time points (Figure 3). Although these differences did not reach statistical significance, they showed a consistent trend in favor of fosinopril. There were no significant differences between the two groups for the endpoints of

![Figure 2](https://via.placeholder.com/150)

*FIGURE 2. Percentage of patients with clinical events occurring during treatment: pooled analysis of three double-blind studies. From Deedwania with permission.*
cointervention, change in NYHA functional class, or LV ejection fraction, and there were no notable differences between treatment groups for signs or symptoms of heart failure. Both ACE inhibitors were well tolerated, and side effects were similar in both groups. The incidence of cardiovascular adverse events was 39.5% in the fosinopril group and 55.5% in the enalapril group. The most common adverse events in patients receiving fosinopril were heart failure (14.0%), hypotension (11.6%), and vertigo (9.3%). In the enalapril group they were hypotension (27.7%), heart failure (19.1%), and weakness (8.5%).

A longer study compared the effects of fosinopril and enalapril over a year (Data on file, Bristol-Myers Squibb). This multicenter, double-blind study randomized patients (n = 254) to receive either fosinopril or enalapril at initial doses of 5 mg once daily, then titrated up to 20 mg as tolerated. Patients had mild-to-moderate heart failure (NYHA functional class II or III) and LV ejection fraction ≤ 40%. After 1 year of therapy, more patients in the fosinopril group had remained free of adverse events (20.5% of fosinopril group vs 16.7% of the enalapril group). For a composite clinical end-point consisting of events indicative of worsening heart failure, there were fewer events associated with fosinopril compared with enalapril (P = .059) (Table 5). Analysis of the time to the first adverse event showed a favorable effect for fosinopril compared with enalapril (P = .031 Cox regression; P = .057 unadjusted log-rank test); time to hospitalization or death did not differ between the two groups. In addition, fosinopril and enalapril produced similar improvements in NYHA functional class, with 59.5% and 48.9% of patients showing an improvement after 1 year in the fosinopril and enalapril groups, respectively. Both ACE inhibitors were well tolerated. The most common adverse events in the fosinopril group were cough (15.6%), dizziness (9.0%), and heart failure (9.0%). In the enalapril group the most commonly reported adverse events were cough (17.4%), dizziness (15.9%), and upper respiratory infection (10.6%).

These studies show that fosinopril is at least as effective as enalapril—an established and commonly used ACE inhibitor. Although not reaching statistical significance, there were trends for better efficacy with fosinopril in both the short- and longer-term studies. Additionally, in the long-term study, fosinopril delayed the time to the first adverse event, suggesting a positive effect on disease progression.

**EFFECT OF FOSINOPRIL ON HEMODYNAMIC PARAMETERS**

Fosinopril produces a significant, sustained beneficial effect on cardiovascular hemodynamics in heart failure patients. Acute hemodynamic effects have been measured following a single dose of 1, 20, or 40 mg of fosinopril or placebo (Borghi et al, unpublished results from the Fosinopril in Acute Myocardial Infarction Study [FAMIS]). Significant reductions in pulmonary capillary wedge pressure, mean arterial blood pressure, systemic vascular resistance, and heart rate were observed, along with an increased stroke index, for fosinopril 20 and 40 mg compared with fosinopril 1 mg. Peak hemodynamic effects were observed 6 to 8 h after a single dose of fosinopril and were sustained for 24 h. Following treatment for 10 weeks with fosinopril 20 and 40 mg once daily, the initial hemodynamic improvements observed with fosinopril 20 and 40 mg were maintained (Figure 4).

**FOSINOPRIL IN MYOCARDIAL INFARCTION**

The effects of fosinopril have also been investigated in patients with acute MI. In this double-blind, placebo-
controlled study, patients treated with fosinopril (initiated at 5 mg and then titrated to 20 mg once daily) for 3 months showed a significantly (P < .04) lower incidence of combined death and moderate-to-severe CHF despite having a worse prognostic profile at baseline. This finding was confirmed in patients without clinical signs of CHF on admission. The authors concluded that fosinopril may be able to prevent or delay the development of CHF following acute MI (Borghi et al, unpublished results from Fosinopril in Acute Myocardial Infarction Study [FAMIS]).

**FOSINOPRIL AND DIASTOLIC FUNCTION**

LV diastolic dysfunction is the first discernible manifestation of heart disease in many hypertensive patients. Diastolic dysfunction is present in approximately 50% of asymptomatic hypertensive patients and may be a precursor for CHF in patients with normal systolic ventricular function (Data on file, Bristol-Myers Squibb). In addition, LV diastolic function is impaired prior to the appearance of LVH. In view of the prevalence of diastolic filling abnormalities in the hypertensive patient population, the effect of some antihypertensive agents on LV function may be beneficial. Clinical trials have been performed to determine the effects of ACE inhibition on LV systolic and diastolic performance. In this study, cardiac function was determined before and after blood pressure control with captopril, lisinopril, and fosinopril. Although all ACE inhibitors decreased blood pressure and reduced vascular resistance, only fosinopril increased stroke volume, peak ejection rate, cardiac output, and peak filling rate, and decreased time to peak ejection rate. Because there is a high incidence of diastolic filling abnormalities in the hypertensive population and increasing recognition that many CHF patients have normal systolic function but abnormal diastolic filling, the effect of an antihypertensive agent on diastolic performance should be strongly considered in the treatment of patients with diastolic dysfunction.

**FOSINOPRIL AND COUGH**

In some patients, ACE inhibitor therapy is associated with an intolerable cough that may necessitate withdrawal of therapy. The cough usually appears within a few days of beginning treatment and can persist for
as long as 4 weeks after drug discontinuation.46 Rechallenge with the same or a different ACE inhibitor has been reported to cause recurrence of the cough.47,48 Following anecdotal evidence suggesting that cough improved or resolved when patients were switched from an alternative ACE inhibitor to fosinopril, a pilot study was designed. This study of 37 hypertensive patients with a previous history of ACE inhibitor-associated cough were randomized to receive therapy with enalapril (5 mg once daily) or fosinopril (10 mg once daily). After 8 weeks of follow-up, the incidence of all cough and nonproductive cough was significantly lower \( P = .02 \) with fosinopril than with enalapril \( 40.6\% \) vs. \( 52.8\% \); \( P = .002 \) and \( 26.7\% \) vs. \( 40.3\% \); \( P \leq .01 \), respectively. These data suggest that in patients requiring an ACE inhibitor, particularly those with a prior history of cough, treatment with fosinopril rather than another ACE inhibitor may provide substantial benefit with regard to the side-effect profile.

CONCLUSION

In summary, fosinopril is the first of a new class of ACE inhibitors and is highly effective in treating the symptoms and slowing the progression of CHF, in addition to improving hemodynamic parameters. In comparative studies fosinopril is at least as effective as enalapril in improving exercise tolerance. Patients taking fosinopril for 1 year had significantly fewer events associated with worsening heart failure than did patients taking enalapril. Fosinopril does not accumulate in patients with renal insufficiency (a common comorbidity in CHF) due to its dual and compensatory routes of excretion. This property is useful because no dose modification is therefore required in patients with impaired renal function. In addition, the side effect profile of fosinopril is generally comparable to that of enalapril, although recent data has suggested that the incidence of cough may be lower with fosinopril than with other ACE inhibitors. Thus, fosinopril provides additional benefits for both the physician and patient in terms of clinical status, diastolic dysfunction, pharmacokinetic characteristics, and side-effect profile.

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