REPORTS ON THERAPY

A Placebo-Controlled Trial of Captopril in Refractory Chronic Congestive Heart Failure

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This work was supported by the Squibb Institute for Medical Research, Princeton, New Jersey and in part by the U.S. Public Health Service (Grant HL 14148) and the Medical Research Service, Veterans Administration, Washington, D.C. Manuscript received December 2, 1982; revised manuscript received May 10, 1983; accepted May 11, 1983.

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In chronic heart failure, decreased contractility of the left ventricle leads to reduced cardiac output with consequent systemic arterial and venous vasoconstriction (1,2). This vasoconstriction, which promotes the vicious cycle of further reductions of stroke volume followed by an increased elevation of vascular resistance, appears to be mediated, in part, by the renin-angiotensin system (3–8). The key component of this system, the potent vasoconstrictor, angiotensin II, also has the effect of stimulating aldosterone secretion (8–12). Thus, angiotensin-converting enzyme inhibition, which prevents the conversion of “inactive” angiotensin I to angiotensin II, may be beneficial in congestive heart failure by reducing systemic vascular resistance and relieving circulatory congestion.

Captopril, an oral angiotensin-converting enzyme inhibitor, has been demonstrated in uncontrolled studies (12–20) to increase cardiac output, reduce vascular resistance and left ventricular filling pressure and provide greater exercise tolerance. In uncontrolled studies (17–19, 21–23), the hemodynamic improvement was maintained for up to 2 years. The present multicenter study of refractory congestive heart failure was conducted to evaluate the clinical efficacy and safety of captopril using a random double-blind, placebo-controlled design.

Methods

Study Patients

This trial was conducted in 13 medical research centers from August 1980 through December 1981. Ninety-two patients with chronic congestive heart failure refractory to digitalis and diuretic therapy were randomly assigned to treatment with either captopril (50 patients) or placebo (42 patients). The age range was 30 to 77 years (four eligible patients who underwent initiation therapy with captopril were not randomized to treatment groups [see Safety section]). In these 92 patients, the cause of heart failure was most commonly ischemic heart disease (56% of patients treated with captopril and 33% of patients treated with placebo) followed by primary myocardial disease in 30% of captopril patients, and 57% of placebo patients. Fifty-four percent were classified in New York Heart Association functional class III and the remainder were almost always classified in grade II. The status of congestive heart failure for most patients was described by investigators as stable (50% captopril, 57% placebo) or deteriorating (46% captopril, 43% placebo). The characteristics of patients in each group are shown in Table 1.

Patients were excluded if they had a supine systolic blood pressure lower than 95 mm Hg, angina pectoris requiring frequent nitrate therapy (>5 nitroglycerin tablets/wk), hypertension not controlled by diuretics, history of myocardial infarction within the previous 4 months, hepatic or renal impairment (serum bilirubin or serum glutamic oxaloacetic transaminase, or both, more than twice the upper limit of normal for the laboratory and creatinine clearance of ≤50 ml/min) or uncorrected valvular or pericardial disease. In medical research centers using the gated radionuclide technique of measuring ejection fraction, patients with an irregular rhythm (atrial fibrillation with irregular ventricular response or frequent [>10/min] premature ventricular complexes) were excluded.

To be eligible for entry, patients had to be capable of
Table 1. Comparability of Treatment Groups

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Captopril (n=50)</th>
<th>Placebo (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (96%)</td>
<td>39 (93%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>60*</td>
<td>55</td>
</tr>
<tr>
<td>Range</td>
<td>37 to 77</td>
<td>30 to 73</td>
</tr>
<tr>
<td>Duration of CHF (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>Range</td>
<td>1 to 144</td>
<td>2 to 204</td>
</tr>
<tr>
<td>Status of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improving slowly</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stable</td>
<td>25 (50%)</td>
<td>24 (57%)</td>
</tr>
<tr>
<td>Deteriorating slowly</td>
<td>22 (44%)</td>
<td>15 (36%)</td>
</tr>
<tr>
<td>Deteriorating rapidly</td>
<td>1 (2%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Cause of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary myocardial disease</td>
<td>15 (30%)</td>
<td>24 (57%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>28 (56%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>5 (10%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>22 (44%)</td>
<td>15 (36%)</td>
</tr>
<tr>
<td>III</td>
<td>27 (54%)</td>
<td>25 (60%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Previous vasodilator therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (48%)</td>
<td>20 (51%)</td>
</tr>
<tr>
<td>Yes—none or slight response</td>
<td>21 (45%)</td>
<td>15 (38%)</td>
</tr>
<tr>
<td>Yes—fair or good response</td>
<td>3 (7%)</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

*The age of the patients in the captopril group was significantly higher (p = 0.04) than that of patients in the placebo group.

CHF = congestive heart failure; n = number of patients, NYHA = New York Heart Association.

...exercising for at least 3 and no more than 12 minutes on a treadmill following a modified Naughton multistage protocol (24) in which no pause for rest was allowed between stages. The study was approved by the committee on human research in each of the 13 participating institutions. Written informed consent was obtained from all patients.

Study Design

Screening and stabilization period. At the beginning of this period, vasodilator therapy was discontinued and the maintenance dosage of digitalis and diuretic drugs was adjusted upward until the investigator was satisfied that an optimal regimen had been achieved.

Patients were followed up on an outpatient basis for at least 2 weeks, during which time one placebo tablet three times daily was prescribed in addition to the digitalis/diuretic regimen. After at least 1 week of this period, an exercise stress test was performed with an end point of dyspnea or fatigue, or both. This was repeated at the end of the period. If necessary, a further test (or tests) was scheduled until two consecutive tests varied by no more than 2 minutes. Patients were then admitted to the hospital for a full physical examination, chest roentgenogram, 12 lead electrocardiogram and measurement of radionuclide left ventricular ejection fraction. Blood and urine specimens were taken for a standard laboratory test panel.

Initiation of therapy with captopril. After the baseline evaluation, patients remained in the hospital for at least 2 days, during which time captopril therapy was initiated and the dose titrated to 50 mg three times daily, if tolerated. (Lack of tolerance was considered to be a significant decrease in blood pressure if accompanied by symptoms or signs of hypotension.) The first dose was 25 mg. Vital signs were measured with the patient supine and standing before and at frequent intervals for 4 hours after this and subsequent dosing during the first 2 days. If the drug was tolerated adequately, two subsequent 25 mg doses were given. At the time of discharge, patients were randomly assigned on a double-blind basis to either captopril or placebo, 25 or 50 mg three times daily. Only those patients not able to tolerate the 50 mg dose were on the lower dose regimen. To keep the principal investigator blinded, during this initiation period and the first 2 weeks of maintenance therapy, patients were under the control of a "third party" investigator.

Double-blind maintenance therapy. Patients received either captopril or placebo for a 12 week double-blind period. Visits were scheduled twice weekly for the first 2 weeks and biweekly thereafier. At the first visit, drug tolerance was assessed and, if the drug was well tolerated, the dose was increased to 100 mg three times daily at the second visit (end of Week 1). The third visit again assessed tolerance. The dose employed during Week 2 was maintained for most patients throughout the remaining 10 weeks of the study; only 28 patients (30%) received less than 100 mg three times daily.

After 2, 4, 8 and 12 weeks of treatment, exercise tolerance testing and laboratory tests were repeated and patients were questioned and examined with regard to symptoms and signs of congestive failure. At the Week 12 visit, radionuclide imaging and radiography for the cardiothoracic ratio were repeated, and the physician’s overall impressions of the patient’s status compared with the baseline condition were recorded. Patients were evaluated by the same physician at each visit. Hematologic variables and a quantitative 12 hour urinary protein determination were measured biweekly.

Apart from the usual reasons for discontinuation, such as severe adverse reactions or concurrent illness, patients were removed from the study if considered ‘‘treatment failures.’’ This was defined as increasing heart failure that required therapeutic intervention not permitted by the protocol.

Statistical methods. Patients were considered eligible for efficacy evaluation if they completed 2 or more weeks of double-blind treatment. For exercise tolerance times, functional class ratings, ejection fractions, cardiothoracic ratios, dyspnea, fatigue, edema and mean values at baseline and at the end of the double-blind treatment were obtained.
Analysis of covariance methods was used to adjust for differ-ences in pretreatment levels to compare the effectiveness of captopril and placebo.

Cohorts of patients who completed 12 weeks of therapy in captopril and placebo treatment groups were examined to evaluate the response changes throughout this period. The mean functional class ratings and exercise tolerance times at pretreatment and at weeks 2, 4, 8 and 12 were obtained. All post-treatment values were compared with the baseline values through two-way analysis of variance methods. An analysis of covariance method was again used to compare the two treatments with respect to changes from baseline at each specified time.

For variables recorded as either present or absent, such as hepatojugular reflux and paroxysmal nocturnal dyspnea, the prevalences at the beginning and at the end of the study were obtained for patients in both treatment groups. The difference between the two groups with respect to changes in prevalence from baseline was assessed using the Z test. The standard error of the change in prevalence was calculated using McNemar’s approach (25).

For ratings of overall impressions by both physicians and patients of the total clinical status, numerical scores were used (see Results). Comparisons between groups with respect to these scores were carried out using Student’s t test.

Double-Blind Evaluation

Of the 92 patients randomly assigned to double-blind treatment, 91 completed 2 or more weeks of therapy and were eligible for efficacy evaluation. One patient assigned to captopril treatment died of an intracerebral hemorrhage before the Week 2 visit.

Clinical course. The clinical course of the 91 remaining patients during double-blind therapy is shown in Figure 1. In the captopril group of 49 patients, 2 failed to complete 12 weeks of therapy: 1 was discontinued as a treatment failure (see Methods) and 1 because of a protocol violation. Among the 42 placebo-treated patients, 14 failed to complete the double-blind period; 4 patients died and 8 were discontinued as treatment failures. One placebo-treated patient was withdrawn because of an adverse reaction to placebo, and one patient was lost to follow-up. The incidence of treatment failure withdrawals among captopril-treated patients was significantly less than in the placebo group (probability [p] < 0.05), and less than the combined total of placebo group withdrawals due to deaths plus treatment failures (p < 0.001).

Functional class (Table 2). Of the 47 patients who completed double-blind therapy with captopril, 30 (61% of the original group) had improved New York Heart Association functional class ratings. Of the 28 placebo-treated patients who completed this period, 10 (24% of the original group) exhibited functional class improvement (Fig. 1). Mean func-

tional class ratings for all patients in each treatment group at the time of the last measurement during the course of double-blind therapy are shown in Table 2. Ratings for captopril-treated patients improved from a mean baseline value of 2.8 ± 0.1 by a mean of 0.52 as compared with a mean ratings improvement of 0.03 from a mean baseline value of 2.9 ± 0.1 for placebo-treated patients. Adjusting for differences in pretreatment values, the degree of change in captopril patients was significantly greater (p = 0.0004). The course of mean functional class changes for patients with values for weeks 2, 4, 8 and 12 is shown in Figure 2. At all time points, mean values for patients in the captopril group were significantly improved over baseline values (p < 0.001), as was the degree of improvement compared with that of placebo-treated patients (p < 0.05).

Exercise capacity (Table 3). Exercise tolerance times were obtained from 48 of the captopril-treated patients and all of the 42 placebo-treated patients. At the time of final measurement, the mean improvement in exercise duration in the captopril group was 24% (494 ± 22 to 614 ± 27 seconds), which was superior to that of the placebo group,
whose exercise capacities were virtually unchanged (480 ± 23 to 483 ± 43 seconds (p < 0.01). In terms of exercise stages under the Naughton protocol, captopril-treated patients exhibited a mean increase in exercise capacity of + 1.0 stage. This was significantly greater than the + 0.4 stage increase of the placebo-treated patients (p = 0.03). Mean exercise tolerance times for the patients whose exercise duration was measured at baseline and at each stipulated follow-up time are shown in Figure 3. At all time points, mean exercise times for patients in the captopril group were significantly improved over baseline values (p < 0.001), and at Week 12, over the corresponding time for placebo-treated patients (p < 0.01). At none of the exercise periods were placebo values significantly different from baseline values.

In captopril-treated patients, both functional class improvement and exercise duration increases appeared to be greater in those who entered therapy in functional classes III and IV and whose heart failure was due to primary myocardial disease as opposed to ischemic heart disease (Table 4). However, the differences between groups were not significant at the 0.05 level.

### Ejection fraction and cardiothoracic ratio (Table 5)

Thirty-three captopril-treated patients and 25 placebo-treated patients provided pre- and post-treatment radionuclide left ventricular ejection fraction data; similarly, 37 captopril-treated patients and 30 placebo-treated patients provided data on comparative cardiothoracic ratio changes. In both cases, improvement in the captopril group was superior with a +16% mean change compared with −1.8% mean change for the radionuclide ejection fraction, and −2.1% mean change compared with +0.3% mean change for the cardiothoracic ratio. Only in the former case was this difference statistically significant (p < 0.05).

### Symptoms and signs of congestive heart failure (Table 6)

During the course of double-blind therapy, all patients in the captopril- and placebo-treated groups provided data suitable for comparing the change in severity of specific symptoms and signs of congestive heart failure. The symptoms compared were dyspnea, fatigue, orthopnea and paroxysmal nocturnal dyspnea. The signs compared were the presence of edema, jugular venous distension and a hepatojugular reflux. In some cases (dyspnea, fatigue, orthopnea and edema), mean severity scores were used; they were obtained by allocating numerical values for the degree of severity of a variable in each patient and then averaging the values for the treatment group (Table 6, footnote). For the remaining variables, the basis of comparison was the percent of patients in each group having the symptom or sign before treatment and at the end of the 12 week period. The results demonstrate a statistically significant superiority for captopril over placebo therapy in relieving dyspnea, fatigue and
orthopnea and reducing edema. In the case of paroxysmal nocturnal dyspnea, jugular venous distension and hepatojugular reflux, there was a uniform trend of more patients improving in the captopril-treated group, although the differences did not achieve statistical significance.

Throughout the 12 week double-blind period, comparisons of symptomatic improvement between the two treatment groups were made by recording and scoring both the physician’s and patient’s impression of efficacy. Data were available for 46 of the captopril-treated patients and 41 of the placebo-treated patients. The results of these subjective analyses are shown in Table 7 (scoring method footnoted). On the basis of average scores, the impression of both physicians and patients was of a significantly superior symptomatic improvement in the captopril-treated group (p < 0.001). The physicians considered that in the captopril group 80% of patients exhibited some degree of improvement, whereas in the placebo group only 27% experienced some improvement. The corresponding impression of patients in the captopril group was that 81% felt improvement whereas of those in the placebo group 30% felt improvement.

Under the study protocol, the only additional treatment permitted was intravenous furosemide for the control of acute exacerbations or symptoms. Ten patients taking placebo and two assigned captopril administration required such intervention; this difference is significant (p < 0.05). During maintenance therapy, an increase in diuretic dosage was not permitted, but dosage reductions were possible. Eleven captopril-treated patients had reductions in diuretic dosage, as did three (7%) placebo-treated patients (difference not significant).

**Safety**

Side effects (hypotensive symptoms). In this study, before treatment randomization, all 96 eligible patients initially received 2 days of therapy with captopril (see Methods). Safety data for captopril thus take into account all patients for the initiation period, and separately, patients randomized to captopril therapy for the double-blind period. Overall, captopril was well tolerated. Side effects, when they did occur, were usually mild and transient.

During the 2 day initiation period, captopril was discontinued in three patients (3%) because of symptomatic hypotension (captopril was discontinued in a fourth patient because of the unrelated development of pneumonia; this patient died several days later). All three hypotensive patients experienced faintness on standing after the first 25 mg dose. Supine blood pressures decreased within 1 to 2 hours from 112/84 to 76/50, 133/78 to 42/28 and 120/70 to 76/50 mm Hg, respectively. All three patients recovered rapidly.

### Table 4. Functional Class Improvement and Exercise Tolerance Time Improvement: Cause of Congestive Heart Failure According to Pretreatment Functional Classification and in Captopril-Treated Patients

<table>
<thead>
<tr>
<th>Pretreatment Characteristic</th>
<th>ETT in Seconds (mean ± SEM)</th>
<th>NYHA CLASS (mean rating ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Pre</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>21*</td>
<td>604 ± 26</td>
</tr>
<tr>
<td>NYHA classes III and IV</td>
<td>27</td>
<td>423 ± 24</td>
</tr>
<tr>
<td>Primary myocardial disease</td>
<td>15†</td>
<td>505 ± 42</td>
</tr>
<tr>
<td>Ischemic myocardial disease</td>
<td>27†</td>
<td>492 ± 29</td>
</tr>
</tbody>
</table>

*Data missing for one patient.
† In six patients, the congestive heart failure was caused by either hypertensive or valvular disease. Also, data were not reported for one patient.
CHF = congestive heart failure; ETT = exercise tolerance time; NYHA = New York Heart Association; Post = after treatment with captopril; Pre = before treatment with captopril; SEM = standard error of the mean.

### Table 5. Comparative Changes in Radionuclide Left Ventricular Ejection Fraction and Cardiothoracic Ratio

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Radionuclide Ejection Fraction (mean ± SEM)</th>
<th>Cardiothoracic Ratio (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Pre</td>
</tr>
<tr>
<td>Captopril</td>
<td>23</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>25</td>
<td>0.19 ± 0.02</td>
</tr>
</tbody>
</table>

*Adjusted for differences in pretreatment levels. †The difference between the two treatment groups is statistically significant (p < 0.05). ‡The difference between the two treatment groups is not significant (p > 0.05).
Post = after treatment with captopril; Pre = before treatment with captopril.
Table 6. Comparative Change in Symptoms and Signs of Congestive Heart Failure in Captopril and Placebo Treatment Groups During 12 Week Double-Blind Therapy

<table>
<thead>
<tr>
<th>Symptoms and Signs of CHF</th>
<th>Captopril Group (n = 49)</th>
<th>Placebo Group (n = 42)</th>
<th>p Value for Difference Between Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Mean score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>2.8</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>2.7</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Orthopnea†</td>
<td>0.3</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Edema§</td>
<td>0.5</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>% of patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>12%</td>
<td>6%</td>
<td>26%</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>44%</td>
<td>27%</td>
<td>52%</td>
</tr>
<tr>
<td>Hepatogenous reflex</td>
<td>40%</td>
<td>25%</td>
<td>52%</td>
</tr>
</tbody>
</table>

*Score: 0 = none; 2.0 = slight; 2.5 = moderate; 3.0 = marked; 4.0 = disabling.
†Score: 0 = none; 1 = 45° elevation; 2 = >45° elevation.
‡Score: 0 = none; 1 = trace; 2 = 1+ to 2+, 3 = 3+ to 4+

CHF = congestive heart failure; n = number of patients; NS = not significant (p > 0.05); p = probability. Post = after treatment with captopril; Pre = before treatment with captopril.

without intervention. One of these patients was given a second dose of 12.5 mg 6 hours later; the supine blood pressure decreased from 88/50 to 60/40 mm Hg after 1½ hours. Captopril was discontinued in this patient at his own request because of the recurrence of faintness on standing. Apart from these three patients, mild clinical symptoms of hypotension (dizziness and lightheadedness) after the first dose were reported for a further 29 patients (30%). All 29 were able to continue therapy, but in some cases with dosage reductions. With subsequent doses during this 2 day period, 12 of the 29 patients experienced symptoms that either decreased, did not recur despite dose increases or recurred transiently. During the 2 day initiation period, another 15 patients (16%) who had not experienced symptoms after the first dose did so after one or more subsequent doses.

In the course of double-blind therapy, 18 (36%) of the 50 patients randomized to captopril therapy experienced hypotensive symptoms. These were usually mild in nature, responding to reductions in dosage of captopril or diuretic drug, or both, and in some cases resolving with no alteration in treatment. One patient experienced lightheadedness and occasional blurring of vision throughout the full 12 weeks of the study. Only two captopril-treated patients who experienced hypotensive symptoms in the double-blind period had not had similar symptoms at some time during the 2 day initiation period. Eight (25%) of the 42 placebo-treated patients experienced hypotensive symptoms in the double-blind period. Three of these patients had similar symptoms during their initial prerandomization captopril therapy. The number of patients in each group affected by hypotensive symptoms in the double-blind period was not significantly different. After the first dose of 25 mg in 91 of the 96 patients, the mean arterial pressure decreased from a pretreatment level of 87 to 68 mm Hg (~21%, p < 0.001). (Three patients received initial doses other than 25 mg. Data were missing for 2 patients.). In contrast, decreases in mean arterial pressure from baseline levels for all captopril-treated patients at Weeks 2 through 12 ranged from 4 to 9%.

Adverse reactions. During the double-blind period of the study, no patients in the captopril-treated group were

Table 7. Physicians’ and Patients’ Global Impressions of Symptomatic Effect of Captopril and Placebo

<table>
<thead>
<tr>
<th>Degree of Improvement</th>
<th>Physicians’ Impression</th>
<th>Patients’ Impression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril (n = 46)*</td>
<td>Placebo (n = 41)*</td>
</tr>
<tr>
<td>Great</td>
<td>4 (8.7%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (32.6%)</td>
<td>6 (14.6%)</td>
</tr>
<tr>
<td>Slight</td>
<td>18 (39.1%)</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>8 (17.4%)</td>
<td>16 (39.0%)</td>
</tr>
<tr>
<td>Worse</td>
<td>1 (2.2%)</td>
<td>14 (34.2%)</td>
</tr>
<tr>
<td>Mean score‡</td>
<td>1.3§</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Data were not reported for one patient. ‡Data were not reported for two patients. ‡Score: +3 = great; +2 = moderate; +1 = slight; 0 = unchanged; −1 = worse. §The difference between the two treatment groups is statistically significant (p < 0.001)
discontinued because of adverse reactions (Fig. 1). One placebo-treated patient was discontinued because of fatigue and unstable gait, thought to be treatment-related. Two patients (4%), each receiving a daily dose of 150 mg of captopril, developed a skin rash (as did one patient in the placebo group). In each case, the rash was transient and the patients continued in the study. Three patients (6%) complained of mild taste alteration with captopril, but for two of them (both receiving 300 mg/day) this was transient. In the third patient (75 mg/day), the taste alteration continued until the end of the trial.

One captopril-treated patient with compromised renal function had worsening of azotemia. This patient entered the study with a serum creatinine level of 1.3 mg/dl and a blood urea nitrogen of 34 mg/dl. By Week 4 of the double-blind period, the serum creatinine was 2.7 mg/dl and the blood urea nitrogen was 75 mg/dl. At the conclusion of the double-blind period, the serum creatinine and blood urea nitrogen were, respectively, 1.9 and 71 mg/dl. The patient continued on captopril therapy after the termination of the study.

Effects on laboratory determinations. Comprehensive blood chemistry studies, complete blood counts and urinalyses were performed in all patients before and during therapy. The effect of captopril on serum potassium was examined. The mean serum potassium level of the captopril-treated patients increased from 4.1 to 4.3 mEq/liter, which was significantly greater than the mean increase (3.8 to 3.9 mEq/liter) in the placebo-treated group (p < 0.05). Potassium supplementation was at the discretion of individual investigators. Thirty-eight (76%) of the patients randomized to captopril therapy were receiving potassium supplements, as were 25 (60%) in the placebo group.

Supplements were discontinued in six of the captopril group and in three of the placebo group. No captopril-treated patients became hypokalemic, whereas three placebo-treated patients (all receiving potassium supplements) developed serum potassium levels below 3.5 mEq/liter. None of these treatment group differences were statistically significant. In the case of serum sodium levels, there were no significant or obvious differences between the two treatment groups during the study period. The mean serum uric acid level in the captopril group decreased by 6.6% compared with an 8% increase in the placebo group, and the mean serum bilirubin level decreased by 24% compared with a 1.4% mean increase in placebo-treated patients. Both these treatment differences are statistically significant (p = 0.01).

Twenty-five (53%) of the 47 captopril-treated patients who completed the double-blind period were receiving a total daily dose of 300 mg. The average daily dose of all 47 patients was 229 mg at Week 2 and 221 at Week 12. During the course of this 3 month study, no patients developed leukopenia, neutropenia or proteinuria.

**Discussion**

Clinical effects on heart failure. This is the largest placebo-controlled study reported to date of any vasodilator drug used in the treatment of heart failure. In this study, comparison of captopril and placebo (both added to a fixed diuretic/digitalis regimen) for severe heart failure demonstrated the efficacy of captopril by significant improvements in New York Heart Association functional class ratings, exercise tolerance times and the physicians' and patients' impressions of symptoms. Corresponding with this evidence for functional improvement was greater alleviation in the captopril group of specific symptoms and signs of heart failure, including dyspnea, fatigue, orthopnea and edema. A significant increase in the left ventricular ejection fraction at rest in the captopril group provides evidence that the symptomatic improvement can, at least in part, be attributed to improved left ventricular performance.

This study was not designed to examine the effect of captopril on mortality from congestive heart failure. Nonetheless, the loss of 12 patients from the placebo group (4 who died and 8 with worsening heart failure) during the 3 month double-blind follow-up period and only 2 in the captopril group (1 early death and 1 treatment failure) raises the possibility that captopril may be effective in altering the natural history of the syndrome.

Role of etiology of heart failure. Although an imbalance in randomization led to a predominance of patients with ischemic heart disease in the captopril group and a preponderance of primary myocardial disease in the placebo group, it is unlikely that this contributed to the therapeutic efficacy of captopril. Indeed, when efficacy was evaluated on the basis of etiology, it appeared that captopril was, if anything, more effective in the primary myocardial disease group than in the ischemic heart group.

Adverse effects. Hypotension, after the first few doses, was the most commonly occurring adverse effect of captopril, resulting in the withdrawal of 3% of the patients. However, there was a rapid attenuation of this initial hypotensive response as evidenced by the fact that from Weeks 2 through 12, the mean arterial pressure decrease in captopril-treated patients (more than half of whom were receiving 300 mg daily) ranged from 4 to 9%, in contrast to 21% after the first 25 mg dose. Also, once the patients were established on a maintenance dose, hypotension was no more common among the captopril-treated patients than among their placebo-treated counterparts. Despite the initial decreases in blood pressure with captopril, clinical symptoms of hypotension, if evident at all, were usually minimal, even when blood pressure reductions were relatively large. Sharpe et al. (21) showed that the hypotension induced by captopril in some patients with heart failure can be minimized by employing starting doses of as low as 6.25 mg three times
daily. Hypotension also may be avoided by reducing or interrupting diuretic therapy before commencing captopril, because diuretic drugs may have the effect of increasing plasma renin activity and, thus, increasing the sensitivity to converting enzyme inhibition.

The favorable effect of captopril on potassium balance, and the clearance of edema in patients already receiving "optimal" doses of digitalis and diuretic drugs, may be due to suppression of aldosterone secretion. However, the possibility of inducing hyperkalemia in an occasional patient (especially if the diuretic dose is decreased) should be considered. The absence of hyperaldosteronism during captopril therapy also could contribute to the apparent absence of the attenuation of therapeutic response observed with other vasodilators (26).

**Therapeutic implications.** The therapeutic efficacy and low incidence of serious side effects observed in this study suggest that captopril may be useful as adjunctive management in patients with severe heart failure refractory to therapy with digitalis and diuretic drugs. This study provides no evidence for the effectiveness of captopril as compared with other vasodilators used to treat heart failure, nor does it address the use of captopril in patients whose symptoms are relieved and exercise tolerance normalized while on treatment with digitalis and diuretic drugs.

References


