Long-Term Antihypertensive Therapy with Captopril
JOHN T. GROEL, M.D., SAMIR S. TADROS, M.D., GERALD R. DRESLINSKI, M.D., AND ALAN C. JENKINS, M.D.

SUMMARY Most forms of hypertension require life-long treatment; thus, it is important to determine the continuing effectiveness and safety of any new therapeutic agent. While participating in various investigational studies, 7103 hypertensive patients received captopril, of whom 4397 were treated for 3 months to 4 years. The 4-year patients included 2498 with mild or moderate essential hypertension (diastolic pressure less than 120 mm Hg), 893 with severe essential hypertension, and 517 with renovascular hypertension. Repeated examinations of these long-term therapy patients, the majority of whom also were receiving a diuretic, indicated no drug tolerance to the combination, i.e., there was continuing control of the blood pressure without significant increases in dosage or addition of other drugs.

Side-effects occurring during the first few months of captopril administration (rash, taste disturbances, and, rarely, neutropenia) were not a problem during prolonged therapy. A few patients (70/7103, or 1.0%) developed proteinuria, usually reversible and seldom associated with any deterioration of renal function. The proteinuria occurred most often in patients who had preexisting renal disease and were receiving high doses of the drug. There were no significant changes in key biochemical parameters. A total of 230 patients discontinued treatment for failure to maintain adequate blood pressure reduction, and 397 for side-effects. The estimated 4-year cumulative frequency of drug discontinuance for side-effects was 11.6% (life table method), which compares favorably with other classes of antihypertensive drugs. The frequency of such side-effects was further reduced, without compromising efficacy, by adding a diuretic to the regimen if 150 mg captopril daily did not produce normotension. It is concluded that captopril provides sustained blood pressure control with minimal side-effects during long-term therapy for hypertension.


KEY WORDS hypertension • captopril • chronic treatment • side effects • tolerance

SINCE hypertension is a chronic, usually asymptomatic disease, it is important that antihypertensive drugs maintain blood pressure control and produce a minimum of untoward reactions during prolonged therapy. Acquired tolerance to the blood-pressure-lowering action of a drug can compromise its long-term use, and side-effects are the most common reason for patient noncompliance.

During the past 5 years, captopril, the first orally active angiotensin I converting-enzyme inhibitor, has been studied in more than 7000 hypertensive patients, many with severe treatment-resistant disease. Similar to other drugs, side-effects most frequently occurred early in therapy, i.e., within the first 3 months. As has been reported by various investigators, they include rash, taste disturbances, hypotension, and, rarely, proteinuria and neutropenia. A total of 4397 patients received captopril under study conditions for more than 3 months, some for as long as 4 years. The present report focuses on the experience of the latter patients as assessed by blood pressure response and dosage requirements, side-effects leading to interruption of therapy, and serial observations of biochemical parameters.

Case Material and Methods
From mid-1977 through 1982, 7103 hypertensive patients received captopril under study conditions. Although certain of the study protocols limited administration of the drug to only a few days or weeks, 4397 patients (average age = 49 years) were treated for time periods ranging from 4 months to 4 years. Follow-up examinations were obtained at 1- to 3-month intervals. The latter patients were studied by several hundred investigators located in the United States and abroad. Detailed individual case records are available for these long-term patients, and serve as the primary source reference for most of the reported results. The most frequent diagnoses were essential hypertension (77%), often severe and resistant to prior multidrug regimens, and renovascular hypertension (12%) (table I).

All participating investigators determined the patients' blood pressure at each visit. Diastolic pressure
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TABLE 1. Characteristics of Patient Population Receiving Long-Term Therapy (n = 4397)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>(\leq 2)</th>
<th>&gt; 2</th>
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</thead>
<tbody>
<tr>
<td>Sex (mean age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (49.1 yrs)</td>
<td>2573</td>
<td>1607</td>
<td>891</td>
</tr>
<tr>
<td>Female (49.9 yrs)</td>
<td>1801</td>
<td>387</td>
<td>496</td>
</tr>
<tr>
<td>Not reported (51.6 yrs)</td>
<td>23</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Type of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential</td>
<td>2498</td>
<td>1607</td>
<td>891</td>
</tr>
<tr>
<td>Mild to moderate (DBP &lt; 120)</td>
<td>883</td>
<td>387</td>
<td>496</td>
</tr>
<tr>
<td>Severe (DBP (\geq 120))</td>
<td>18</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Unknown severity</td>
<td>517</td>
<td>185</td>
<td>332</td>
</tr>
<tr>
<td>Renovascular</td>
<td>481</td>
<td>197</td>
<td>284</td>
</tr>
<tr>
<td>Other</td>
<td>4397</td>
<td>2390</td>
<td>2007</td>
</tr>
</tbody>
</table>

Figure 1 indicates only 4050 patients because blood pressures for some time-points are missing for 347 patients. DBP = diastolic blood pressure (supine).

was defined as the disappearance of the sound (Korotkoff Phase V). A comprehensive battery of biochemical determinations, including, but not limited to, serum potassium, creatinine, glucose, cholesterol, and uric acid was obtained for each patient at least every 6 months. Complete blood counts and urinalyses (frequently including 12- or 24-hour quantitative urinary protein determinations) were done at periodic intervals. Side-effects considered by the investigator as possibly due to the drug were recorded, and those requiring its discontinuation are presented in this report.

The differing numbers of patients assessed at various follow-up time points, as presented in the Results section, are due to protocol restrictions as to maximal duration of treatment; the arbitrary deadline (end 1982) for inclusion of follow-up observations; loss to follow-up; and discontinuance of the drug because of inadequate blood pressure control or side-effects. A cohort of 495 patients treated for at least 2 years is described.

In a unique study specifically designed to duplicate the usual medical practice conditions, 4068 patients received captopril for varying time periods up to 1 year. Findings of the study are described separately. Nearly 2300 of the patients participating in this special study were treated for at least 4 months and, therefore, also are included in the summarization of results for the total (n = 4397) long-term therapy population.

Any acquisition of tolerance to the antihypertensive effect of captopril was determined by correlating follow-up blood pressure values with the dosage of captopril and the need for additional antihypertensive drugs. The risk of patients having to discontinue therapy because of loss of blood pressure control or for adverse reactions during a specific time interval, and the frequency of such discontinuation among all patients treated for up to a stated length of time, have been estimated using a life table method.

Results

Long-Term Effects on Blood Pressure

The blood pressure-lowering effect of captopril when given for prolonged periods, either alone or together with another antihypertensive agent (most often a diuretic), is shown in figure 1. The numbers of patients studied decreased from 4397 at 3 months to 25 at 4 years. The principal reasons for the progressive decrease in the number of patients were protocol restrictions as to maximal duration of treatment, the 1982 deadline for inclusion of follow-up observations, and loss to follow-up. Captopril also was discontinued in 230 of the 7103 patients due to its failure to control blood pressure, and in 397 because of side-effects. The mean blood pressure of patients who received the drug, either singly or together with a diuretic, for longer than 3 months was consistently less than 146/90 mm Hg (pretreatment = 176/109 mm Hg) during treatment periods ranging up to 4 years.

A cohort of 495 individuals was treated for 2 years. The mean blood pressure during this time period ranged narrowly from 138/89 to 136/88 (pretreatment = 169/110 mm Hg). As shown in figure 2, the mean blood pressure of the cohort at 2 years was no different than after 3 months on the captopril regimen. The daily dose of captopril averaged 341 mg at 3 months and 317 mg after 2 years. After 1 and 2 years, similar proportions of patients were receiving captopril monotherapy (42% vs 40%) and captopril plus a diuretic (43% vs 43%).

Captopril was withdrawn in 230 of the total 7103 patients for failure to maintain control of blood pressure. Since study patients received captopril for varying lengths of time, a life table procedure was employed to obtain an estimate of 6.5% for the 4-year frequency of drug discontinuance due to treatment failures. One-third of the failures occurred within the first 3 months, and none after the 2nd year.

Side-Effects

Adverse reactions of sufficient severity to warrant discontinuance of captopril occurred in 397 of the 7103 patients receiving treatment for up to 4 years. The estimated cumulative frequency of drug discontinuance for side-effects was 11.6% (life table method). Two-thirds of the discontinuances occurred within 3 months after starting captopril. The risk of side-effects warranting cessation of therapy was 4.6% for the first 3 months, and 7.3% for the next 45 months (fig. 1). The predominant early side-effects were rashes or taste disturbances (table 2). Neutropenia occurred in 14 patients, all within the first 3 months. Proteinuria sufficient to cause discontinuation of captopril was observed in 37 patients, almost always after the 3rd treatment month. Hypotension caused discontinuance in 40 patients, usually after a short period of therapy; orthostatic hypotension was rare. Varied side-effects, possibly attributable to captopril, e.g., gastrointestinal distress, weakness or fatigue, cough, unspecified chest pain, mouth ulcers, caused therapy discontinuance in a few patients. Fewer than 130 patients discontinued...
FIGURE 1. Total patient population. Blood pressure response to long-term therapy with captopril, including numbers and frequencies of treatment failures and patients discontinuing treatment for adverse reactions.

TABLE 2. Risk of Side-Effects Resulting in Discontinuation of Captopril Therapy (Life Table Method)

<table>
<thead>
<tr>
<th>Total</th>
<th>&gt; 3 mos</th>
<th>&gt; 6 mos</th>
<th>&gt; 12 mos</th>
<th>&gt; 24 mos</th>
<th>&gt; 36 mos</th>
<th>&gt; 48 mos</th>
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</thead>
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<tr>
<td>Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 7103</td>
<td>4397</td>
<td>3614</td>
<td>1704</td>
<td>511</td>
<td>163</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Total</th>
<th>&gt; 3 mos</th>
<th>&gt; 6 mos</th>
<th>&gt; 12 mos</th>
<th>&gt; 24 mos</th>
<th>&gt; 36 mos</th>
<th>&gt; 48 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>267</td>
<td>46</td>
<td>62</td>
<td>17</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>(4.6)</td>
<td>(1.2)</td>
<td>(2.9)</td>
<td>(1.9)</td>
<td>(1.5)</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2</td>
<td>5</td>
<td>22</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>28</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>247</td>
<td>19</td>
<td>32</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>433</td>
<td>51</td>
<td>76</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Life table method.
†Some patients discontinued therapy because of more than one side-effect.
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Mean
Supine
Blood Pressure
± SD 
(mm Hg)

3 6 12 18 24

Mean Daily Dose
Captopril 350mg 325mg 300mg

Therapeutic Regimens
Captopril Alone 48% 45% 42% 41% 40%
Captopril/Diuretic 37% 41% 43% 43% 43%
Captopril/Diuretic/Other(s) 11% 10% 12% 12% 11%
Captopril/Other(s) 4% 4% 3% 4% 6%

FIGURE 2. Twenty-four month cohort (n = 495) from total patient population. Blood pressure response and therapeutic regimens.

captopril because of such miscellaneous side-effects; the number appears greater in table 2 since some patients reported multiple reactions, e.g., a patient who complained of nausea, shortness of breath, and abdominal cramps.

Proteinuria was the only notable side-effect occurring with any frequency during long-term therapy. From the total captopril study program, adequate urinary protein excretion data are available for 5769 patients. Proteinuria (1 g/24 hours, or 3+ dipstick reading, on two occasions), was observed in 70 patients, and was the reason for discontinuation of captopril in 37 of them. It most often developed between the 3rd and 9th months of therapy, appeared to be dose-related, and occurred primarily in patients with a history of renal parenchymal or renovascular disease (table 3). The incidence of proteinuria was 3.5% in patients with preexisting renal disease who were receiving more than 150 mg captopril daily, as compared with 0.2% in patients without renal disease and receiving 150 mg or less daily (p < 0.0001). Thirty-three patients continued on captopril despite the proteinuria, and the condition had cleared spontaneously in 18 instances at the time of this report. In 62 of the 70 patients who developed proteinuria, serial estimates of renal function were available. In those patients with normal renal function prior to therapy, the mean serum creatinine was unaffected by the proteinuria (pretreatment, 1.1; last follow-up, 1.2 mg/dl; n = 19). When pretreatment renal function was abnormal, it frequently declined further in patients exhibiting proteinuria (mean serum creatinine pretreatment, 2.2; last follow-up, 3.1 mg/dl; n = 43); in some cases the decline could not be differentiated from progression of the underlying renal disease.

TABLE 3. Relative Frequency of Captopril-Associated Proteinuria in Patients with Serial Urinary Protein Determinations (n = 5769)

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting renal disease</td>
<td>19/3573</td>
<td>46/2196</td>
</tr>
<tr>
<td>0.5%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Captopril daily dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 150 mg</td>
<td>4/2126</td>
<td>15/1447</td>
</tr>
<tr>
<td>&gt; 150 mg</td>
<td>12/1180</td>
<td>36/1016</td>
</tr>
<tr>
<td>0.2%</td>
<td>1.0%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Biochemical parameters, including serum potassium, creatinine, glucose, uric acid, and cholesterol, were assessed at regular intervals and remained essentially unchanged after three years of therapy (fig. 3).

**Low Dosage Regimen**

Within the overall clinical program, 4068 patients, most of whom had severe treatment-resistant hypertension, first received captopril under the usual medical practice circumstances (General Usage Study). The drug was administered alone or together with a diuretic according to a regimen in which diuretic was added if 150 mg captopril daily did not reduce the diastolic blood pressure below 90 mm Hg. With this low-dose captopril regimen, only one-third of patients eventually required more than 150 mg daily. Treatment failed in 104 patients (4.4%). The estimated cumulative frequency (life table method) of therapy discontinuance for adverse reactions during the first 12 months was 5.5% (fig. 4).

**Discussion**

The present experience with captopril, most often employed together with a diuretic, in 7103 patients with several types and grades of hypertension (representing more than 5000 patient-years), attests to the long-term efficacy and safety of the drug, as earlier described in several clinical trials of more limited size.5-11 The cumulative withdrawal frequency for side-effects of captopril was 11.6% after 4 years. This compares favorably with the estimated 14% and 16% reported for bendrofluazide and propranolol in hypertensive populations also representing over 5000 patient-years each.12 The lesser frequency of side-effects with captopril occurred despite the relatively high dosage employed, and is especially noteworthy because the patients treated with this drug often had severe and complicated hypertensive disease, whereas those treated with the diuretic and beta-blocker all had mild hypertension.

Once a satisfactory dosage of captopril, and any diuretic requirement, had been determined during the first 3 months, drug tolerance did not develop. Furthermore, the estimated risk of discontinuance of captopril for side-effects after the 3rd month was only 7.3%. (As might be expected, the risk of significant side-effects was greatest during the first few months.) Rash and taste disturbances, the most frequent early side effects...
of captopril, seldom were a problem during long-term therapy. Captopril-associated proteinuria was seen in 70 patients (1.0%), the same prevalence rate as that previously reported.1 It most often developed during the 3rd to 9th months of therapy. The possibility of an association of proteinuria and membranous glomerulopathy in such patients has been raised,13 but a carefully controlled evaluation of renal biopsy specimens casts doubt on the strength of any such association.14 Neutropenia did not occur beyond the 3rd treatment month in this study population.

The treatment plan in a majority of the patients called for increasing the dose of captopril up to 450–600 mg daily before adding a second antihypertensive agent, leading to relatively high average maintenance doses (range = 317 to 350 mg captopril daily). This may account in part for the observed "frequency" of significant side-effects, since adding a diuretic to the regimen, rather than increasing the captopril dosage above 150 mg daily, reduced the estimated frequency of discontinuance of the drug for adverse reactions during the first 12 months of therapy by approximately one-third. The frequency of discontinuance for treatment failure was not increased. Earlier reports15-18 also support the proposition that side-effects to captopril can be considerably diminished by the use of lower, but still effective daily dosage, most often in conjunction with modest doses of a diuretic.

Side-effects of other antihypertensive agents that compromise adherence to therapy (compliance) by interfering with normal activities, e.g., fatigue, lethargy, impotence, weakness, dizziness, rarely occur with captopril. Captopril has no effect on biochemical homeostasis, e.g., serum glucose, uric acid, cholesterol, creatinine, or potassium concentrations. The presently reported comprehensive experience with captopril demonstrates that after an effective dosage regimen has been established, tolerance does not develop to the drug. Its relatively benign side effects profile may afford better patient acceptance of therapy and could lead to its consideration for early therapy in many hypertensive patients.
References

Long-term antihypertensive therapy with captopril.
J T Groel, S S Tadros, G R Dreslinski and A C Jenkins

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