Angiotensin-Converting Enzyme Inhibition With Fosinopril Sodium in the Prevention of Restenosis After Coronary Angioplasty

Walter Desmet, MD; Matty Vrolix, MD; Ivan De Scheerder, MD; Johan Van Lierde, MD; Jos L. Willems, MD; Jan Piessens, MD

Background Several angiotensin-converting enzyme inhibitors have antiproliferative effects in a rat model after carotid artery balloon injury. Methods and Results We conducted a randomized, double-blind, placebo-controlled trial to assess the effect of fosinopril, a novel angiotensin-converting enzyme inhibitor, in restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received fosinopril or matched placebo 10 mg at least 18 hours before PTCA, 20 mg at least 4 hours before PTCA, and 40 mg daily for 6 months. In addition, all patients received aspirin. Coronary angiograms before PTCA and immediately after PTCA as well as at 6-month follow-up were quantitatively analyzed. A total of 509 patients were recruited. The final per-protocol population consisted of 153 fosinopril-treated and 151 placebo-treated patients. Restenosis rates according to the National Heart, Lung, and Blood Institute criterion (loss of ≥50% of the initial gain [primary end point]) were 45.7% and 40.7% in the fosinopril and control groups, respectively (not significant). The respective mean differences in minimal coronary luminal diameter between post-PTCA and follow-up angiograms were −0.59±0.71 mm and −0.51±0.67 mm (not significant). Clinical events during the 6-month follow-up period, analyzed on an on-treatment basis, were ranked according to the most serious event. The respective numbers in the fosinopril and the control groups were for death, 0 and 0; myocardial infarction, 0 and 0; coronary artery bypass graft surgery, 1 and 3; repeat PTCA, 35 and 35; recurrent signs of ischemia necessitating early repeat coronary angiography and managed medically, 6 and 7; and none of the above, 111 and 106. All these differences were insignificant. Conclusions Administration of fosinopril in a dose of 40 mg daily during 6 months after PTCA does not prevent restenosis and has no effect on overall clinical outcome. (Circulation. 1994;89:385-392.)

Key Words • angioplasty • fosinopril

Restenosis remains the major factor limiting the long-term success of percutaneous transluminal coronary angioplasty (PTCA), and to date, no treatment regimen has shown indisputable efficacy in preventing this phenomenon.1-11 Previous experimental work demonstrated that smooth muscle cell proliferation plays an important role in the restenosis process. Locally produced angiotensin II might act as a comitogen through binding to specific angiotensin II receptors, present in high numbers on medial smooth muscle cells.12-15 In addition, in normotensive rats with balloon-induced carotid artery injury, pretreatment with high doses of angiotensin-converting enzyme (ACE) inhibitors decreased the neointimal proliferation by 80%, but this beneficial effect could not be reproduced in a similar pig model.16-19

Fosinopril sodium is an ester prodrug of a new inhibitor of ACE. Fosinopril contains a phosphinic acid group instead of a sulfhydryl group and undergoes metabolic hydrolysis, primarily by gut and liver, to the active diacid fosinoprilat, which is extensively protein bound. In healthy subjects, absorption of fosinopril averages 36%, and the bioavailability of fosinoprilat averages 29%. The terminal elimination half-life of fosinoprilat after intravenous administration is 12.4 hours. In healthy subjects, excretion is about equally divided between biliary and renal routes.

The present single-center trial was undertaken to test the influence of a clinical dose of this novel inhibitor of ACE on the occurrence of angiographically documented restenosis and on clinical events during a 6-month follow-up period after successful PTCA.

Methods

Study Population All patients scheduled for elective PTCA in our center were considered for inclusion. The study protocol was approved by the Ethical Committee of the University Hospital, Leuven, Belgium, and oral witnessed informed consent was obtained before randomization.

Exclusion criteria consisted of age >80 years, women of childbearing potential, inability to withdraw calcium channel blockers and nitrates before PTCA, PTCA for restenosis, PTCA for total occlusion, PTCA of a saphenous vein or internal mammary artery graft, ACE inhibitor treatment within 1 month before entry, systolic blood pressure <100 mm Hg or diastolic pressure >95 mm Hg at entry, a history of cerebrovascular accidents, significant cardiac valvular disease, significant renal or hepatic disease, acute myocardial infarction within 2 weeks before entry, leukopenia or neutropenia, a history of collagen vascular disease, current therapy with

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**TABLE 1. Reasons for Exclusion**

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients screened</td>
<td>1156</td>
<td>100</td>
</tr>
<tr>
<td>No. of patients recruited</td>
<td>509</td>
<td>44.0</td>
</tr>
<tr>
<td>PTCA for restenosis</td>
<td>180</td>
<td>15.6</td>
</tr>
<tr>
<td>Not hospitalized on day before PTCA</td>
<td>90</td>
<td>7.8</td>
</tr>
<tr>
<td>Decision for PTCA to be made during angiography</td>
<td>84</td>
<td>7.3</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>43</td>
<td>3.7</td>
</tr>
<tr>
<td>ACEI treatment</td>
<td>41</td>
<td>3.5</td>
</tr>
<tr>
<td>Significant concomitant disease</td>
<td>41</td>
<td>3.5</td>
</tr>
<tr>
<td>Atherectomy, laser, or stent implantation planned</td>
<td>27</td>
<td>2.3</td>
</tr>
<tr>
<td>No informed consent given</td>
<td>26</td>
<td>2.2</td>
</tr>
<tr>
<td>History of CVA</td>
<td>22</td>
<td>1.9</td>
</tr>
<tr>
<td>Logistic reasons</td>
<td>19</td>
<td>1.6</td>
</tr>
<tr>
<td>Malignancy</td>
<td>15</td>
<td>1.3</td>
</tr>
<tr>
<td>Inability to withdraw calcium channel blockers and nitrates</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>PTCA of a bypass graft</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>Other reasons* (&lt;1% each)</td>
<td>35</td>
<td>3.0</td>
</tr>
</tbody>
</table>

PTCA indicates percutaneous transluminal coronary angioplasty; ACEI, angiotensin-converting enzyme inhibitor; and CVA, cerebrovascular accident.

*Inclusion in another trial: age >80 years; aortic stenosis; familial homozygous hypercholesterolemia; intolerance for ACE inhibitors; depression; allergy to iodinated agents; PTCA for total occlusion; systolic blood pressure <100 mm Hg.

cytotoxic or immunosuppressant drugs, and a history of drug or alcohol abuse (Table 1).

Of the 1156 patients screened between April 1991 and January 1992, 509 patients (44%) were enrolled.

After randomization, patients were discontinued early (i.e., before hospital discharge) from study medication when symptomatic or significant hypotension (systolic blood pressure <85 mm Hg) developed as well as for a number of anatomic and procedural reasons. First, medication was discontinued in patients who did not comply with the definition of successful PTCA, i.e., an initial measured percent diameter stenosis of >50% reduced by at least 20% to a residual stenosis of <50%.

Second, patients who had developed a total occlusion between the diagnostic procedure and the PTCA were also discontinued. Finally, treatment was discontinued when stent implantation or urgent bypass surgery was indicated or when other adverse procedural events occurred.

**Study Medication**

After randomization, trial medication was started at least 18 hours before the PTCA procedure. The first dose consisted of 10 mg of fosinopril or matching placebo. At least 4 hours before PTCA, 20 mg was administered, and on the day after PTCA the dose was increased to 40 mg, which was continued until follow-up angiography. Concomitant therapy with calcium channel blockers was discontinued on the day before PTCA. During the hospital stay, blood pressure was monitored hourly for 3 hours after every drug administration. If systolic blood pressure fell below 85 mm Hg or if symptomatic hypotension occurred, treatment was discontinued. If systolic blood pressure was <100 mm Hg but >85 mm Hg, the 20-mg dose was maintained during the follow-up period.

**Follow-up Evaluation**

Patients visited their referring cardiologist after 2 and 4 months for interview, cardiac examination, electrocardiography, laboratory tests, and pill count. The same procedures were repeated at 6 months, when the follow-up angiography was performed in our center. However, in patients with early recurrence of symptoms or evidence of silent ischemia, coronary angiography was carried out earlier. During follow-up, patients were considered treatment compliant only if at least 80% of the medication was taken, as judged from the pill counts at 2, 4, and 6 months, and only these patients were used for the final evaluation of the drug effect.

**PTCA Procedure and Quantitative Angiographic Analysis**

PTCA was performed according to standard procedures, but choices of vascular access, balloon type and size, inflation duration, and inflation pressure were left to the discretion of the operator. An intravenous bolus of heparin 10 000 IU was administered at the beginning of the procedure, followed by an intravenous infusion at a rate of 1000 IU/h, which was continued for 24 hours. If the procedure lasted for more than 1 hour, an additional bolus of heparin 5000 IU was given. Coronary arteriograms were obtained with a real-time digital image acquisition and processing system (Polytron 1000, Siemens AG, Erlangen, Germany). Images were acquired at 25 frames per second in a 512×512 matrix, with a pixel depth of 10 bits, equivalent to 1024 gray steps per pixel. Thereafter, images were either analyzed on-line or stored on hard disk or streamer tape for later analysis. Each lesion was analyzed in two approximately orthogonal projections, selected to maximally avoid superimposition and vessel foreshortening. Idential projections and source-patient-image intensifier distances were used for the pre- and post-PTCA angiograms as well as for the follow-up angiogram in each patient. Before contrast injection, both before and after PTCA, as well as at follow-up, 200 μg intracoronary nitroglycerin was given to induce maximal vaso dilatation. All measurements were performed on se-
Table 2. Baseline Characteristics of the Per-Protocol Population

<table>
<thead>
<tr>
<th></th>
<th>Fosinopril Patients (N=153)</th>
<th>Control Patients (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>118/35</td>
<td>118/33</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.0±8.4</td>
<td>59.3±9.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.5±10.6</td>
<td>73.8±10.3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.2±8.2</td>
<td>169.0±9.2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66.7±10.8</td>
<td>65.4±10.1</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135.5±19.6</td>
<td>135.1±17.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.6±9.6</td>
<td>79.7±9.4</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>158.7±47.1</td>
<td>161.1±43.4</td>
</tr>
<tr>
<td>Angina class (CCS), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>12 (7.8)</td>
<td>9 (6.0)</td>
</tr>
<tr>
<td>Class I</td>
<td>26 (17.0)</td>
<td>18 (11.9)</td>
</tr>
<tr>
<td>Class II</td>
<td>38 (24.8)</td>
<td>30 (19.9)</td>
</tr>
<tr>
<td>Class III</td>
<td>41 (26.8)</td>
<td>50 (33.1)</td>
</tr>
<tr>
<td>Class IV</td>
<td>36 (23.5)</td>
<td>44 (29.1)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>67 (43.8)</td>
<td>70 (46.4)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>57 (37.3)</td>
<td>58 (38.4)</td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td>80 (52.3)</td>
<td>91 (60.3)</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; LDL, low-density lipoprotein; and CCS, Canadian Cardiovascular Society functional class. Data are expressed as mean±SD. All differences between the two treatment groups are insignificant.

Table 3. Anatomic Baseline Characteristics of the Per-Protocol Lesions

<table>
<thead>
<tr>
<th></th>
<th>Fosinopril Group (175 Lesions)</th>
<th>Control Group (172 Lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel dilated, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>59 (33.7)</td>
<td>88 (39.5)</td>
</tr>
<tr>
<td>LAD</td>
<td>65 (37.1)</td>
<td>62 (36.1)</td>
</tr>
<tr>
<td>LCx</td>
<td>51 (29.2)</td>
<td>42 (24.4)</td>
</tr>
<tr>
<td>Number of sites dilated, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>133 (86.9)</td>
<td>130 (86.1)</td>
</tr>
<tr>
<td>Two</td>
<td>18 (11.8)</td>
<td>21 (13.9)</td>
</tr>
<tr>
<td>Three</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lesion type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandemlike</td>
<td>29 (16.6)</td>
<td>34 (19.8)</td>
</tr>
<tr>
<td>Length &gt;2×vessel diameter</td>
<td>72 (41.1)</td>
<td>89 (51.7)</td>
</tr>
<tr>
<td>Lesion in &gt;45° bend*</td>
<td>52 (29.7)</td>
<td>72 (41.9)</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>11 (6.3)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Calcified</td>
<td>33 (18.9)</td>
<td>34 (19.8)</td>
</tr>
<tr>
<td>Eccentric</td>
<td>129 (73.7)</td>
<td>129 (75.0)</td>
</tr>
<tr>
<td>Lesion complexity score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>29 (16.6)</td>
<td>25 (14.5)</td>
</tr>
<tr>
<td>Type B1</td>
<td>79 (45.1)</td>
<td>64 (37.2)</td>
</tr>
<tr>
<td>Type B2</td>
<td>56 (32.0)</td>
<td>72 (41.9)</td>
</tr>
<tr>
<td>Type C</td>
<td>11 (6.3)</td>
<td>11 (6.4)</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; LAD, left anterior descending artery; and LCx, left circumflex artery. *P=.02; all other differences between the two treatment groups are insignificant.

According to the American College of Cardiology/American Heart Association Task Force classification system.25,26

Statistical Methods and Analysis

At the time the original protocol was designed, a restenosis rate of 30% according to NHBLI criterion 4 within the 6 months subsequent to initially successful PTCA was expected. To detect a postulated one-third reduction in the incidence of restenosis due to fosinopril, 313 patients per group having the required three angiograms (pre- and post-PTCA and at follow-up) were necessary to achieve a power of 0.80, allowing a type I error of 0.05 (two-tailed). Assuming that of all randomized patients, 1% would not complete the PTCA procedure, that 10% would experience unsuccessful PTCA, that follow-up angiograms would be unavailable in 14% of those successfully treated, and thus that identification of restenosis would be precluded in 23.4% of randomized patients, the sample size was fixed at 410 patients per group (313.0.766=410) to maintain study power for evaluating the primary end point.

At the time 509 patients were randomized, however, the sponsor decided to stop the study. This decision was based on the report that another ACE inhibitor failed to alter the restenosis rate in the MERCATOR trial23 in conjunction with the results of an interim analysis of our first 100 patients who completed the study, indicating no trends of the effect of fosinopril on clinical or angiographic restenosis rate. However, the overall incidence of angiographically defined restenosis...
Results

Patients

During the enrollment period, 1156 patients were screened, of whom 509 were randomized. Trial medication was discontinued during the hospital stay in a total of 173 patients. Hypotension, defined as above, occurred in 22 patients. All other early discontinuations were for anatomic or procedure-related reasons (Fig 1). In 20 patients, after the pre-PTCA control angiogram, the lesion was no longer considered an indication for PTCA. In 23 patients, a total occlusion had developed within the interval between the diagnostic and the therapeutic procedures. Before PTCA, the degree of stenosis appeared to be <50% in 37 patients. An unsatisfactory PTCA result, ie, inadequate stenosis reduction as defined above, was encountered in 48 patients. Bail-out stenting and emergency bypass graft surgery were performed in 8 and 7 patients, respectively. Finally, 8 additional patients were discontinued early for various reasons: technical problems with the angiographic measurements and acute vessel closure in 3 patients each and a major dissection resulting in a limited myocardial infarction and protocol violation in 1 patient each. The subdivision of these early discontinuations by treatment group is depicted in Fig 1. Hypotension was more frequent after fosinopril (P = .005), and total occlusions were more frequent after placebo (P = .03), all other differences being insignificant.

As a result of these early discontinuations, a total of 336 study patients were discharged from the hospital: 169 fosinopril-treated and 167 placebo-treated. Of these patients, follow-up angiography was not obtained in a total of 52 patients: 7 patients were noncompliant in taking their study medication; in 2 patients late symptomatic hypotension developed; and in 9 patients treatment had to be interrupted because of other adverse events (unstable angina and rash or pruritus in 2 patients each; excessive perspiration, retroperitoneal bleeding, gastric ulcer, acute myocardial infarction, and asystole with successful resuscitation in 1 patient each). Follow-up angiography was refused by 6 additional patients. Finally, 8 patients were excluded for various reasons: 3 patients were lost to follow-up; in 4 patients, quantitative coronary angiography was not available for technical reasons; and 1 patient violated the protocol. The subdivision of these late dropouts between the two treatment groups is also depicted in Fig 1, all differences being insignificant.

Thus, the final per-protocol population consisted of 304 patients, 153 treated with fosinopril and 151 treated with placebo. In the fosinopril group, a total of 138 patients were discharged from the hospital on the full 40-mg dose and 15 on the reduced 20-mg dose. In the control group, the respective numbers were 140 and 11. The clinical and angiographic baseline characteristics of this per-protocol population are given in Tables 2 and 3. All differences between both treatment groups were insignificant, except for a significantly greater number of patients in the control group with a lesion in a >45° bend.

Effects of Fosinopril on Angiographic End Points

Table 4 summarizes the quantitative angiographic findings of the per-protocol population. PTCA increased the MLD by 1.24 ± 0.35 mm and by 1.16 ± 0.38 mm in the fosinopril and control groups, respectively (not significant [NS]). The corresponding decreases in percent diameter stenosis were 42.8 ± 13.9% and 40.2 ± 14.8% (NS). At follow-up, the loss in MLD compared with the result immediately after PTCA was −0.59 ± 0.71 mm in the active treatment group and −0.51 ± 0.67 mm in the control group, resulting in a treatment effect of −0.0795 mm (95% confidence interval of −0.236 to 0.077 mm). Expressed as percent diameter stenosis, the loss at follow-up was 20.5 ± 23.0% in the patients treated with fosinopril and 17.5 ± 23.6% in the control group (NS).

Fig 2 represents a cumulative distribution curve of MLD before PTCA, after PTCA, and at follow-up in both treatment groups; at each of these three stages, both curves are virtually superimposed. Fig 3 depicts the cumulative distribution of the change in MLD from before PTCA to follow-up, demonstrating that the net gain at the end of the follow-up period was comparable in the two treatment groups. Finally, Table 5 summarizes the restenosis rates in the per-protocol population per lesion according to seven currently used restenosis criteria; irrespective of the criterion used, the difference in restenosis rate between the two treatment groups was insignificant.

Effects of Fosinopril on Clinical End Points

During follow-up, dose reduction was indicated in 10 fosinopril-treated patients, invariably because of symptomatic hypotension. In the control population, dose reduction of study medication was not observed. The clinical status of the patients at the end of the follow-up period is given in Table 6. No patient of the per-protocol population died or suffered a myocardial infarction. In the fosinopril- and the placebo-treated groups, 77.1% and 70.2% of the patients, respectively, remained asymptomatic, but 9.8% and 10.6% of the respective patients were readmitted with angina at rest (NS). Early repeat PTCA was indicated in 19 fosinopril-treated and 18 control patients (of whom 2 patients had PTCA for another lesion), but elective bypass surgery was preferred in an additional 1 and 3 patients, respectively (NS). The various clinical indications for these interventions are listed in Table 6. At the time of the scheduled 6-month hospital admission, PTCA was performed in conjunction with the diagnostic procedure in 16 fosinopril- and 17 placebo-treated patients (NS). The indication was either angina pectoris, silent ischemia, or strictly angiographic, when a critical restenosis jeopardized a large area of viable myocardium.
TABLE 4. Quantitative Angiographic Analysis of the Per-Protocol Patients

<table>
<thead>
<tr>
<th></th>
<th>Fosinopril Group (N=153)</th>
<th>Control Group (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstruction diameter, mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>0.90±0.31</td>
<td>0.92±0.32</td>
</tr>
<tr>
<td>After PTCA</td>
<td>2.14±0.37</td>
<td>2.08±0.40</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.54±0.70</td>
<td>1.57±0.66</td>
</tr>
<tr>
<td><strong>Reference diameter, mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>2.90±0.60</td>
<td>2.92±0.59</td>
</tr>
<tr>
<td>After PTCA</td>
<td>2.97±0.59</td>
<td>2.97±0.60</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.97±0.58</td>
<td>2.96±0.57</td>
</tr>
<tr>
<td><strong>Difference in obstruction diameter, mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After vs before PTCA</td>
<td>1.24±0.35</td>
<td>1.16±0.38</td>
</tr>
<tr>
<td>Follow-up vs after PTCA*</td>
<td>−0.59±0.71</td>
<td>−0.51±0.67</td>
</tr>
<tr>
<td><strong>Diameter stenosis, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>69.2±11.9</td>
<td>68.8±12.1</td>
</tr>
<tr>
<td>After PTCA</td>
<td>26.4±11.2</td>
<td>28.6±11.6</td>
</tr>
<tr>
<td>Follow-up</td>
<td>46.9±23.6</td>
<td>46.1±23.1</td>
</tr>
<tr>
<td><strong>Difference in diameter stenosis, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After vs before PTCA</td>
<td>−42.8±13.9</td>
<td>−40.2±14.8</td>
</tr>
<tr>
<td>Follow-up vs after PTCA</td>
<td>20.5±23.0</td>
<td>17.5±23.6</td>
</tr>
</tbody>
</table>

PTCA indicates percutaneous transluminal coronary angioplasty. Data are expressed as mean±SD. All differences between both treatment groups are insignificant.

*SE difference=0.0796; Difference=−0.0795; 95% confidence interval=−0.236 to 0.0771.

Clinical events during the 6-month follow-up period were also analyzed on an intention-to-treat basis and ranked according to the most serious event. The respective numbers in the fosinopril and the control groups were, for death, 2 and 0; myocardial infarction, 4 and 3; coronary artery bypass graft surgery, 15 and 10; repeat PTCA, 51 and 53; recurrent signs of ischemia necessitating early repeat coronary angiography and managed medically, 11 and 11; and none of the above, 172 and 177. All these differences were insignificant.

**Discussion**

The present data show that ACE inhibition with fosinopril fails to prevent angiographic restenosis after successful PTCA of primary coronary arterial stenoses. Furthermore, the incidence of late clinical cardiovascular events was similar during fosinopril and placebo treatment. These findings are in complete agreement with the results of the MERCATOR trial, in which no influence of the ACE inhibitor cilazapril on angiographic restenosis and on clinical end points could be demonstrated.

The trial design of the present study, however, differed in some aspects from the design of the above-mentioned study. In the present trial, study medication was initiated the day before the PTCA procedure, whereas in MERCATOR it was not started until the evening after successful PTCA. We preferred the for-

![Cumulative distribution curve (CUM%, cumulative percentage of patients) of the minimal lumen diameter (MLD) before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at 6-month follow-up in both treatment groups.](http://circ.ahajournals.org/content/images/12f4-2.png)
mer approach because experimental studies had demonstrated maximal inhibition of neointimal proliferation after pretreatment with ACE inhibitors. This earlier drug administration, however, did not beneficially affect the end points of the study. As a consequence of this strategy, a substantial number of patients had to be discontinued early for procedural reasons. Patients were discontinued when no PTCA was performed, when a total occlusion had developed during the interval between the diagnostic procedure and PTCA, when the immediate pre-PTCA stenosis was measured as <50%, or when the procedural gain was insufficient. In a small number of patients, trial medication was discontinued because of stent implantation or emergency coronary surgery after a complicated PTCA procedure. The total number of early discontinuations was very similar in both treatment groups, but hypotension was a more frequent cause in fosinopril-treated patients, and a total vessel occlusion was more frequently observed in the control group. We do not believe, however, that this sequence of events introduced any bias regarding the prevention of late restenosis. We preferred the present way of handling the data to a “true” intention-to-treat analysis because the high number of early discontinuations for procedural and anatomic reasons, although comparable in both treatment groups, can only be expected to prohibit meaningful interpretation of the data. Furthermore, it seems futile to compare angiographic data obtained in noncompliant patients.

Selection of doses was based on a review of data obtained in hypertensive patients and consistent with the objective of efficacy combined with acceptable safety. The most consistently effective dose of fosinopril in previous hypertension studies was 20 mg administered once daily. In normal subjects, ACE inhibition at 12 hours was 100% for both 20 and 40 mg of fosinopril. At 24 hours, 40 mg produced 98% inhibition, and 20 mg produced 80% inhibition. Within this range, no dose-related adverse effects could be identified. On the basis of these data, a daily dose of 40 mg of fosinopril was chosen for this study, but in spite of these considerations, 18 of 247 fosinopril-treated patients versus only 4 of the 242 control patients had to be discontinued early because of hypotension. In addition, in 15 of the 153 fosinopril-treated patients, dose titration had to be stopped at 20 mg, and in another 10 patients, the 40-mg dose had to be reduced to 20 mg because of hypotension.

In the present study, compared with MERCATOR, more severe lesions located in larger vessels were dilated: the respective pre-PTCA MLD values were 0.91 and 1.01 mm and the respective reference vessel diameters 2.91 and 2.63 mm, leading to calculated percent diameter stenoses of 69.0% in the present study versus 60.8% in the MERCATOR trial. In addition, our procedural gain of 1.20 mm was much higher than the 0.77 mm obtained in MERCATOR, so that, despite the more severe initial lesion, the residual stenosis was less severe (mean, 27.5% versus 32.9%). Subsequently, however, this larger procedural gain was offset to some extent by a greater loss in MLD (−0.55 mm versus −0.28 mm), leading to negligible differences between the two studies in the final 6-month follow-up result. Indeed, at this time, the MLDs obtained in the two studies were almost identical. In terms of percent stenosis, however, the values in the present study were slightly higher (46.5% versus 43.9%) because of a larger mean vessel diameter. The larger loss in MLD in the present study can best be explained by the larger initial gain itself, a relation recently reported by Serruys and colleagues.

**TABLE 5. Restenosis Rates per Lesion According to Frequently Used Definitions**

<table>
<thead>
<tr>
<th>Restenosis Criteria</th>
<th>Fosinopril Group (N=175)</th>
<th>Control Group (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30% increase in % diameter stenosis at follow-up (NHLBI 1), n (%)</td>
<td>46 (26.3)</td>
<td>40 (23.3)</td>
</tr>
<tr>
<td>&gt;70% diameter stenosis at follow-up, n (%)</td>
<td>22 (12.6)</td>
<td>22 (12.8)</td>
</tr>
<tr>
<td>Return to within 10% of the pre-PTCA diameter stenosis (NHLBI 3), n (%)</td>
<td>46 (26.3)</td>
<td>47 (27.3)</td>
</tr>
<tr>
<td>Loss of &gt;50% of the initial gain after PTCA (NHLBI 4), n (%)</td>
<td>80 (45.7)</td>
<td>70 (40.7)</td>
</tr>
<tr>
<td>% Diameter stenosis at follow-up &gt;50%, n (%)</td>
<td>69 (39.4)</td>
<td>64 (37.2)</td>
</tr>
<tr>
<td>Loss of ≥0.72 mm in MLD from post-PTCA to follow-up, n (%)</td>
<td>58 (33.1)</td>
<td>64 (37.2)</td>
</tr>
<tr>
<td>Loss of ≥0.36 mm in MLD from post-PTCA to follow-up, n (%)</td>
<td>103 (58.9)</td>
<td>87 (50.6)</td>
</tr>
</tbody>
</table>

NHLBI indicates National Heart, Lung, and Blood Institute; PTCA, percutaneous transluminal coronary angioplasty; and MLD, minimal lumen diameter.

All differences between the two treatment groups are insignificant.


Table 6. Clinical Status at Follow-up

<table>
<thead>
<tr>
<th>Angina class (CCS) at follow-up, n (%)</th>
<th>Fosinopril Patients (N=153)</th>
<th>Control Patients (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>118 (77.1)</td>
<td>106 (70.2)</td>
</tr>
<tr>
<td>Class I</td>
<td>4 (2.6)</td>
<td>9 (6.0)</td>
</tr>
<tr>
<td>Class II</td>
<td>10 (6.5)</td>
<td>14 (9.3)</td>
</tr>
<tr>
<td>Class III</td>
<td>6 (3.9)</td>
<td>6 (4.0)</td>
</tr>
<tr>
<td>Class IV</td>
<td>15 (9.8)</td>
<td>16 (10.6)</td>
</tr>
</tbody>
</table>

Early (<6 months) repeat coronary angiography, n

<table>
<thead>
<tr>
<th>Indication</th>
<th>Fosinopril Patients</th>
<th>Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Management

<table>
<thead>
<tr>
<th>Repeat PTCA</th>
<th>Fosinopril Patients</th>
<th>Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat PTCA</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>CABG</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Conservative</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>PTCA of another lesion</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Repeat PTCA at 6-month visit, n

<table>
<thead>
<tr>
<th>CCS indicates Canadian Cardiovascular Society functional class; AMI, acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft surgery. All differences between both treatment groups are insignificant.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 6. Clinical Status at Follow-up</strong></td>
</tr>
<tr>
<td><strong>Angina class (CCS) at follow-up, n (%)</strong></td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
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<td><strong>Class III</strong></td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
</tr>
<tr>
<td><strong>Early (&lt;6 months) repeat coronary angiography, n</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>AMI</strong></td>
</tr>
<tr>
<td><strong>Angina</strong></td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Conservative</strong></td>
</tr>
<tr>
<td><strong>PTCA of another lesion</strong></td>
</tr>
<tr>
<td><strong>Repeat PTCA at 6-month visit, n</strong></td>
</tr>
</tbody>
</table>

As a consequence, restenosis rates calculated according to the most frequently used criteria were also slightly higher in the present study than in MERCATOR, but this observation did not compromise the long-term efficacy of the PTCA procedure. Indeed, although a greater initial gain was followed by a greater loss, the resultant long-term gain was still greater in our study: 22.5% diameter reduction versus 16.9% in MERCATOR. In both studies, these angiographic findings were clinically reflected in similar repeat revascularization rates of approximately 15% during the follow-up period.

Several hypotheses can be formulated to explain why ACE inhibitors fail to prevent restenosis after PTCA. First, the lack of effect on restenosis in clinical studies may be dose related. Indeed, in the rat model, doses up to 70 times higher than in humans have been used. Consequently, it is conceivable that only megadoses of an ACE inhibitor, with unavoidable side effects prohibiting their clinical use, are effective in preventing restenosis. Second, the antiproliferative action of these drugs may be species related. High doses of cilazapril (10 mg·kg⁻¹·d⁻¹) and captopril (100 mg·kg⁻¹·d⁻¹) have been effective in preventing neointimal proliferation in the rat carotid artery model, whereas in the swine and baboon models, no significant benefit of several ACE inhibitors could be demonstrated. Therefore, it seems plausible that rats do not represent the right experimental model for studying the effects of ACE inhibitors on human neointimal proliferation. Finally, it is also conceivable that the muscular response of healthy animal arteries to experimental injury is substantially different from the pathophysiological mechanisms underlying restenosis after therapeutic angioplasty of atherosclerotic human coronary arteries.

Conclusions

Fosinopril, when administered in a dose of 40 mg daily, did not prevent restenosis and did not favorably influence the overall clinical outcome after PTCA even when the treatment was started the day before the procedure. In conjunction with the cilazapril experience, it seems extremely unlikely that, in patients, any beneficial effect on restenosis can be expected from this class of drugs.

Acknowledgments

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