Fosinopril Versus Amlodipine Comparative Treatments Study
A Randomized Trial to Assess Effects on Plasminogen Activator Inhibitor-1

Marco Pahor, MD; Lonneke V. Franse, PhD, MPH; Steven R. Deitcher, MD; William C. Cushman, MD; Karen C. Johnson, MD, MPH; Ronald I. Shorr, MD; Kandice Kottke-Marchant, MD, PhD; Russell P. Tracy, PhD; Grant W. Somes, PhD; William B. Applegate, MD, MPH

Background—ACE inhibitors and calcium antagonists may modulate fibrinolysis. We conducted a randomized controlled trial to assess the effects of these drugs on plasminogen activator inhibitor-1 (PAI-1) antigen, an inhibitor of fibrinolysis.

Methods and Results—Participants with hypertension and type 2 diabetes mellitus (n=96, 51% black) were randomized after an initial 4 weeks of placebo to double-blind 20 or 40 mg fosinopril or 5 or 10 mg amlopidine daily for 4 weeks in a fixed-dose regimen. After 4 weeks of placebo washout, the patients received 4 weeks of crossover treatments. After treatment with placebo, systolic and diastolic blood pressure were 143±2 and 86±1 mm Hg and plasma PAI-1 was 43.4±2.3 ng/mL. Amlodipine achieved a greater systolic and diastolic blood pressure reduction than fosinopril (10 mm Hg versus 8 mm Hg, P=0.029, and 5 mm Hg versus 3 mm Hg, P=0.040, respectively) but tended to increase PAI-1, whereas fosinopril tended to decrease PAI-1 (5.4±3.6 versus −3.8±2.5 mg/mL, P=0.045). The PAI-1 changes depended on drug dose (6.5±6.1 and 3.4±3.9 ng/mL with amlopidine 10 and 5 mg, respectively, and −0.4±3.1 and −7.4±4.0 ng/mL with fosinopril 20 and 40 mg, respectively, P for trend 0.024). No significant differences between fosinopril and amlopidine were found for short-term changes in tissue plasminogen activator antigen, fibrinogen, C-reactive protein, and interleukin-6. The findings were similar in black and white participants.

Conclusions—Short-term treatment with fosinopril significantly reduced PAI-1 compared with amlopidine in a dose-dependent fashion. This effect, which was independent of blood pressure reduction, may account for the improved clinical outcomes achieved with ACE inhibitors compared with calcium antagonists. (Circulation. 2002;105:457-461.)

Key Words: diabetes mellitus ■ drugs ■ etiology ■ hypertension ■ trials

Angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists are recommended for treating hypertension in patients with type 2 diabetes mellitus based on the efficacy of these drugs in lowering elevated blood pressure and lack of adverse metabolic effects. Several studies suggest that other mechanisms in addition to blood pressure control may be important in determining the therapeutic efficacy of these agents.1-3

Impairment of fibrinolysis may play a relevant role in promoting atherothrombotic events in patients with hypertension and diabetes mellitus. Elevated plasma markers of fibrinolysis, such as plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator antigen (tPA), identify high-risk individuals.4-7 In patients with diabetes mellitus, the plasma level of PAI-1, an inhibitor of the fibrinolytic system, is increased compared with nondiabetic counterparts,8 and PAI-1 is also higher in hypertensive patients.9

ACE inhibitors and calcium antagonists may affect fibrinolysis, because both angiotensin II and cellular calcium regulate the production of PAI-1 either directly or by modulating the inflammatory response, which in turn promotes secretion of PAI-1.10 Clinical data on the effects of ACE inhibitors and calcium antagonists on fibrinolysis are limited,4,12 and information in hypertensive patients with type 2 diabetes mellitus is virtually lacking. The primary objective

Received October 31, 2001; revision received November 12, 2001; accepted November 14, 2001.

From the Sticht Center on Aging, Department of Internal Medicine (M.P., W.B.A.), Wake Forest University School of Medicine, Winston-Salem, NC; Institute for Research in Extramural Medicine (L.V.F.), Vrije Universiteit, Amsterdam, the Netherlands; Departments of Vascular Medicine (S.R.D.) and Clinical Pathology (K.K.-M.), Cleveland Clinic, Cleveland, Ohio; Memphis Veteran Affairs Medical Center (W.C.C.) and Department of Preventive Medicine (K.C.J., R.I.S., G.W.S.), Memphis, Tenn; and Department of Biochemistry (R.P.T.), University of Vermont, Burlington, Vt.

Dr Pahor has received research grants from Bristol Myers Squibb and Pfizer; he has also received honoraria from Bristol Myers Squibb.

Correspondence to Marco Pahor, MD, Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Blvd, Winston Salem, NC 27157. E-mail mpahor@wfubmc.edu

© 2002 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

457
of this randomized controlled trial was to compare the effects of the ACE inhibitor fosinopril with the calcium antagonist amlodipine on plasma PAI-1 antigen in persons with type 2 diabetes and hypertension. Blood pressure, angiotensin II, tPA antigen, fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6) were measured as secondary outcomes. Because several earlier trials suggested that ACE inhibitors may be more effective than calcium antagonists for the prevention of cardiovascular events, we hypothesized that fosinopril may have more favorable effects on fibrinolysis than amlodipine.

**Methods**

**Participants**

Fosinopril Versus Amlodipine Comparative Treatments Study (FACTS) was a double-blind, crossover, randomized, controlled trial to compare the effects of fosinopril with amlodipine on plasma PAI-1 antigen in persons with type 2 diabetes and hypertension. The trial was approved by the local institutional review board, and informed consent was obtained from the study participants. Participants were recruited from the community in Memphis, Tennessee. Diabetes mellitus was either previously diagnosed by a physician (as reported by the participants) or newly diagnosed during the screening for the trial. Diabetes mellitus had to be diagnosed at age ≥45 years as determined by self-report. Newly diagnosed diabetes mellitus was defined in any one of the following 3 ways, confirmed on a different day by any one of these 3 tests: (1) fasting plasma glucose ≥126 mg/dL; (2) casual plasma glucose ≥200 mg/dL with the classic diabetes mellitus symptoms of increased urination, increased thirst, and unexplained weight loss; or (3) oral glucose tolerance test value of ≥200 mg/dL in the 2-hour sample. After the initial screening, a 2- to 8-week antihypertensive medication washout period was followed by a 4-week placebo period. Blood pressure was measured in the morning in sitting position, and we used the average of 3 measures at each visit. The average of 2 visits during the initial placebo phase had to be ≥85 mm Hg for diastolic blood pressure or ≥130 mm Hg for systolic blood pressure. Patients with average diastolic blood pressure ≥110 mm Hg or average systolic blood pressure ≥180 mm Hg were excluded. Other exclusion criteria were recent history of coronary heart disease, stroke, or any other severe morbid condition with poor prognosis, serum creatinine >2.5 mg/dL, relevant proteinuria, contraindications to calcium antagonists or ACE inhibitors, or specific indications for these drugs other than hypertension and regular use of nonsteroidal anti-inflammatory agents (except for low-dose aspirin), corticosteroids, or hormone replacement therapy.

**Intervention**

After 4 weeks of placebo, the participants meeting the entry criteria were randomized to double-blind fixed-dose fosinopril 20 or 40 mg or amlodipine 5 or 10 mg daily for 4 weeks. The dose was assigned at random. The blinded study drugs were supplied by Bristol Myers Squibb and allocated according to a computer-generated blocked randomization sequence. The study drugs were given in fixed dose in the morning. After an additional 4 weeks of placebo washout, the participants received 4 weeks of crossover treatments. Clinic visits were scheduled at the end of each of the 4-week study periods (placebo, randomized treatments, washout placebo, and crossover treatments).

**Blood Sampling and Assays**

At each clinic visit, fasting blood samples were obtained between 7 and 10 AM by peripheral venipuncture after the patient had been sedentary in the sitting or supine position for at least 15 minutes. The initial 10 mL of drawn blood was not used for fibrinolytic component testing. The samples were processed within 1 hour of the blood draw. Samples were placed in a refrigerated centrifuge (4°C) and spun at 3,000 rcf for 15 minutes to derive platelet-poor plasma. Immediately after centrifugation, the plasma was aliquoted and stored frozen at <−70°C until analysis.

All assays and assessments were done blinded to treatment. Plasma PAI-1 antigen, tPA antigen, and IL-6 were measured in duplicate by means of commercial ELISA. The average of 2 measures was used in the data analyses. The typical coefficient of variation (CV) for these assays is 8.4%. Reagents for the PAI-1 and tPA assays were obtained from American Diagnostica Inc. Reagents for the IL-6 assays were obtained from R&D Systems Inc. For IL-6, we used the high-sensitivity HS600 Quantikine kit (detection range <0.10 pg/mL, 0.156 to 10 pg/mL).

CRP was assayed by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem). Antibodies were used to coat microtiter-plate wells, and biotinylated CRP, together with the patient plasma, was diluted 1:700 in assay buffer (PBS with 0.1% Tween 20 and 1% BSA). The excess was then washed off, and the amount of bio inflated protein was estimated by the addition of avidin-peroxidase (Vectastain, Vector Laboratories). Purified CRP was used as the standard, with protein concentrations as determined by the manufacturer and confirmed by absorbance at 280 nm. The CRP assay was standardized according to the WHO First International Reference Standard with a sensitivity of 0.08 μg/μL, with a standard reference range between 0.5 and 2.5 μg/L. In previous studies conducted in our laboratory, the mean coefficient of variation for CRP across assay runs was 4.2%.

Fibrinogen was measured by an automated clot rate assay using the ST4 instrument (Diagnostica Stago/American Bioproducts) with College of American Pathologists reference material. Proficiency was checked with the College of American Pathologists Coagulation Proficiency Testing Program. Both frozen and lyophilized controls were used. The typical CV for this assay is 2.9%.

Angiotensin II peptide was extracted from 1-mL samples of EDTA plasma using 1-mL C-18 Sep-Pak columns (Peninsula Laboratories). After resuspension of the evaporated peptide extract, angiotensin II was measured with a competitive radiommunossay (Peninsula Labs). The assay is based on the competition between labeled 125-I peptide and unlabeled peptide (either unknown or standard) binding to a limited quantity of specific antibody. The average interassay CV was 11%, and typical within-assay CVs were 3.5% to 6.5%.

**Sample Size and Data Analyses**

A sample size of 93 participants was calculated to have 80% power (α 0.05) to detect a 8 ng/mL difference in PAI-antigen change between fosinopril and amlodipine, given a mean of 40 ng/mL and a standard deviation of difference in the response of matched pairs of 34. The estimate of such an effect size was based on previous studies. The ANOVA and the paired t test were used to compare...
TABLE 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SEM or Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.5±1.0</td>
</tr>
<tr>
<td>Women</td>
<td>25%</td>
</tr>
<tr>
<td>Black</td>
<td>51%</td>
</tr>
<tr>
<td>Native American</td>
<td>6%</td>
</tr>
<tr>
<td>White</td>
<td>41%</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td>31.4±0.6</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.97±0.01</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>7.3±0.8</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>9.3±1.0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3%</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1%</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>206±4</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>48±2</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>157±9</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.3±1.2</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>167±7</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>8.3±0.2</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.91±0.02</td>
</tr>
</tbody>
</table>

The baseline characteristics of the 88 participants who completed the trial are listed in Table 1. The mean age was 59.5 years, more than half were black, and 55% were obese (body mass index ≥30 kg/m^2). The average duration of diabetes mellitus and hypertension was 7.3 years (range, 0 to 31 years) and 9.3 years (range, 0 to 50 years). The prevalence of history of individual cardiovascular diseases determined by self-report was ≤3%.

Results

A total of 174 prospective participants were screened, 78 were excluded because they did not meet the inclusion criteria, and 96 were randomized (Figure 1). The main reasons for exclusion were failure to meet blood pressure criteria (n=21) and history of recent acute myocardial infarction or stroke (n=7). Eight of the 96 randomized participants dropped out during follow-up, and 88 completed the trial (Figure 1). Of the 4 participants who dropped out while they were taking fosinopril, 1 had chest pain, 1 had headache, and 2 withdrew consent. Of the 2 participants who dropped out while they were taking amlodipine, 1 had chest pain and 1 withdrew consent. Both participants who dropped out while they were taking placebo withdrew consent.

The baseline characteristics of the 88 participants who completed the trial are listed in Table 1. The mean age was 59.5 years, more than half were black, and 55% were obese (body mass index ≥30 kg/m^2). The average duration of diabetes mellitus and hypertension was 7.3 years (range, 0 to 31 years) and 9.3 years (range, 0 to 50 years). The prevalence of history of individual cardiovascular diseases determined by self-report was ≤3%.

Systolic and diastolic blood pressure after treatment with placebo, fosinopril, and amlodipine. Numbers within the bars indicate the blood pressure level in mm Hg.

![Figure 2](image)

59.5 years, more than half were black, and 55% were obese (body mass index ≥30 kg/m^2). The average duration of diabetes mellitus and hypertension was 7.3 years (range, 0 to 31 years) and 9.3 years (range, 0 to 50 years). The prevalence of history of individual cardiovascular diseases determined by self-report was ≤3%.

Systolic and diastolic blood pressure after treatment with placebo were 143±2 mm Hg and 86±1 mm Hg, respectively (Figure 2). Both active treatments significantly reduced blood pressure compared with placebo (P<0.001). Amlodipine achieved a significantly greater blood pressure reduction than fosinopril (10 mm Hg versus 8 mm Hg for systolic blood pressure reduction, P=0.029, and 5 mm Hg versus 3 mm Hg for diastolic blood pressure reduction, P=0.040). Higher doses of the drugs achieved 1 to 3 mm Hg greater blood pressure reductions than lower doses. Systolic blood pressure was 133 and 131 mm Hg after treatment with amlodipine 5 and 10 mg, respectively, and 136 and 134 mm Hg after treatment with fosinopril 20 and 40 mg, respectively. Diastolic blood pressure was 83 and 80 mm Hg after treatment with amlodipine 5 and 10 mg, respectively, and 83 and 82 mm Hg after treatment with fosinopril 20 and 40 mg, respectively.

After treatment with placebo, the plasma levels were 43.4±2.3 ng/mL for PAI-1, 10.1±0.3 ng/mL for tPA, 306±6 mg/dL for fibrinogen, 2.9±0.3 µg/mL for CRP, 3.4±0.2 ng/mL for IL-6, and 6.32±1.18 pg/mL for angiotensin II (Table 2). PAI-1 decreased by 3.8±2.5 ng/mL after treatment with amlodipine, and it increased by 5.4±3.6 ng/mL after treatment with fosinopril (P=0.045 for the comparison of change with fosinopril versus amlodipine, difference=9.2 ng/mL). Such changes were dependent on drug dose. PAI-1

TABLE 2. PAI-1 (Primary Outcome) and Other Biological Markers After Treatment With Placebo and Change After Treatment With Fosinopril and Amlodipine

<table>
<thead>
<tr>
<th></th>
<th>PAI-1, ng/mL</th>
<th>IPA, ng/mL</th>
<th>PAI-1/IPA Ratio</th>
<th>Fibrinogen, mg/dL</th>
<th>CRP, µg/mL</th>
<th>IL-6, ng/mL</th>
<th>Angiotensin II, pg/mL</th>
<th>Fasting Plasma Glucose, mg/dL</th>
<th>HbA1C, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>43.4±2.3</td>
<td>10.1±0.3</td>
<td>4.3</td>
<td>306±6</td>
<td>2.9±0.3</td>
<td>3.4±0.2</td>
<td>6.32±1.18</td>
<td>168±6</td>
<td>8.2±0.2</td>
</tr>
<tr>
<td>Fosinopril change vs placebo</td>
<td>−3.8±2.5</td>
<td>−0.1±0.3</td>
<td>−0.1±0.2</td>
<td>−3±5</td>
<td>−0.1±0.2</td>
<td>−0.2±0.1</td>
<td>−0.13±0.33</td>
<td>4±6</td>
<td>−0.06±0.08</td>
</tr>
<tr>
<td>Amlodipine change vs placebo</td>
<td>5.4±3.6</td>
<td>0.2±0.3</td>
<td>0.4±0.3</td>
<td>−4±9</td>
<td>−0.2±0.2</td>
<td>0.1±0.3</td>
<td>0.65±0.35</td>
<td>13±5</td>
<td>−0.01±0.07</td>
</tr>
<tr>
<td>P for fosinopril vs amlodipine</td>
<td>0.045</td>
<td>0.37</td>
<td>0.16</td>
<td>0.91</td>
<td>0.05</td>
<td>0.032</td>
<td>0.037</td>
<td>0.11</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*Angiotensin II was measured in 16 participants who were given the higher dose of fosinopril and amlodipine.
increased by $6.5 \pm 6.1$ and $3.4 \pm 3.9$ ng/mL after treatment with amlodipine 10 and 5 mg, respectively, and it decreased by $0.4 \pm 3.1$ and $7.4 \pm 4.0$ ng/mL after treatment with fosinopril 20 and 40 mg, respectively ($P$ for trend $0.024$, Figure 3). The higher dose of fosinopril was associated with a greater decrease in PAI-1, and the higher dose of amlodipine was associated with a greater increase in PAI-1 ($P=0.029$ for the comparison of change with fosinopril 40 mg versus amlodipine 10 mg). Angiotensin II was measured in 16 participants who were given 40 mg fosinopril and 10 mg amlodipine. Angiotensin II decreased by $0.13 \pm 0.33$ pg/mL after treatment with fosinopril, and it increased by $0.65 \pm 0.35$ pg/mL after treatment with amlodipine ($P=0.037$ for the comparison of change with fosinopril versus amlodipine, difference $=0.78$ pg/mL). The drug-associated changes in tPA, PAI-1/tPA ratio, fibrinogen, CRP, IL-6, fasting plasma glucose, and HbA1C were not statistically significant (Table 2).

Compared with white participants, in black participants the baseline blood pressure tended to be higher and the blood pressure reduction achieved with amlodipine and fosinopril tended to be greater, but these comparisons according to race and treatment were not statistically significant (Table 3). Among the black participants, the drug-related changes in PAI-1 tended to be more pronounced than in white participants (Table 3). In the race-specific analyses, the drug-related changes in tPA, fibrinogen, CRP, and IL-6 were not significantly different between fosinopril and amlodipine.

**Discussion**

A 4-week treatment with fosinopril resulted in changes toward a significantly lower level of PAI-1 compared with amlodipine. Compared with placebo, fosinopril tended to reduce PAI-1, whereas amlodipine tended to increase PAI-1. The dose-dependent effects on PAI-1 strengthen the validity of the findings. Whereas single-drug therapy in fixed dose with 5 or 10 mg amlodipine resulted in a greater blood pressure reduction compared with 20 or 40 mg fosinopril, fosinopril produced more favorable effects on PAI-1. The findings were similar in white and black participants.

The present results support the hypothesis that mechanisms different from blood pressure control may be important in determining the therapeutic efficacy of antihypertensive drugs. In the Heart Outcomes Prevention Evaluation trial, most of the benefit of ramipril was unrelated to blood pressure lowering. Moreover, in several recent randomized trials, calcium antagonists were compared with ACE inhibitors and other drugs, and although blood pressure lowering was similar, there were trends toward higher rates of cardiovascular events in subjects taking the calcium antagonists. The effects of ACE inhibitors and calcium antagonists on PAI-1 may in part explain the relevant differences in clinical outcomes found in these trials.

The results of FACTS are in agreement with other trials. In one study, 120 patients were randomized to ramipril or placebo 24 hours after an acute myocardial infarction to assess the effects on fibrinolytic markers. After 2 weeks, PAI-1 antigen and activity were significantly lower in the ramipril group compared with placebo by 44% and 22%, respectively. In 15 postmyocardial infarction patients, imidapril significantly decreased PAI-1 levels but not tPA after 7 and 28 days of treatment compared with pretreatment values, and no changes were seen in 15 placebo-treated patients. In another study with imidapril in 40 postmyocardial infarction patients, imidapril significantly reduced PAI-1 activity by 60% within 48 hours compared with placebo. In the present study, which looked at patients who were in stable condition, the observed changes in PAI-1 were much smaller. The difference in drug effect size on PAI-1 between the present study and studies conducted after an acute myocardial infarction is probably explained by the difference in acuity of the patient’s condition. Taken together, these trials suggest that the effects of ACE inhibition on PAI-1 can occur after short-term treatment.

In the Angina Prognosis study in Stockholm trial that compared verapamil to metoprolol, tPA antigen and PAI-1 activity, but not the type of treatment, predicted coronary events. Compared with baseline values, verapamil and metoprolol use were associated with a 10% decrease and 2% increase in tPA ($P<0.001$ for treatment difference), but

**TABLE 3. Blood Pressure and PAI-1 After Treatment With Placebo and Change After Treatment With Fosinopril and Amlodipine According to Race**

<table>
<thead>
<tr>
<th></th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Diastolic Blood Pressure, mm Hg</th>
<th>PAI-1, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>Placebo</td>
<td>140±2</td>
<td>144±2</td>
<td>86±1</td>
</tr>
<tr>
<td>Fosinopril vs</td>
<td>−5.9±2.2</td>
<td>−9.2±1.7</td>
<td>−2.2±1.3</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine vs</td>
<td>−11.8±1.7</td>
<td>−11.6±2.0</td>
<td>−4.1±1.0</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P for fosinopril vs amlodipine=0.028.

None of the comparisons of white vs black race were statistically significant.
changes in PAI-1 activity were not significant. Finally, in a recent study of 46 hypertensive patients, the use of enalapril was associated with a significant decrease in PAI-1, whereas the use of nitrendipine was associated with a significant increase in PAI-1 over 3 months of treatment, which is similar to our findings.

In the present trial, tPA, fibrinogen, CRP, and IL-6 changes did not differ significantly between treatments. Preclinical and clinical studies suggest that both ACE inhibitors and calcium antagonists may modify tPA, fibrinogen, CRP, and IL-6. Our study, which was primarily designed to assess short-term effects on PAI-1, could not exclude potential effects on these markers over longer periods of treatment. Also, we could not assess whether the drug effects on PAI-1 were sustained or more pronounced over the longer term.

It is noteworthy that the blood pressure reduction and PAI-1 changes achieved with fosinopril or amlodipine were similar in black and white participants. These results on blood pressure reduction, may in part explain by differences in patient populations or types of drugs used in the trials and suggests that black patients may respond well to certain ACE inhibitors.

The use of higher doses of the drugs achieved only a minimal advantage on blood pressure control (1 to 3 mm Hg greater reduction in systolic and diastolic blood pressure by doubling the dose of either fosinopril or amlodipine) but caused a major impact on PAI-1 changes. This finding may have important clinical implications. Presently, drug titration is primarily based on blood pressure reduction, whereas changes in other markers that are not usually measured, such as angiotensin II and PAI-1, may affect the clinical outcomes.

The use of higher doses of amlodipine by increasing PAI-1 may promote adverse therapeutic effects. This mechanism may in part explain the higher rates of cardiovascular events associated with the use of higher doses of calcium antagonists found in several studies. On the contrary, the use of higher doses of fosinopril, by decreasing PAI-1, may improve the therapeutic effect of the drug.

In conclusion, short-term treatment with fosinopril significantly reduced PAI-1 in a dose-dependent fashion compared with amlodipine. This effect, which was independent of blood pressure reduction, may in part account for the improved clinical outcomes achieved in several trials with ACE inhibitors compared with calcium antagonists. Our findings also suggest that in addition to lowering blood pressure, effects on other markers, such as angiotensin II and PAI-1, may be important factors to be used for dose titration of antihypertensive agents.

Acknowledgments

Supported by grants from Bristol Myers Squibb, Princeton, NJ, and Rome, Italy, and NIH grant P60AG10484. We thank Beate Griffin, RN, for supervising the study, Lynn Lichtermann, RN, for recruitment, and Lisa Jones, RN, for study coordination.

References


Fosinopril Versus Amlodipine Comparative Treatments Study: A Randomized Trial to Assess Effects on Plasminogen Activator Inhibitor-1

Circulation. 2002;105:457-461
doi: 10.1161/hc0402.102929

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/4/457

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://wwww.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/