Effects of Fosinopril and Pravastatin on Carotid Intima-Media Thickness in Subjects With Increased Albuminuria

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Background and Purpose—Elevated urinary albumin excretion (UAE) is associated with an increased carotid intima-media thickness (IMT). Because angiotensin-converting enzyme inhibitors as well as statins have been shown to lower UAE and the progression of IMT, we assessed the effects of fosinopril and pravastatin on carotid IMT in subjects with an increased UAE (15 to 300 mg/24 h).

Methods—IMT was measured at the posterior wall of the left common carotid artery using radio-frequency signal analysis obtained by M-mode ultrasonography. 642 subjects were double-blind randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo and were available for intention-to-treat analysis.

Results—Mean age was 51 ± 11 years, 65% were male, the median UAE was 22.5 (15.5 to 40.8) mg/24 h, and the mean IMT at baseline was 0.77 ± 0.18 mm. The overall progression rate of IMT in 4 years was 0.037 ± 0.006 mm. No significant difference in IMT progression was found between fosinopril, pravastatin, or matching placebo. IMT after 4 years was predicted by IMT at baseline, age, gender, pulse pressure, and low-density lipoprotein cholesterol levels. Furthermore, a higher incidence of clinical events was observed in subjects with an IMT ≥ 1 mm after a mean follow-up of 46 ± 7 months (hazard ratio, 3.13; 95% confidence interval, 1.59 to 6.16; P = 0.001).

Conclusions—In subjects with an increased UAE, treatment with fosinopril and pravastatin showed no significant effect on carotid IMT. Furthermore, an IMT < 1 mm at baseline is an important indicator for event-free survival. (Stroke. 2005;36:649-653.)

Key Words: ACE inhibitors • albuminuria • carotid arteries • controlled clinical trials • statins

An increased urinary albumin excretion (UAE) is an indicator for the presence of multiple cardiovascular risk factors and is associated with an increased risk of cardiovascular morbidity and mortality in patients with known cardiovascular disease, as well as in subjects of the general population.1 Similarly, carotid intima-media thickness (IMT) is widely accepted as surrogate cardiovascular clinical endpoint and is often used in clinical trials to evaluate the efficacy of interventions. Angiotensin-converting enzyme (ACE) inhibitors and statins have been shown to decrease cardiovascular events in subjects at high risk.2,3 Both drugs have also been shown to lower UAE and to halt the progression of IMT in high-risk populations. Unknown is whether an intervention aimed at lowering UAE will reduce the progression of IMT in lower-risk populations.

Therefore, the objective of this study was to assess the effects of the ACE inhibitor fosinopril and the statin pravastatin on carotid IMT in a population with an increased UAE (15 to 300 mg/24 h).

Materials and Methods

The Prevention of Renal and Vascular EnDstage Disease Intervention Trial (PREVEND) IT is an investigator-initiated, single-center, double-blind, randomized, placebo-controlled trial with a 2 × 2 factorial design. Subjects were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo. Details of the PREVEND IT objectives, design, methods, and main results have been reported previously.4 A brief summary follows.

Subjects

The PREVEND Intervention Trial is a predefined substudy of the PREVEND program. The objective of the PREVEND program is to assess the value of microalbuminuria as an indicator of increased cardiovascular and renal risk in the general population. A total of 8592 subjects completed the screening program.5 A total of 1439 subjects fulfilled the inclusion criteria for the PREVEND IT. The key entry criteria of the PREVEND IT were persistent microalbumi-
minuría (one urinary albumin concentration >10 mg/L in an early morning spot urine and at least one 15 to 300 mg/24 h in 2×24-hour urine samples), a blood pressure of <160/100 mm Hg and not using antihypertensive medication, a total cholesterol <8.0 mmol/L, or <5.0 mmol/L in case of previous myocardial infarction, and not using lipid-lowering medication. From April 1998 to June 1999, 864 subjects were willing to participate in the PREVEND IT and were randomized to study medication.

**Measurements**

Urinary albumin excretion was measured as the mean of 2 24-hour urine collections. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg L⁻¹ and intra-assay and inter-assay coefficients of variation of <2.2% and 2.6%, respectively (Dade Behring Diagnostic). Serum total cholesterol and serum creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak). The primary endpoint was the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity. Cardiovascular hospitalization was defined as hospitalization for documented nonfatal myocardial infarction or myocardial ischemia, heart failure, peripheral vascular disease, and/or cerebrovascular accident.

**Carotid IMT Measurements**

IMT measurements were performed using a Pie Medical Scanner 200 device with a linear array transducer of 7.5 MHz, as reported previously. The IMT was measured at the posterior wall of the left common carotid artery ∼1 cm proximal to the bulbus at 3 different positions. A B-mode image was obtained of the carotid artery, after which an M-line was positioned perpendicular to the posterior wall, resulting in an M-line perpendicular to the posterior wall of the left common carotid artery. The radio-frequency signals and the electrocardiogram were stored on hard disk for 3 periods of 4 minutes showing an intima-media complex. The wall thickness calculation software (Pie Medical). The recorded files were processed using the wall thickness calculation section of the Wall Track System 2.0 software (Pie Medical). The mean of the 3 measurements was used to calculate IMT. When the echographer found a plaque and carotid IMT could therefore not be analyzed, the IMT measurement was not performed. The intra-observer variability in our laboratory is 0.051 mm, or 8.1% of the mean IMT, and is independent of wall thickness (R²=0.13, nonsignificant). Analysts blinded for patient characteristics and previous images performed all off-line analyses.

The study was approved by the institutional review board and conducted in accordance with the guidelines of Helsinki. Informed consent was obtained from all subjects before randomization.

### Statistical Analysis

All analyses were performed on an intention-to-treat basis and probability values were 2-sided and needed to be <0.05 to be significant. PREVEND IT was powered to demonstrate a relative risk reduction of 35% in cardiovascular morbidity and mortality. The planned sample size of 450 subjects in each medication group (450 fosinopril versus 450 placebo or 450 pravastatin versus 450 placebo given the 2×2 factorial design) provided ~80% power to detect this difference. No separate power analysis for the IMT measurements was performed. Baseline characteristics are given as means±SD. Change in systolic and diastolic blood pressure, IMT, total cholesterol, and low-density lipoprotein cholesterol are expressed as mean±SE. In case of a skewed distribution, the median (interquartile range) is presented. Differences between treatment groups were evaluated by Student t test for the normally distributed continuous variables, or with the Wilcoxon 2-sample test if data were skewed. To investigate that no withdrawal bias had occurred and therefore underestimation of the intervention, we performed a “worst case” analysis by replacing missing values with the mean or the worst IMT progression observed in the entire population after 4 years of follow-up. Statistical analyses of changes in IMT were performed with 2-way analysis of variance to account for the 2 individual drug treatments. To explore the association between IMT at baseline, microalbuminuria, and cardiovascular risk factors at baseline, we used the Pearson or Spearman correlation tests, when appropriate. For optimal distribution, urinary albumin excretion was transformed to natural logarithm. The change in mean IMT in the common carotid artery was the primary endpoint measure. The impact of baseline mean IMT on clinical events was evaluated by dichotomizing the parameter into the lowest 9 deciles against the highest decile (IMT >1.0 mm). Results are presented by hazard ratios with 95% confidence intervals. Multivariate backward regression analysis was used to evaluate which factors predict IMT at end of study. All calculations were performed with SPSS version 11.0 software (SPSS Inc).

### Results

From the 864 randomized subjects in the PREVEND IT, IMT was measured in 776 subjects at baseline and in 681 subjects after 4 years. Finally, baseline and follow-up IMT data and subsequently the change in IMT were available in 642 subjects.

Baseline characteristics of all randomized subjects (n=642) with available baseline and follow-up IMT measurements are summarized in Table 1. The same characteristics and baseline IMT were found when we analyzed all subjects with an available baseline IMT measurement (n=776).
TABLE 2. Pearson and Spearman Correlation Coefficients Between Mean Intima-Media Thickness of the Common Carotid Artery at Baseline and the Presence of Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intima-Media Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.58*</td>
</tr>
<tr>
<td>Male gender†</td>
<td>0.12*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.34*</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.29*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.19*</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.13*</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.14*</td>
</tr>
<tr>
<td>Current smoking†</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.19*</td>
</tr>
<tr>
<td>Urinary albumin excretion</td>
<td>0.14*</td>
</tr>
<tr>
<td>Previous cardiovascular event†</td>
<td>0.12*</td>
</tr>
<tr>
<td>Use of cardiac drugs†</td>
<td>0.15*</td>
</tr>
</tbody>
</table>

*P<0.01.
†Spearman correlation coefficient.

As reported previously,4 fosinopril treatment decreased mean (±SE) systolic and diastolic blood pressure significantly after 3 months of treatment (−5.24±0.8 mm Hg and −4.02±0.4 mm Hg, both P<0.001). Pravastatin lowered total cholesterol and low-density lipoprotein cholesterol after 3 months with 1.2±0.04 mmol/L and 1.2±0.04 mmol/L, respectively (both P<0.001). No significant effect was found on the level of high-density lipoprotein cholesterol and triglycerides. In addition, fosinopril lowered the urinary albumin excretion significantly after 3 months (median urinary albumin excretion −5.47 mg/24 h; interquartile range, −14.1, 1.0; P<0.001). Pravastatin had no effect on albuminuria.

Mean IMT value at baseline was 0.77±0.18 mm and was significantly correlated with several cardiovascular risk factors, including urinary albumin excretion (Table 2). During 46±7 months, 40 (5.2%) endpoints occurred in 776 subjects. Baseline IMT was 0.89±0.23 mm in subjects in whom an endpoint developed in comparison to an IMT of 0.77±0.18 mm in subjects without an endpoint. A significantly higher incidence of clinical events was observed in subjects with an IMT >1 mm at baseline (hazard ratio, 3.13; interquartile range, 1.59 to 6.16; P=0.001; Figure 1). As shown in Figure 2, the relative risk reduction observed in subjects with an IMT >1 mm receiving fosinopril (46.3%) was comparable to the relative risk reduction in subjects with an IMT <1 mm receiving fosinopril (52.8%). In contrast, the absolute risk reduction was higher in the group with an IMT >1 mm, 6.8% (95% confidence interval, −6.4% to 20.0%) versus 2.9% (−0.07% to 5.9%). No differences were found in the pravastatin arm.

The mean IMT increased 0.037±0.006 mm during 4 years in the total population. The effect of treatment on IMT is presented in Table 3. IMT was significantly higher in all groups after 4 years of follow-up. Pravastatin and fosinopril did not have any effect on IMT during 4 years of follow-up. When we replace the missing values by the mean or the worse IMT progression observed in the entire population after 4 years of follow-up, the results showed again no significant effect of fosinopril and pravastatin on carotid IMT. When the study population was divided into 4 groups to explore the additive effect of fosinopril and pravastatin, the mean change in carotid IMT was 0.045±0.013 mm in the placebo group, 0.026±0.011 mm in the fosinopril group, 0.042±0.013 mm in the pravastatin group, and 0.036±0.013 mm in the group with both fosinopril and pravastatin. A 2-way analysis of variance, used to evaluate the effects and interactions of the factorial design between fosinopril and pravastatin, showed no association with the main effect terms (fosinopril, P=0.324; pravastatin, P=0.774), and no evidence for statistically significant interaction between fosinopril and pravastatin (P=0.641) in regard to changes in IMT.

In a backward multivariate regression analysis using potentially predictive variables of carotid IMT, the IMT after 4 years was significantly associated with baseline IMT, gender, age, pulse pressure, and low-density lipoprotein cholesterol (Table 4).

**Discussion**

PREVEND IT confirms that IMT is a significant predictor of cardiovascular events in subjects with an increased UAE (15 to 300 mg/24 h). However, fosinopril and pravastatin therapy during 4 years has no effect on the progression of IMT of the common carotid artery in middle-aged, albuminuric subjects.

The effect of pravastatin on the rate of progression of IMT of the common carotid artery has been studied extensively. The Pravastatin Lipids and Atherosclerosis in the Carotids (PLAC II)6 study was the first double-blind randomized clinical trial that demonstrated that pravastatin reduced the progression of IMT in hypercholesterolemic patients with coronary heart disease. However, they included subjects with an IMT ≥1.3 mm. The present study investigated IMT at an earlier point in the atherosclerotic process (mean IMT 0.77 mm at baseline). Furthermore, the LIPID Atherosclerosis Substudy7 demonstrated a beneficial effect of pravastatin in subjects with a mean IMT of 0.79 mm at baseline, mean cholesterol levels of 5.7 mmol/L, but with a history of myocardial infarction or unstable angina. In contrast to
previous reports, the Regression Growth Evaluation Statin Study (REGRESS) showed no treatment effect of pravastatin on the far wall of the common carotid artery, but they did find a highly significant effect on the combined carotid and femoral artery IMT in male patients with coronary artery disease. In concordance with our results, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol study (ARBITER) demonstrated an IMT progression of 0.025 mm after 1 year of treatment with pravastatin in hypercholesterolemic patients, of whom 46% had known cardiovascular disease. Baseline IMT was 0.63 mm in this study.

To date, limited data are available on the effect of fosinopril on IMT. Migdalis et al demonstrated a positive effect of fosinopril on carotid mean maximal IMT in diabetic patients with hypertension, but this small study was not double-blind or placebo-controlled. One study that confirm our results of the study was the ongoing randomized, double-blind, clinical trial Prevention of Atherosclerosis with Ramipril Trial (PART-2) showed no beneficial effect of ramipril on IMT. Furthermore, Stanton et al demonstrated that the common carotid IMT was more reduced by amlodipine treatment than lisinopril therapy. In summary, these data of controlled clinical trials are not all in favor of ACE inhibition on IMT and further studies are necessary to reveal the mechanisms underlying these paradoxical results.

As mentioned, the baseline IMT of our population was lower than randomized trials performed in subjects with high cardiovascular risk. However, the mean IMT of our study is comparable to the baseline IMT of 0.76 mm found in the population-based Rotterdam study, which was also performed in the Netherlands. These results suggest that the baseline IMT values found in our study are comparable to the general population. In addition, in our study we found a significant progression of carotid IMT during 4 years of follow-up, which might be explained as the natural thickening of the carotid IMT by aging.

Interestingly, mean IMT measured at baseline was a significant predictor of cardiovascular events in this middle-aged, albuminuric population. These results suggest that IMT measurements could be useful as screening tool in populations with an intermediate risk profile.

In our study, we could not demonstrate a beneficial effect of pravastatin and fosinopril on the IMT of the posterior wall of the left carotid artery. However, the rate of progression of IMT was lower in the active treatment groups compared to the placebo group (Figure 2).

**TABLE 3. Intima-Media Thickness of the Carotid Artery at Baseline and After 4 Years of Treatment (Only Nonmissing Values Presented) and the Mean Change in IMT**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Active</th>
<th>Placebo</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD IMT at baseline, mm</td>
<td>0.77±0.18</td>
<td>0.77±0.17</td>
<td>0.77±0.18</td>
<td>0.77±0.18</td>
</tr>
<tr>
<td>Mean±SD IMT at 4 y, mm</td>
<td>0.81±0.17*</td>
<td>0.80±0.16*</td>
<td>0.81±0.17*</td>
<td>0.81±0.16*</td>
</tr>
<tr>
<td>Mean±SE change IMT, mm</td>
<td>0.043±0.009</td>
<td>0.031±0.008</td>
<td>0.035±0.009</td>
<td>0.039±0.009</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; SE, standard error.

*Significantly different from the value of entry P<0.01.
common carotid artery. Nevertheless, we cannot exclude a potential beneficial effect on other segments of the IMT of the carotid or femoral artery. However, we have confirmed the relation between IMT and cardiovascular events in our population. Furthermore, traditional cardiovascular risk factors were correlated with IMT at baseline and after 4 years of follow-up, which substantiates the robustness of the data. In addition, like in several other IMT intervention studies, we used the mean change in IMT of the far wall of the left common carotid artery as primary outcome, which is preferable to obtain a reliable and reproducible IMT. IMT measurements were analyzed off-line based on M-line signal processing using the wall track system. This method is comparable with commonly used manual B-mode method with off-line storage of images by video recording, as published by Wilkens et al. Finally, the strength of our study is the use of one core laboratory for offline reading and the single-center design. PREVEND IT demonstrated a significant reduction in albuminuria by fosinopril and a trend in reducing cardiovascular events. Pravastatin treatment did not result in a reduction of albuminuria or cardiovascular events after 4 years of follow-up. The neutral effect on carotid IMT is in line with the results found in the main study of PREVEND IT. This nonsignificant effect on cardiovascular events and the lack of any association between treatment and regression of IMT might be explained by the lower-than-previously-described risk population as reflected by the lower mean IMT. Another explanation could be the relatively short follow-up period in this primary prevention setting, which might result in a low power because of the small numbers of events. Future randomized clinical trials using carotid IMT as a surrogate cardiovascular endpoint have to include subjects at higher cardiovascular risk than described in PREVEND IT or extend the period of treatment to demonstrate a significant effect on carotid IMT.

We conclude that in subjects with an increased UAE, treatment with fosinopril and pravastatin showed no significant effect on carotid IMT. Furthermore, an IMT <1 mm at baseline is an important indicator for event-free survival.

Acknowledgments

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References


TABLE 4. Multivariate Backward Regression Analysis Presenting All Significant Predictors of Intima-Media Thickness at End of Study

<table>
<thead>
<tr>
<th>B</th>
<th>SE</th>
<th>Partial Correlation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT at baseline</td>
<td>0.403</td>
<td>0.037</td>
<td>0.40</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>0.001</td>
<td>0.17</td>
</tr>
<tr>
<td>Male</td>
<td>0.025</td>
<td>0.011</td>
<td>0.09</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.001</td>
<td>0.000</td>
<td>0.11</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.016</td>
<td>0.006</td>
<td>0.11</td>
</tr>
</tbody>
</table>

IMT indicates intima-media thickness; LDL, low-density lipoprotein.
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