Early Carotid Atherosclerosis in Healthy Middle-Aged Women
A Follow-up Study

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Background and Purpose: Few longitudinal data about early atherosclerotic lesions of the carotid arteries are available in general populations. The main purpose of this study was to investigate risk factors for development and regression of intimal-medial thickening and atheromatous plaques.

Methods: Initial and 2-year examinations of the carotid arteries with high-resolution B-mode ultrasonography were performed in 308 apparently healthy women aged 45 to 55 years. The development of new atheromatous plaques and new intimal-medial thickening and the disappearance of preexisting plaques and intimal-medial thickening defined the four outcomes of interest.

Results: The development of plaques occurred more frequently in women with intimal-medial thickening than in women with normal carotid arteries at baseline (14.4% versus 7.2%, P < .05). A regression was seen in 21.7% of the women with preexisting plaques. Development of intimal-medial thickening occurred in 47.5% of the women with normal carotid arteries whereas 20.2% of the women with preexisting intimal-medial thickening showed a regression of their lesions. Multiple logistic regression showed that smoking (regression coefficient ± SE: 1.281 ± 0.450; P < .005), baseline levels of systolic blood pressure (regression coefficient ± SE: 0.031 ± 0.015; P < .04) and apolipoprotein B (regression coefficient ± SE: 0.016 ± 0.007; P < .03) were independently associated with the development of plaques, whereas the presence of an intimal-medial thickening did not reach the significance level (regression coefficient ± SE: 0.639 ± 0.436; P < .15). Independent predictors of the development of intimal-medial thickening were age (regression coefficient ± SE: 0.124 ± 0.058; P < .04) and, with a borderline significance level, (log)triglycerides (regression coefficient ± SE: 0.854 ± 0.451; P < .06). Low levels of low-density lipoprotein cholesterol (regression coefficient ± SE: 0.027 ± 0.009; P < .004) were associated with its regression.

Conclusions: This longitudinal study emphasizes the interest of B-mode ultrasonography in the monitoring of early carotid lesions. It gives further support to the hypothesis that intimal-medial thickening may be an early indicator of the atherosclerotic process. (Stroke. 1993;24:1837-1843.)

Key words • carotid artery diseases • epidemiology • ultrasonics • women

It is widely recognized that the severity and the progression of carotid atherosclerosis are associated with an increased risk of transient ischemic attack, stroke, and myocardial infarction. A better knowledge of risk factors involved in the progression and the regression of carotid atherosclerosis therefore appears to be of importance in the prevention and management of cardiovascular diseases. Data on progression and regression of carotid atherosclerosis mainly derived from angiographic or ultrasound studies performed either in symptomatic or in high-risk subjects with relatively advanced atherosclerotic lesions. Little information is available in general populations. The recent availability of noninvasive procedures such as high-resolution B-mode ultrasonography allows the detection and monitoring of minimal alterations of the arterial wall in healthy populations. In the last years, several cross-sectional epidemiological studies have investigated risk factors for early carotid atherosclerosis, but few of them have distinguished diffuse intimal-medial thickening (intimal-medial thickening) from localized atherosclerotic lesions (plaques) of the arterial wall. Our cross-sectional results had revealed significant associations between the major cardiovascular risk factors and the presence of both intimal-medial thickening and plaques in apparently healthy women, suggesting that intimal-medial thickening might be the early phase of the atherosclerotic process. A longitudinal approach may lead to a better understanding of the pathological basis of early changes in the arterial wall and help to unravel the relations between intimal-medial thickening and atheromatous plaques.

We therefore conducted a 2-year follow-up study in our middle-aged female population using repeated B-mode ultrasonography of the carotid arteries. We aimed to determine whether initial intimal-medial thickening was related to subsequent development of
atheromatous plaques, and more generally to investigate risk factors for development and regression of both atheromatous plaques and intimal-medial thickening.

**Subjects and Methods**

The initial study population consisted of apparently healthy French women who volunteered for a standard health check-up at the Center of Preclinical Investigations in Paris, France. They were invited to participate in the study if they were aged 45 to 54 years, were born in France, and gave an informed consent to further clinical and biological investigations. Between January 1988 and November 1989, an ultrasound examination of the carotid arteries was performed in 518 women free of cardiovascular disease and diabetes. The baseline examination also included height and weight measurements, blood pressure recording, biological measurements, and assessment of medical history and personal habits (smoking, use of antihypertensive drugs and sex hormones) with a self-administered questionnaire. The women were invited to a 2-year reexamination from January 1990 to October 1991. Among the 518 recruited women, 105 (20.3%) were lost to follow-up and 413 underwent a clinical reexamination. However, the follow-up ultrasound assessment of the carotid arteries could not be performed for logistic reasons in 105 women. Thus, 308 women underwent a complete reexamination. Their baseline characteristics were compared with those of women who were not followed-up or were followed-up incompletely. There were no significant differences between them in cardiovascular risk-factor levels (age, smoking status, blood pressure, and blood lipids) and in the degree of carotid atherosclerosis. The prevalence rates of intimal-medial thickening and atheromatous plaques were respectively 33.8% and 7.5% in women who underwent a complete reexamination and 26.2% and 10.9% in those who did not.

Details of the protocol of ultrasound examination were given elsewhere. Briefly, B-mode ultrasound imaging was performed at both examinations by a single trained physician according to the same protocol with a 7.5 MHz transducer having an axial resolution of 0.5 mm. At the follow-up examination, the examiner had no knowledge of the results obtained at the first examination. The study protocol entailed scanning the near and far walls of carotid bifurcations and of the common carotid arteries (CCAs) in their mid and distal portions. All measurements were made at the time of scanning with the instrument's electronic calipers to the nearest 0.25 mm. Two types of lesions were recorded by the sonographer: intimal-medial thickening and atheromatous plaque. The intimal-medial thickness was defined as the distance between the medial-adventitial interface and the luminal-intimal interface. The intimal-medial thickness was measured on the central portion of a longitudinal B-mode scan visualizing the mid and distal CCA (generally, about 2 cm below the beginning of the dilatation of the distal CCA). The measurements were made on the far wall and the parallelism of the echogenic lines characterizing the interfaces was a necessary condition for choosing the site of measurement. The distribution of intimal-medial thickness in previous studies led us to consider the arterial wall thickness as abnormal if it was greater than or equal to 0.75 mm, and only the presence or the absence of an intimal-medial thickening was recorded by the sonographer. The CCA and carotid bifurcation of both sides were scanned for detection of atheromatous plaques. A localized echo structure encroaching into the vessel lumen was considered to be a plaque if the distance between the medial-adventitial interface and the internal side of the lesion was greater than or equal to 1.75 mm. In view of the characteristics of our B-mode system, this cut point was chosen to avoid any confusion with an intimal-medial thickening, especially in the carotid bifurcation. At each examination, the degree of carotid atherosclerosis was graded into three categories: no atherosclerosis, intimal-medial thickening (when no other lesion was noted in the CCA and the carotid bifurcation), and plaque (with or without intimal-medial thickening of the mid CCA). The intersonographer reproducibility of the degree of carotid atherosclerosis was assessed in 24 subjects scanned by two independent sonographers one day apart (sonographer 1 also performed the B-mode scans in the population study). The \(\kappa\) coefficient was 0.62, indicating that agreement between the two sonographers was substantial (95% confidence interval, 0.37 to 0.87; \(P<.001\)). Hard copies of real-time images were made in 23 subjects by sonographer 1 and reread 2 months later by both sonographers. They were unaware of the results of the real-time reading. The intrareader (sonographer 1) reproducibility was very good (\(\kappa\) coefficient: 0.86; 95% confidence interval, 0.68 to 1), whereas the interreader reproducibility (sonographers 1 and 2) was weaker but remained substantial (\(\kappa\) coefficient: 0.71; 95% confidence interval, 0.47 to 0.95).

Similar clinical information was obtained at both examinations. Body mass index was computed as weight (kg) divided by height squared (m\(^2\)). Blood pressure was measured in duplicate (by a trained nurse and a physician) with a sphygmomanometer in the patient in a supine position after a 10-minute rest. Mean values were used in the statistical analysis. Women were classified as smokers if they smoked at least one cigarette per day and as nonsmokers if they had never smoked or had stopped smoking at the time of examination.

At baseline examination, blood samples were drawn from each subject between 9 AM and 12 PM. Total cholesterol, triglycerides, glucose, high-density lipoprotein (HDL) cholesterol, apolipoprotein A-1 (Apo A1) and apolipoprotein B (Apo B), and fibrinogen were measured according to methods previously described. Low-density lipoprotein (LDL) cholesterol was computed with the Friedewald formula.

Standard procedures from Statistical Analysis Systems software (SAS, Cary, NC) were used for statistical analysis. Women were separated into different subgroups according to the outcome of interest. Thus, the development of new plaques was studied after exclusion of women with plaques at baseline, whereas the regression of plaques was examined in those with plaques at baseline. The development of new intimal-medial thickening was studied in women with normal carotid arteries at baseline after exclusion of those who developed plaques during the follow-up. The regression of intimal-medial thickening was examined in women with intimal-medial thickening at baseline after exclusion of those who showed a progression to plaques during the follow-up. Logistic regressions were used to assess the relations.
between the baseline levels of cardiovascular risk factors and the evolution of carotid atherosclerosis in the various subgroups. Triglycerides and fibrinogen were logarithmically transformed for statistical testing but, for more clarity, means were computed with natural values.

**Results**

Longitudinal changes in the degree of carotid atherosclerosis are shown in Table 1. Globally, a regression was seen in 27 women (8.8%), whereas the development of new atherosclerotic lesions was observed in 114 women (37%). The development of new plaques was seen in 13 women (7.2%) with normal carotid arteries and 15 (14.4%) with intimal-medial thickening at baseline. Among 23 women with plaques at first examination, 5 women (21.7%) regressed to intimal-medial thickening, whereas 1 woman was considered to have normal carotid arteries 2 years later. A progression to intimal-medial thickening was observed in 86 women (47.5%) with normal carotid arteries at baseline. Among 104 women with intimal-medial thickening at baseline, 21 (20.2%) had normal carotid arteries at the follow-up examination.

Predictive factors for development of new plaques were examined by combining women with normal carotid arteries and those with intimal-medial thickening at baseline. In Table 2, women who developed plaques during the follow-up period were compared with those who did not. Significant univariate predictors of development of plaques were smoking and high levels of systolic blood pressure, total cholesterol, LDL cholesterol, and Apo B. The presence of an intimal-medial thickening and high blood glucose levels at baseline was associated with the development of plaques at a borderline significance level. Women who progressed to plaques also tended to be older and to have higher diastolic blood pressure than did women without progression to plaques. No association was observed between progression to plaques and HDL cholesterol, Apo A1, and fibrinogen. Simultaneous introduction of initial intimal-medial thickening, smoking, systolic blood pressure, Apo B, and blood glucose in a multiple regression model showed that systolic blood pressure, smoking, and Apo B remained independent predictors of progression to plaques whereas intimal-medial thickening and blood glucose did not. Further adjustment for age did not consistently modify these results. Introduction of total cholesterol instead of Apo B in the regression model yielded similar findings (P<.05). On the other hand, LDL cholesterol did not remain a significant predictor of progression to plaques after adjustment for smoking, intimal-medial thickening, systolic blood pressure, and blood glucose (P<.13). Women who showed a regression of their plaques (n=6) tended to have a more favorable cardiovascular risk profile at baseline than women with nonregressing plaques (n=17). They were younger (mean±SD, 49.3±2.6 versus 51.9±2.9 years; Wilcoxon test, P<.06), and leaner (body mass index mean±SD, 20.8±1.4 kg/m² versus 23.4±2.5 kg/m²; Wilcoxon test, P<.07) and showed lower diastolic blood pressure (mean±SD, 78.7±6.9 versus 85.3±7.1 mm Hg; Wilcoxon test, P<.07) and triglyceride levels (mean±SD, 53.8±7.9 versus 67.2±14.3 mg/dL; Wilcoxon test, P<.05) than women with plaques at both examinations. Moreover, the mean initial plaque thickness tended to be lower in regressing plaques than in stable plaques (2.0±0.6 versus 2.6±0.8 mm, respectively; Wilcoxon test, P<.07).

Finally, Table 3 shows baseline levels of cardiovascular risk factors according to progression to intimal-medial thickening in women initially free of any carotid lesions and according to regression of intimal-medial thickening in women with intimal-medial thickening at first examination. Age and triglycerides were the only variables significantly associated with the development of intimal-medial thickening. A negative borderline association was also seen with smoking. Total cholesterol, LDL cholesterol, and Apo B tended to be higher in women who progressed to intimal-medial thickening than in those who did not, but not significantly so. In multiple regression analysis, the development of intimal-medial thickening remained significantly associated with age (P<.04) and with triglycerides at a borderline significance level (P<.06) but not with smoking (P<.20). On the other hand, in univariate analysis, low levels of total cholesterol, LDL cholesterol, and Apo B were significantly associated with regression of intimal-medial thickening, whereas age was not. Because of the strength of their interrelations (correlation coefficients

**Table 1. Definition and 2-Year Evolution of Carotid Atherosclerotic Lesions in 308 Middle-Aged Women**

<table>
<thead>
<tr>
<th>Definitions of Carotid Atherosclerotic Lesions</th>
<th>First Examination</th>
<th>No Atherosclerosis (n=104)</th>
<th>Intimal-Medial Thickening (n=159)</th>
<th>Plaque (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial wall thickness of the mid CCA &lt;0.75 mm, no plaques on the CCA and carotid bifurcation</td>
<td>No atherosclerosis (n=181)</td>
<td>45.3% (n=82)</td>
<td>47.5% (n=86)</td>
<td>7.2% (n=13)</td>
</tr>
<tr>
<td>Arterial wall thickness of the mid CCA ≥0.75 mm, no plaques on the CCA and carotid bifurcation</td>
<td>Intimal-medial thickening (n=104)</td>
<td>20.2% (n=21)</td>
<td>65.4% (n=68)</td>
<td>14.4% (n=15)</td>
</tr>
<tr>
<td>Echostucture encroaching into the lumen of the CCA and/or carotid bifurcation with thickness ≥1.75 mm; with or without intimal-medial thickening of the mid CCA</td>
<td>Plaque (n=23)</td>
<td>4.3% (n=1)</td>
<td>21.7% (n=5)</td>
<td>73.9% (n=17)</td>
</tr>
</tbody>
</table>

CCA indicates common carotid artery.
### TABLE 2. Predictors of Development of Carotid Atherosclerotic Plaques in Middle-Aged Women

<table>
<thead>
<tr>
<th>Baseline Risk Factors</th>
<th>Development of Plaques*</th>
<th>Univariate Analysis†</th>
<th>Multivariate Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=28)</td>
<td>No (n=257)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical and ultrasound variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.1† (2.7)</td>
<td>49.2 (2.9)</td>
<td>.126</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 (2.9)</td>
<td>23.0 (2.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135.9 (15.0)</td>
<td>129.0 (13.2)</td>
<td>.013</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84.0 (8.2)</td>
<td>81.2 (8.9)</td>
<td>.123</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>46.4</td>
<td>23.3</td>
<td>.010</td>
</tr>
<tr>
<td>Intimal-medial thickening, %</td>
<td>53.6</td>
<td>34.6</td>
<td>.053</td>
</tr>
<tr>
<td><strong>Lipid variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>236.8 (44.8)</td>
<td>216.8 (38.0)</td>
<td>.012</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>69.4 (11.2)</td>
<td>66.6 (15.3)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>151.3 (40.2)</td>
<td>136.4 (36.1)</td>
<td>.045</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>80.6 (76.2)</td>
<td>67.8 (29.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dL)</td>
<td>172.0 (21.2)</td>
<td>167.9 (25.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>126.3 (40.1)</td>
<td>108.9 (24.7)</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Other variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>101.5 (9.5)</td>
<td>98.8 (7.9)</td>
<td>.091</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>312.9 (63.7)</td>
<td>304.4 (58.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and NS, not significant.

*Significance tests, regression coefficients (b), and standard errors (SE) obtained from logistic regressions.

†Means (standard deviations) unless stated otherwise.

NS P > .20.

## Discussion

The present longitudinal study aimed to describe the rates of development and regression of early carotid atherosclerotic lesions and to determine the predictive risk factors for these changes. Our results suggest that both the development of intimal-medial thickening and small plaques are relatively common in middle-aged women. Altogether, new carotid plaques appeared in 9.8% of the women initially free of plaques and a new intimal-medial thickening was detected in 47.5% of the women initially free of any carotid lesions after a 2-year follow-up period. On the other hand, our results suggest, in accordance with a previous work, that spontaneous regression of early atherosclerotic lesions also may occur since preexisting intimal-medial thickening and plaques were no longer observed in 20.2% and 26.0% of the women, respectively.

Several methodological considerations should be kept in mind before interpreting our findings. First, as the recruitment of the study subjects was made on a voluntary basis, our sample cannot be considered representative of the French middle-aged female population. A self-selection bias leading to an over-representation of women at high risk of cardiovascular disease, and thus to high risk of carotid atherosclerosis progression, could partly explain the accelerated development of intimal-medial thickening and, to a lesser extent, of plaques observed in our study. Moreover, the relatively high proportion of women who were lost to follow-up might have strengthened this selection bias. Examination of baseline characteristics did not reveal, however, any significant differences between women who underwent an ultrasonographic reassessment and those who did not. Second, our results are dependent on the reliability of B-mode ultrasonography for detecting changes in carotid atherosclerosis. The strength of the present study lies in the fact that the intrasonographer variability represents the only source of variability. The intrasonographer reproducibility of the degree of carotid atherosclerosis was 0.62, whereas the interreader and the intrareader reproducibility were 0.71 and 0.86, respectively. It is generally accepted that the major part of variability in B-mode measurements is due to differences between sonographers, whereas the intrasonographer and the intrareader/interreader variability appears smaller. Thus, it is likely that the intrasonographer reproducibility, not assessed in the present study, would have been better than the intersonographer reproducibility. However, misclassifications have certainly occurred in some instances. The lack of precision of our B-mode system and poor visualization of the interfaces (because of anatomic characteristics or obesity) might partly explain misclassifications. We reanalyzed our longitudinal data by computing a coefficient from data given in Table 1. The concordance between the degree of carotid atherosclerosis obtained at first examination and that obtained at follow-up examination was poor (κ, 0.26; 95% confidence interval, 0.17 to 0.34). It signifi-
TABLE 3. Predictors of Development and Regression of Intimal-Medial Thickening in Middle-Aged Women

<table>
<thead>
<tr>
<th>Baseline Risk Factors</th>
<th>Development of Intimal-Medial Thickening*</th>
<th>Regression of Intimal-Medial Thickening*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables</td>
<td>Yes (n=86)</td>
<td>No (n=82)</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.6‡ (2.9)</td>
<td>48.4 (2.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.2 (2.4)</td>
<td>22.8 (3.2)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128.4 (10.4)</td>
<td>127.8 (11.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.9 (6.9)</td>
<td>80.2 (9.0)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>16.3</td>
<td>26.8</td>
</tr>
<tr>
<td>Lipid variables</td>
<td>Total cholesterol, mg/dL</td>
<td>217.9 (35.3)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>67.7 (14.4)</td>
<td>68.0 (15.6)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>135.9 (33.5)</td>
<td>129.4 (35.3)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>71.6 (35.8)</td>
<td>61.8 (22.1)</td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dL</td>
<td>169.5 (24.5)</td>
<td>168.4 (26.0)</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>109.2 (24.6)</td>
<td>103.2 (22.8)</td>
</tr>
<tr>
<td>Other variables</td>
<td>Glucose, mg/dL</td>
<td>99.5 (7.9)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>311.0 (50.7)</td>
<td>296.5 (53.5)</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant; and NE, not entered.

*Development of intimal-medial thickening was studied in women with normal carotid arteries at baseline, after exclusion of those who developed plaques, whereas regression of intimal-medial thickening was studied in women with intimal-medial thickening at baseline, after exclusion of those who developed plaques.

†Statistical tests, regression coefficients (b) and standard errors (SE) obtained from logistic regressions. Multiple stepwise procedure was used for regression of intimal-medial thickening.

‡Means (standard deviations) unless stated otherwise.

§P < .05; †P < .01; NS P > .20.

cantly differed from the k values obtained in the reproducibility studies suggesting that longitudinal changes did not simply reflect random measurement errors. However, systematic errors at any serial examination might have led to a bias in observed changes in carotid atherosclerosis. A training effect is unlikely because similar prevalence rates of intimal-medial thickening and plaques were observed during the first year and the second year of the recruitment period. On the other hand, we cannot exclude the fact that the knowledge of the time of examination by the sonographer might result in an artificially high rate of progression. It should be emphasized, nevertheless, that the follow-up examination was performed without knowledge of the initial degree of atherosclerosis and that relatively high rates of regression were observed. Although these considerations suggest that the extent of this bias is probably low, the rates of progression and regression found in our study need to be taken with caution and confirmed in larger similar populations.

Our rates of carotid disease progression and regression cannot be directly compared with those found in previous studies. First, most previous longitudinal studies were performed either in patients with risk factors for atherosclerosis or clinical symptoms of coronary or peripheral disease or in subjects with asymptomatic neck bruits. A disease progression is more likely in subjects with advanced atherosclerotic lesions than in subjects with a less severe disease.10,11 Second, the rates of disease progression and regression seem to be quite variable according to the methods used to assess carotid atherosclerosis. Most previous studies used either angiography6,11 or duplex scanning or continuous-wave Doppler3,6,10 and gave very conflicting results. B-mode ultrasonography appears a much more sensitive method to detect small changes in early carotid atherosclerosis. Previous ultrasonographic studies provided rates of regression and progression relatively close to those found in the present study. The study of Hennerici et al9 showed that 19% of the lesions observed in 31 patients had regressed (because of reduction or disappearance), whereas 30% had progressed over 18 months. Similarly, the follow-up of 51 patients with carotid atherosclerotic lesions revealed a significant reduction of the plaque score obtained by summing the maximum axial thickness measurements in four carotid segments of both sides in 20% of the subjects and a progression in 20%.12 To our knowledge, only the Kuopio Ischemic Heart Disease Risk Factor study has provided information on longitudinal changes in intimal-medial thickness of the common carotid arteries.13 The mean increase in intimal-medial thickness over 2 years was 0.12 mm in 100
men aged 42 to 60 years. The rate of progression was very high in this Finnish population since 83% of the subjects increased their intimal-medial thickness by at least 0.10 mm, whereas only 9% of them reduced it by at least 10 mm. Technical characteristics of our B-mode system led us to use a qualitative and relatively crude definition of intimal-medial thickening, which prevents comparison of our findings with those of Salonen et al. Because of the imprecision of our measurements, the high rates of change in intimal-medial thickening observed in our study need to be considered with caution. However, they suggest an overall trend for an increase in intimal-medial thickness with time in middle-aged women, which is consistent with that observed in middle-aged Finnish men.

Our study showed that smoking, high levels of total cholesterol (or Apo B), and blood pressure were independent predictors of development of carotid plaques in women initially free of atheromatous plaques and thus confirmed our cross-sectional results(194,149),(800,826). Numerous cross-sectional ultrasonographic studies have reported associations between the severity of carotid atherosclerosis and age, hypertension or high blood pressure, smoking, and an unfavorable lipid profile in both healthy and high-risk populations. On the other hand, very few longitudinal studies have investigated risk factors for progression of carotid atherosclerosis and yielded inconsistent results. In some of these studies, accelerated progression of carotid atherosclerosis was associated with increasing age, hypertension, smoking, high total or LDL cholesterol, whereas these risk factors did not emerge as significant predictors in the other studies. One explanation for the discrepancies between studies lies in differences in populations. Our study investigated very early phases of carotid atherosclerosis in apparently healthy women initially free of any atherosclerotic plaques. On the other hand, previous studies generally examined progression of preexisting atherosclerotic lesions in high-risk populations. Thus, it is likely that potential risk factors such as hypertension, smoking, or hyperlipidemia that have already affected these populations had only a limited influence on further progression of advanced atherosclerotic lesions. It has been suggested that local factors might be more important than systemic factors in the evolution of stenosing plaque. To our knowledge, factors associated with spontaneous regression of small plaques have not been previously studied. Although our results remain inconclusive because of our small sample size, they suggest that a regression might occur for smaller plaques in subjects with a favorable cardiovascular risk profile. These findings support the hypothesis that repair mechanisms involving both local and metabolic factors may take place at the onset of carotid atherosclerosis.

The significance of an ultrasonographically detected intimal-medial thickening is still unclear. This is due partly to the inability of ultrasound methods to discriminate between the intimal and the medial layer of the arterial wall. Although atherosclerosis is recognized as a disorder of the intima, an increase in the intimal-medial thickness has been considered as an early indicator of the atherosclerotic process by several ultrasonographic studies. Associations between increased intimal-medial thickness and enhanced levels of cardiovascular risk factors, the extent of coronary atherosclerosis or an increased risk of myocardial infarction give some support to this assumption. In the present study, we found a borderline association between initial diffuse intimal-medial thickening and the subsequent development of carotid plaques. This association was slightly reduced after adjustment for cardiovascular risk factors. These results are consistent with the hypothesis that common mechanisms underlie both types of lesions which may be considered as successive manifestations of the atherosclerotic process. The observation of an association between initial lipoprotein levels and the regression of intimal-medial thickening (and to a lesser extent the development of intimal-medial thickening) suggests a major contribution of atherogenic lipoproteins in the early changes of the arterial wall. However, other factors may be involved in the development of intimal-medial thickening. Thus, intimal-medial thickening has also been viewed as a physiological adaptive response to mechanical stresses or to age-related structural changes in the arterial wall such as a decrease in the elastin-to-collagen ratio. In accordance with a previous study, age emerged as a major risk factor for development of intimal-medial thickening. Interestingly, no association was found between age and the regression of intimal-medial thickening. This suggests that irreversible changes in the structure of the arterial wall related to aging might be partially responsible for the increase in the intimal-medial thickness. On the other hand, we failed to show any association between blood pressure and either the development or the regression of intimal-medial thickening. This latter result contrasts with the cross-sectional associations previously reported. However, the longitudinal study in Finnish men also failed to detect any association between initial blood pressure and changes in intimal-medial thickness. Our negative finding may be due to a lack of statistical power or to the relatively short duration of follow-up. Another possible interpretation is that high blood pressure might be a consequence rather than a cause of intimal-medial thickening.

Whatever the mechanisms leading to intimal-medial thickening, our study suggests an increased susceptibility to formation of atherosclerotic lesions in women with diffuse intimal-medial thickening of the CCAs. Clearly, this result needs to be confirmed in larger longitudinal studies using more precise and more reliable ultrasonographic measurements of both intimal-medial thickness and plaques. Better knowledge of the factors involved in the development and regression of intimal-medial thickening appears to be of special importance for the prevention of early atherosclerosis.

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