Dose-Dependent Effect of Aspirin on Carotid Atherosclerosis

Carsten Ranke, MD; Hartmut Hecker, PhD; Andreas Creutzig, MD; and Klaus Alexander, MD

Background. Antiplatelet treatment with aspirin is well established as secondary prophylaxis after a transient ischemic attack or minor ischemic stroke, but the effect of aspirin treatment on the course of carotid atherosclerosis is unknown. We investigated the effect of aspirin on the initial stages of carotid atherosclerosis.

Methods and Results. Patients were recruited from a prospective, randomized, double-blind clinical trial to compare two doses of aspirin (900 mg versus 50 mg daily) with regard to restenoses after lower limb angioplasty. Of the 383 patients admitted to the angioplasty trial, 27 patients with 104 small carotid atheroma (<50% lumen narrowing) were examined at entry and after 1 year of aspirin treatment with the use of a high-resolution ultrasound duplex system. Disease progression and regression were defined by a change of maximal plaque area (as measured by longitudinal ultrasound sections) of more than 2 SDs of the method. The change in plaque area was significantly different for the treatment groups: Average plaque size remained unchanged after treatment with 900 mg aspirin daily but increased markedly after treatment with 50 mg aspirin daily (p=0.011). There were significantly more lesions in the 50-mg group showing progression than in the 900-mg group (23 plaques [47%] versus 13 plaques [24%], p=0.025). Ultrasonic disappearance of a lesion was observed only in the 900-mg group in nine cases (seven soft plaques and two ulcerative plaques, p=0.018). The six patients on 50 mg aspirin who continued smoking during the study showed significantly more progression compared with the seven nonsmokers in the 50-mg group (17 plaques [59%] versus six plaques [30%], p=0.038).

Conclusions. The results of our study indicate that aspirin treatment slows carotid plaque growth in a dose-dependent fashion, with a dose of 900 mg daily more efficient than 50 mg daily. (Circulation 1993;87:1873–1879)

Key Words • carotid • artery • atherosclerosis • ultrasound • aspirin

Antiplatelet treatment with aspirin can reduce the incidence of serious vascular events by 25% among patients at high risk of occlusive arterial disease.1 A comparison of high- and medium-dose (1,200 mg versus 300 mg daily)2 and of medium- and low-dose aspirin treatment (283 mg versus 30 mg daily)3 revealed similar clinical effects of the different doses with regard to secondary prevention of vascular events after a transient ischemic attack or minor ischemic stroke.

There is strong evidence that the natural course of peripheral arterial occlusive disease can be slowed under long-term treatment with aspirin,4 but the effect of aspirin treatment on the course of carotid atherosclerosis is unknown. Low doses of aspirin might be advantageous because the synthesis of the proaggregatory thromboxane A2 in platelets is inhibited to a greater extent than the production of the antiaggregatory prostacyclin in the vessel wall.5,6

High-resolution ultrasound duplex system analysis of small carotid atheroma revealed spontaneous progression as well as regression after an 18-month follow-up period.7 In another duplex ultrasound study on patients with inherited hypercholesterolemia, the reduction of carotid plaque volume correlated with low density lipoprotein elimination.8 It was our aim to study the effect of different doses of aspirin on progression and regression of small carotid atheroma.

Methods

Eligible Patients

Patients were recruited from a prospective, randomized, double-blind clinical trial of high versus low-dose aspirin treatment to prevent restenoses of the lower limb arteries after percutaneous transluminal angioplasty. The Low Dose Aspirin Trial on Restenosis After Angioplasty (LARA)* was performed to study the efficacy and side effects of a daily 50-mg dose of aspirin compared with a 900-mg dose. Primary outcome event was the angiographically proven occurrence of restenosis at the angioplasty site; other clinical end points were the occurrence of intolerable side effects, lower limb ischemia due to lesions distant to the angioplasty site, death, stroke, and myocardial infarction. We expected a

*Details will be reported separately and are available from Dr. Ranke.

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Supported by grants from the Bundesministerium für Forschung und Technologie.

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Received June 16, 1992; accepted February 3, 1993.
high prevalence of carotid atherosclerosis in our study patients and decided to investigate prospectively the effect of aspirin on progression and regression of carotid atheroma during the LARA study. Eligibility criteria for both the carotid sonography study and the larger angioplasty trial were stated initially in August 1986. Patients who were eligible for the angioplasty trial had duplex ultrasound examinations after randomization and angioplasty. Patients were invited for a 12-month ultrasonic follow-up examination later when they met the criteria for the carotid sonography study.

Patients with symptomatic peripheral arterial occlusive disease were eligible for the angioplasty study if arteriography revealed stenoses of the iliac or femoral artery or femoral artery occlusions (<10 cm) and if the lesions seemed appropriate for angioplasty after consultation between vascular surgeon and radiologist. Patients with disorders of blood coagulation, gastroduodenal ulcer, or with angioedema or asthma due to aspirin allergy were excluded, as were patients on hemodialysis and patients with reduced life expectancy due to malignancies or severe coronary heart disease.

Patients were recruited for the carotid sonography study after angioplasty, when a high-quality B-scan image of the common carotid artery, the carotid bulb, and the proximal 2 cm of the internal and external carotid arteries could be obtained revealing the presence of small carotid plaques with <50% lumen narrowing. To exclude possible error due to observer variability, only patients from one of the two study centers (Hannover Medical School) were recruited for the carotid sonography study.

Ethical approval was given by the hospital ethics committee. In accordance to the Declaration of Helsinki, all patients gave their written consent after receiving extensive information about the background and purpose of the study by discussion as well as through a printed information sheet.

Randomization and Treatment

Blocked randomization was performed with a block size of 4 using random permuted blocks. Coded aspirin was prepared by the pharmacy, and blinded treatment allocation was obtained by central randomization. The randomization code was kept sealed in numbered opaque envelopes and was unknown to any of the participants in the study. A total of 383 patients were admitted to the angioplasty trial, and 40 patients were assigned for concurrent participation in the carotid sonography study.

Treatment with antiplatelet drugs other than the study aspirin was not permitted; agents improving tissue perfusion (e.g., pentoxifylline) were withdrawn. Accompanying medication was left unchanged during the study and included lipid-lowering drugs in four patients (two in the 900-mg group and two in the 50-mg group), nifedipine (four patients versus three patients), diuretics (two patients versus four patients), and antihypertensive drugs (three patients versus one patient).

Ultrasound Examination

Carotid sonography was performed at entry and again 12 months later by an experienced investigator (C.R.) following a standardized protocol. We used a duplex system with a high-resolution B-scan imaging device (7.5 MHz) combined with a 3-MHz pulsed Doppler (Dias- sonics Inc., Milpitas, Calif.). The lateral resolution is 0.7 mm, and the axial resolution is 0.2 mm. The common carotid artery, the carotid bulb, and the proximal 2 cm of the internal and external carotid arteries were scanned consecutively in a series of longitudinal sections from an anterior to a posterolateral view. When a plaque was detected, it was examined in a series of cross-sectional scans to estimate the angle of interrogation that would lead to a perpendicular longitudinal view at the site of maximal plaque thickness. The transducer then was rotated, and perpendicular longitudinal scans were performed until the plaque thickness appeared maximal on the real-time image. Plaque area was calculated from the plaque circumference on the frozen monitor by the duplex system software.

Reproducibility and precision of plaque area measurements were estimated by performing the scanning procedure twice within 2 days for 15 carotid plaques. The correlation coefficient r for both plaque area measurements was calculated as a measure of reproducibility using linear regression analysis (r = 0.993, p < 0.001). A change in the plaque area of 0.05 cm² (twice SD of the method) or more was used to define progression or regression of each plaque. The standard deviation SD was calculated from the mean variance of the two repeated measurements xᵢ, yᵢ of 15 different plaques:

\[ SD_p = \sqrt{\frac{\sum(x_i - y_i)^2}{n}} \]

According to the criteria of Hennerici et al.,7 lesions were classified with regard to their ultrasound characteristics into fibrous, soft, hard, and ulcerative plaques. Plaque area, morphology, and location were recorded with a real-time image on a videoprinter (Mitsubishi Video Copy Processor P60B).

Of the 40 patients initially assigned for participation in the carotid ultrasound study, 13 patients were withdrawn from the LARA trial (Table 1). Compliance testing was performed 1, 3, 6, 9, and 12 months after angioplasty by marking the study medication with riboflavin (urine fluorescence) and by measurement of platelet aggregation. Duplex system analysis of 27 patients (19 men and eight women; age range, 33–79 years; mean age, 57.6 years) could be performed at entry and after 12 months and revealed a total of 104 plaques.

Statistical Analysis

The statistical program BMDP3V (BMDP Statistical Software, Inc., Los Angeles, Calif.) was used with a microcomputer. The comparison of the two treatment
TABLE 2. Clinical Baseline Characteristics of the Two Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>900-mg Dose (n=14)</th>
<th>50-mg Dose (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, SD)</td>
<td>56.4 (10.2)</td>
<td>58.8 (13.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (71)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (29)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Smokers (by history) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>13 (93)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>During the study</td>
<td>5 (36)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;160 mm Hg (%)</td>
<td>5 (36)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Hyperlipidemia (by history) (%)</td>
<td>7 (50)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Diabetes mellitus (by history) (%)</td>
<td>1 (7)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Hyperuricemia (by history) (%)</td>
<td>2 (14)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Lower limb ischemia (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>12 (86)</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Rest pain</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Ischemic ulcer</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg) (SD)</td>
<td>156 (20)</td>
<td>160 (19)</td>
</tr>
<tr>
<td>Broca-Index†</td>
<td>103 (12)</td>
<td>103 (13)</td>
</tr>
</tbody>
</table>

Values are given as mean.
*Mean (SD) from seven follow-up examinations.
†Calculated from body weight (W) (kg) and height (H) (cm): Broca-Index=[W/(L-100)]100.

Groups was based on the treatment analysis principle: Only the 27 patients with continuous aspirin treatment for 12 months were included in the analysis. The two treatment groups were compared with regard to change in plaque size as expressed by the difference between the plaque area at entry and after 1 year of aspirin treatment. New lesions had zero area at entry, and vanished plaques had zero area after 1 year. A mixed-model ANOVA was used for analysis of individual plaques because more than one observation was contributed by each patient. In addition, two-group t-tests were performed for comparison of change in total plaque area (the sum of all individual plaque area values per patient). For binary variables, a modified \( \chi^2 \) test was used with correction for within-patient dependencies. If only a small subgroup of patients were analyzed or if the event under study had a small probability of occurrence, an exact permutation test based on pairwise comparisons was used because it allows multiple responses per patient. Two-sided tests were performed for analysis of dose effects, and one-sided tests were used for analysis of risk factors.

**Results**

Blocked randomization created balanced treatment groups with regard to clinical baseline characteristics (Table 2) and to the localization and ultrasonic morphology of the carotid atheroma (Table 3). The change in individual plaque size after 1 year of aspirin treatment was significantly different for the treatment groups (\( p=0.011 \), mixed-model ANOVA): Average plaque size remained unchanged after daily treatment with 900 mg aspirin daily but increased markedly after treatment with 50 mg aspirin (Figure 1 and Table 4). The difference in plaque size change between the two groups was 0.05 cm\(^2\) (95% confidence interval, 0.01 to 0.09 cm\(^2\)). The total plaque area was calculated as the sum of all individual plaques per patient (mean ± SD, 2.9±1.8 plaques per patient; range, one to eight). Comparable to the individual plaque analysis, the total plaque area increased markedly in the 50-mg group and remained constant after treatment with 900 mg aspirin daily (Figure 2 and Table 5) (\( p=0.050 \), two-group t-test). Thirty-six plaques (35%) showed progression, 22 plaques (21%) showed regression, and 46 (44%) remained unchanged. Simultaneous progression and regression of disease were observed in eight patients (30%; Table 6). There were significantly more plaques

**TABLE 3. Ultrasonographic Baseline Characteristics of the Two Treatment Groups**

<table>
<thead>
<tr>
<th></th>
<th>900-mg Dose (55 plaques)</th>
<th>50-mg Dose (49 plaques)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid bulb</td>
<td>15 (27)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Common carotid artery</td>
<td>20 (36)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>14 (25)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>External carotid artery</td>
<td>6 (11)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Type of plaque (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft plaque</td>
<td>47 (85)</td>
<td>44 (90)</td>
</tr>
<tr>
<td>Hard plaque</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Fibrous plaque</td>
<td>4 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Ulcerative plaque</td>
<td>3 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total plaque area* (cm(^2)) (SD)</td>
<td>0.53 (0.39)</td>
<td>0.57 (0.41)</td>
</tr>
</tbody>
</table>

*Sum of all plaque area values per patient as measured by longitudinal ultrasound sections.

**FIGURE 1. Scatterplots of individual plaque area values at entry (x axis) and after 1 year of treatment with aspirin (y axis). Zero area was used for new or vanished lesions, respectively. Panel A: 900 mg group (55 plaques). Panel B: 50 mg group (49 plaques).**

*Details are available from Dr. Hecker.*
in the 50-mg aspirin group showing disease progression
than in the 900-mg aspirin group \( p=0.025 \); Figure 3).

At least one risk factor (smoking, hypertension, hy-
perlipidemia, diabetes, hyperuricemia) was recorded in
74% (20 of 27) of our patients. The presence of one or
more risk factors was associated with an increased rate
of disease progression in the 50-mg aspirin group
\( p=0.06; \) Table 7). The most important risk factor with
regard to disease progression was smoking: The six
patients on 50 mg aspirin who continued smoking
during the study showed significantly more progression
compared with the seven nonsmokers in the 50-mg

group \( p=0.038; \) Table 8). The other risk factors accen-
tuated the difference between the treatment groups
with regard to progression and regression of disease.

After 12 months, there were seven new lesions (five
soft plaques and two fibrous plaques) in the 900-mg
aspirin group and five new lesions in the 50-mg aspirin

group (three soft plaques, one fibrous plaque, and one
 ulcerative plaque; \( p=NS \)). Ultrasonic disappearance of
a lesion was recorded only in the 900-mg aspirin group
in nine cases (seven soft plaques and two ulcerative
plaques; \( p=0.018 \)). In both treatment groups, healing of

![Figure 2. Scatterplots of total plaque area per patient at
entry (x axis) and after 1 year of treatment with aspirin (y
axis). Panel A: 900-mg group (14 patients). Panel B: 50-mg
 group (13 patients).](image)

**Table 4. Results of Individual Plaque Area Measurements at
Entry and After 1 Year of Aspirin Treatment**

<table>
<thead>
<tr>
<th>Plaque area</th>
<th>At entry</th>
<th>After 1 year</th>
<th>Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(55 plaques)</td>
<td>Mean (cm²) 0.136 0.136</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD        0.118 0.126</td>
<td>0.078</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI    0.104–0.167 0.102–0.170</td>
<td>−0.021–0.021</td>
<td></td>
</tr>
<tr>
<td>50 mg Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(49 plaques)</td>
<td>Mean (cm²) 0.152 0.207</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD        0.105 0.110</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI    0.122–0.182 0.175–0.238</td>
<td>0.028–0.081</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.

*Plaque area at entry minus plaque area after 1 year.

\( tp=0.011 \) (mixed-model ANOVA, two-sided test).

**Table 5. Results of Total Plaque Area Measurements (Sum of
All Plaque Area Values per Patient) at Entry and After 1 Year of
Aspirin Treatment**

<table>
<thead>
<tr>
<th>Plaque area</th>
<th>At entry</th>
<th>After 1 year</th>
<th>Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14 patients)</td>
<td>Mean (cm²) 0.53 0.53</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD        0.39 0.37</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI    0.30–0.76 0.32–0.75</td>
<td>−0.10–0.10</td>
<td></td>
</tr>
<tr>
<td>50 mg Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(13 patients)</td>
<td>Mean (cm²) 0.57 0.78</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD        0.41 0.67</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI    0.32–0.83 0.37–1.19</td>
<td>0.01–0.40</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.

**Total plaque area at entry minus total plaque area after 1 year.

\( tp=0.050 \) (two-sided \( t \) test for independent samples).

one ulcer crater was observed, with the lesions changed
into soft plaques.

**Discussion**

This is the first prospective, randomized, double-
blind study of the effect of different aspirin doses on
progression and regression of small carotid atheroma.
Our patients were participants in the LARA trial who
had peripheral arterial occlusive disease treated by
percutaneous transluminal angioplasty. The results of
our duplex ultrasound study on a subgroup of these
patients with small carotid atheroma showed that high-
dose aspirin inhibited progression of carotid plaques.

Previous studies on the natural course of nonstenotic

carotid atheromatous lesions using high-resolution
duplex system analysis had shown disease progression
and regression after 6 months in 24% and 10%;\(^10\) and after
18 months in 30% and 19%.\(^7\) The duplex ultrasound
study of Roederer et al.,\(^11\) included medium- and high-
grade carotid stenoses and revealed disease progression
in 25% and regression in only 2% after 12 months. The
proportion of patients who showed progression was not
affected by antplatelet treatment with aspirin or dipyr-
idamole. Subsequent follow-up studies on stenoses of
the carotid artery, including medium- to high-grade
diameter reduction, showed comparable rates of pro-

**Table 6. Numbers of Patients With Progression and
Regression of Small Carotid Atheroma After 1 Year of
Aspirin Treatment**

<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>900-mg Dose of aspirin (14)</th>
<th>50-mg Dose of aspirin (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression and no change</td>
<td>3 (21.4)</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Only progression</td>
<td>1 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>Regression and no change</td>
<td>1 (7.1)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Only regression</td>
<td>1 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>Progression and regression</td>
<td>5 (35.7)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>No change</td>
<td>3 (21.4)</td>
<td>1 (7.7)</td>
</tr>
</tbody>
</table>
Aspirin Treatment and Carotid Plaque Growth

Figure 3. Bar graphs of progression and regression of small carotid atheroma (as defined by a change in plaque area of more than 2 SD of the method) for both treatment groups. *Two-sided \( \chi^2 \) test (modified for than one observation in one patient).

Regression but lower regression rates \( (4%, 5%, 13\) or no regression\(^{14-19} \). Regression of carotid atheroma occurs mainly at an early stage of atherosclerosis, showing dynamic progression and repair.\(^7 \) We observed simultaneous regression and progression in 30% (eight of 27) of our patients with small carotid atheromatous plaques. The occurrence of regression of atherosclerosis in the sense of regression of a manifest plaque remains a subject of discussion,\(^17-20 \) but recent studies revealed again the regression of coronary artery stenoses\(^{21,22} \) and of carotid plaques.\(^8 \) Regression was restricted in our study to soft plaques and ulcerative plaques. Ultrasonic disappearance of an atheroma was observed only in the 900-mg group in nine plaques (\( p=0.018 \)).

The superiority of the higher-dose aspirin regimen in our study with regard to progression and regression of small carotid atheroma is difficult to explain. Low-dose aspirin inhibits proaggregatory thromboxane to a greater extent than the antiaggregatory prostacyclin,\(^5,6 \) and 50 mg/day may be the best dose.\(^23,24 \) On the other hand, in an animal study on the antithrombotic action of aspirin, another antithrombotic effect of aspirin independent of platelet cyclooxygenase inhibition was described that required high doses of 20 mg/kg per day. In addition to its antiplatelet activity, aspirin may affect the course of atherosclerosis, acting as an anti-inflammatory agent at higher doses. The formation of atherosclerotic plaques has some features in common with the inflammatory process,\(^26 \) and the role of macrophages in atherogenesis has been discussed.\(^27 \) In an animal study,\(^28 \) the rate of plaque initiation or progression was reduced after treatment with an anti-inflammatory steroid. An ultrasonographic follow-up study on patients with carotid atherosclerosis revealed a close association of increased white blood cell count with accelerated progression of disease.\(^29 \) Our findings appear to be inconsistent with the results of a large clinical trial\(^3 \) revealing a low dose of aspirin (30 mg) being effective in the secondary prevention of vascular events after a transient ischemic attack or minor ischemic stroke. The reduction of embolism from high-grade carotid stenoses after treatment with low-dose aspirin probably is an effect of thromboxane synthesis inhibition, but higher aspirin doses may suppress carotid plaque growth by mechanisms independent of its antiplatelet effects.

In the presence of risk factors, an endothelial injury leads to migration and proliferation of smooth muscle cells and fibrous plaque formation according to the revised response-to-injury hypothesis.\(^30 \) Important risk factors for carotid atherosclerosis are smoking,\(^11,12,13,29,30,31,32 \) hypercholesterolemia,\(^8,20 \) diabetes mellitus,\(^11,32 \) and hypertension.\(^13,32 \) The presence of risk factors was associated with an increased rate of disease progression in the 50-mg group of our study. After treatment with 50 mg aspirin daily, the patients who had continued smoking during our study showed significantly more disease progression compared with the patients who had stopped smoking.

Our study was not placebo controlled, and the majority of our patients exhibited at least one risk factor. Because life-style changes without medical treatment were able to change coronary atherosclerosis toward regression,\(^22 \) future studies on the course of carotid atherosclerosis should evaluate the effect of improvements in risk factors in comparison to treatment with aspirin. Another possible limitation of our study was the small number of patients who were assigned for participation in the carotid sonography study. The patient-to-patient comparison only approached significance (\( p=0.05 \)), but the additional analysis of individual plaques is justified because eight patients (30%) showed progression and regression simultaneously (Table 6).

Our results are confined to patients with small atheromatous plaques and might not hold true for those with >50% carotid artery stenoses. The relatively high proportion of withdrawals in our study is a possible cause of selection bias because only patients who took aspirin reliably for 12 months were included in the analysis. Most withdrawals were due to noncompliance or gastrointestinal side effects (11 of 13 patients); two patients had vascular events. Both events (stroke and restenosis

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>900-mg Dose of Aspirin (55 Plaques)</th>
<th>50-mg Dose of Aspirin (49 Plaques)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>Progression</td>
</tr>
<tr>
<td>0</td>
<td>13</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>1-4</td>
<td>42</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>3 (15)</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*\( p=0.06 \) (one-sided permutation test*).
of the femoral artery, respectively) occurred in the 50-mg group. Follow-up data on these patients are not available, but their presumably higher rate of disease progression would have increased the difference between both treatment groups if they were included in the analysis.

Our results indicate that the natural course of early carotid atherosclerosis can be slowed under treatment with aspirin in a dose-dependent fashion. A daily dose of 50 mg aspirin would be insufficient in presence of one or more risk factors. It is important to know how low a dose of aspirin would remain clinically effective because higher doses are associated with more gastrointestinal side effects.\textsuperscript{2,3,33} Thus, additional prospective studies on the course of carotid atherosclerosis are needed to estimate the dose of aspirin necessary to slow carotid plaque growth.

Acknowledgments

We thank Prof. J.C. Frölich (Division of Clinical Pharmacology, Hannover Medical School) for randomization and for pharmacological advice, and we thank H.J. Kniffka (Pharmacy, Hannover Medical School) for preparing the aspirin. The following physicians also took part in the study: H.J. Avenarius, L. Caspary, M. Galanski, R. Grote, Ph. Hendrickx, A. Majewski, U. Radeke, P. Rieder, S. Specht, H.H. Wagner (Hannover Medical School), and G. Laska (Zentralkrankenhaus 'Links der Weser,'\textsuperscript{1} Bremen).

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Dose-dependent effect of aspirin on carotid atherosclerosis.
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Circulation. 1993;87:1873-1879
doi: 10.1161/01.CIR.87.6.1873
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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