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Danish Very-Low-Dose Aspirin After Carotid Endarterectomy Trial

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The effect of very-low-dose aspirin as an antithrombotic agent was evaluated blindly in 301 patients who had recently undergone carotid endarterectomy. After randomization, 150 patients received aspirin and 151 received placebo. The two groups were comparable with regard to age, sex, blood pressure, previous cerebrovascular events, and smoking habits. The effect of the study medication on platelet aggregation was measured twice in each patient during the first 2 months and at each follow-up visit; the dose was individually adjusted. In 76% of the patients receiving aspirin, 50 mg/day gave satisfactory platelet inhibition, 13% needed 60 mg/day, 8% needed 70 mg/day, and 3% needed 100 mg/day. Platelet aggregation was found to be inhibited in only 1.2% of the measurements in the patients receiving placebo. Observation during treatment averaged 21 months; total intention-to-treat follow-up averaged 25 months. For the combined outcome events of transient ischemic attack, stroke, acute myocardial infarction, and vascular death, aspirin reduced risk by 11% (95% confidence limits: −38% to 48%, $p>0.1$). Thus, there was no significant effect of very-low-dose aspirin in our trial. (*Stroke* 1988;19:1211–1215)

Antiplatelet therapy with aspirin has gained wide acceptance as prophylaxis against thromboembolism. Even though some studies[1,2] have been unable to demonstrate clinical benefit, an overview[3] of 10 different trials[1,2,4–11] in patients with cerebrovascular disease demonstrated an average risk reduction of 23% for important vascular events such as acute myocardial infarction (AMI), stroke, or vascular death with doses of aspirin ranging from 0.3 to 1.5 g/day.

The optimum dose of aspirin has not yet been determined as most trials have used 1 g or more. However, the UK-TIA Aspirin Trial[10] showed equal effects of 300 and 1200 mg/day, and a study in patients with unstable angina[12] showed a significant effect of 324 mg/day. The lower the dose, the fewer the side effects; therefore, there is good reason to choose the lowest effective dose. Theoretically, a lower dose might even be more effective than a high dose. With very low doses, production of prostacyclin in the vessel wall may be partially preserved,[13] and although the clinical applications of prostacyclin in cerebrovascular disease are still limited,[14–17] its documented ability to reduce platelet aggregation[18] might be important to preserve. The inhibition of platelet cyclooxygenase requires a very low dose of aspirin, which results in near-cessation of thromboxane production, inhibition of platelet aggregation,[19,20] and increase of bleeding time.[18]

Such considerations formed the background for our present trial in which we examined the prophylactic effect of very-low-dose aspirin individually titrated to prevent in vitro platelet aggregation in patients having undergone carotid endarterectomy.

Subjects and Methods

We entered the 301 patients into the trial 1 week to 3 months after carotid endarterectomy for extracranial arterial stenosis, from January 1982 to December 1986. Two centers were involved, with 258 patients recruited from Rigshospitalet and 43 from Aalborg. Inclusion into the study was delayed until 3 months in some patients because some surgeons wanted anticoagulant therapy continued for 3 months.

The inclusion criterion was that patients had undergone elective carotid endarterectomy without sustaining an incapacitating neurologic deficit. Exclusion criteria were place of residence preventing follow-up, allergy to aspirin, necessary medication that affected platelet function, anticoagulation therapy lasting >3 months, previous intracerebral hematoma, dementia (which was anticipated to interfere

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with compliance), and reluctance to participate for any reason.

Interviews and neurologic examinations were performed before and after surgery, 3 months after entry, and every 6 months thereafter. The planned duration of the individual treatment period was 27 months, but participants were encouraged to stay in the trial longer. Any patient in whom the study medication was stopped after 27 months was considered to have completed the trial.

The study medication was prepackaged and coded by Leo Pharmaceuticals, Copenhagen, Denmark. The numbered packages were given to the patients consecutively. The tablets contained either 50 mg aspirin or placebo, and both were designated Arabyl. The patients were instructed to take one tablet daily and were provided with a pillbox having each small space for the pills marked with a day of the week. The patients were instructed to avoid all drugs containing aspirin and nonsteroidal anti-inflammatory drugs. For pain relief paracetamol was recommended.

The doctors and the patients were blind as to study medication, while the laboratory technician had access to the code to evaluate the platelet aggregation results and to decide on dose adjustments.

In each patient, platelet aggregation after stimulation with sodium arachidonate[18] was measured using a Born aggregometer twice during the first 2 months after the start of the study medication and again at each subsequent follow-up visit. If platelet inhibition was <80%, it was measured again 1 week later and the aspirin dose was increased in 10-mg increments until satisfactory inhibition had been obtained. At random, some patients in the placebo group also had their doses adjusted with placebo tablets resembling 10-mg Arabyl tablets.

The events recorded were transient ischemic attack (TIA), amaurosis fugax, retinal infarction, stroke, AMI, vascular death, and nonvascular death; disabling stroke and death were terminating events. Patients who sustained TIA, minor nondisabling stroke, or AMI were encouraged to stay in the trial; however, a number of patients with such events insisted on switching to a known treatment. These patients and patients who discontinued the study medication for other reasons were followed for 1 year according to the intention-to-treat principle.

TIA and amaurosis fugax were defined according to the classification of the Ad Hoc Committee.[21] Minor stroke was defined as an acute neurologic deficit lasting >24 hours but <1 week. Major strokes with deficits lasting >1 week could be either nondisabling or disabling. The criteria for AMI were those recommended by the New York Heart Association.[22] Vascular death was defined as fatal stroke, fatal AMI, or sudden unexpected death in a person without preceding acute illness.

At the time of initiation of the trial, published results of the prophylactic effect of aspirin[1,4–8] were not so convincing that it was considered unethical to withhold the active drug from the placebo group. The trial fulfilled the principles of the Helsinki Declaration II and was approved by the local ethical committee. All patients gave informed consent to participate.

Based on a long-term follow-up study of patients operated on for carotid artery stenosis,[23] the expected event rate for stroke and TIA combined was 12%/yr and the risk of death was 7.6%/yr.

Our intention was to not overlook a 50% reduction in risk with a power $(1-\beta)$ of 0.80 and α of 0.05; this would require 150 patients or 300 patient-years of observation in each group.

The cumulative probability of survival free of events in the two groups was compared using the nonparametric Gehan's (Lee-Desu) test.[24] The various events were analyzed separately and in combinations for the treatment period during which the study medication was actually taken and for the period of intention-to-treat follow-up. If a patient had more than one event, the most serious event (in the order AMI, TIA, amaurosis fugax, retinal infarction, nondisabling stroke, and disabling stroke or death) was considered for analysis. The relative risk reduction was estimated using the proportional hazards model.[25,26]

Results

Of the 301 patients, 150 were randomized to aspirin and 151 to placebo. The sex, previous cerebrovascular events, and presence of risk factors such as claudication, diabetes, hypertension, and current smoking habits are given in Table 1. There was no significant difference between the two groups for any item. Five patients in the aspirin group and four in the placebo group were operated on for "asymptomatic" stenosis, the symptoms being dizziness, tinnitus, and syncope. The remainder had TIA, stroke, or both. The two groups also did not differ with regard to blood pressure, hemoglobin, thrombocyte count, or plasma creatinine and plasma cholesterol concentrations (Table 2). The distribution and severity of extracranial angiographic lesions was similar in the two groups, and there were almost equal numbers of right- and left-sided operations. Bruits over the neck vessels were heard in two thirds of the patients. The average treatment period was 21 months, and the average intention-to-treat follow-up was 25 months.

Dose of Aspirin

The initial aspirin dose of 50 mg/day gave satisfactory platelet inhibition in 76% of the patients, while 13% needed 60 mg/day, 8% needed 70 mg/day, and 3% needed 100 mg/day. In the placebo group, 18% had a dose adjustment. Of 709 measurements of platelet aggregation in the aspirin group, 33 (5%) showed insufficient or no platelet inhibition; after dose adjustment, all aspirin patients eventually obtained satisfactory platelet inhibition. In the placebo group, seven of 597 measurements (1.2%) showed platelet inhibition, indicating that aspirin or

TABLE 1. Distribution of Sex, Previous Cerebrovascular Events, and Presence of Some Risk Factors in Aspirin and Placebo Groups, Danish Very-Low-Dose Aspirin After Carotid Endarterectomy Trial

	Aspirin		Placebo	
	No.	%	No.	%
Sex				
Male	99	66	96	64
Female	51	34	55	36
Previous cerebrovascular events				
Transient ischemic attack	110	73	109	72
Stroke	79	53	74	49
Acute myocardial infarction	23	15	19	13
Risk factors				
Claudication	25	17	37	25
Diabetes	10	7	12	8
Hypertension, by history	57	38	51	34
Smoking	112	75	117	77

a similar drug had been taken; the patients were again instructed to avoid such medication.

Gastrointestinal side effects caused withdrawal from the trial in three patients in the aspirin group and four in the placebo group. The reasons for withdrawal are listed in Table 3. There were slightly more withdrawals in the placebo group. However, when the various reasons for withdrawal were analyzed separately, no single cause was significantly more frequent in the placebo group than in the aspirin group. Altogether, 20% of the subjects stopped taking the study medication before the scheduled time without having sustained an event.

Observed Events

Table 4 gives the number of events occurring during the treatment period in men and women in the two groups. The most impressive difference was in vascular death, for which the placebo group was favored, but not significantly.

Figure 1 illustrates the cumulative probability of surviving without events for individual and combined events. For stroke and for stroke and TIA combined as well as for all vascular events combined there was a trend in favor of the aspirin group during the first 18 months of study medication, after which the difference disappeared; the difference did not reach significance ($\chi^2 = 0.93$, $p = 0.34$). For the entire trial, the estimated risk reduction concerning all vascular events was 11% based on the hazard rate; the 95% confidence interval for this estimate ranged from a 43% risk reduction to a 38% risk increase. The hazard rates, that is, the event rate estimated as [(number of events)/(total observed survival time)] were 0.16 for aspirin and 0.18 for placebo. Separate analysis for women and men yielded a nonsignificant risk reduction of 24% in men and a risk increase of 19% in women.

The intention-to-treat analysis, that is, including the period after stopping the study medication in patients without terminating events, gave almost identical results, with no significant differences between the groups.

TABLE 2. Age, Blood Pressure, Hemoglobin, Platelet Count, Plasma Creatinine Concentration, and Cholesterol Concentration in Aspirin and Placebo Groups at Entry Into Danish Very-Low-Dose Aspirin After Carotid Endarterectomy Trial

	Aspirin ($n = 150$)	Placebo ($n = 151$)
Age (yr)	58.9 ± 8.0	59.1 ± 8.1
Systolic blood pressure (mm Hg)	148 ± 22	150 ± 24
Diastolic blood pressure (mm Hg)	85 ± 12	85 ± 12
Hemoglobin (mmol/l)	8.8 ± 0.8	8.7 ± 0.9
Platelet count ($\times 10^9$/l)	262 ± 63	269 ± 74
Plasma creatinine (mmol/l)	0.12 ± 0.01	0.11 ± 0.01
Plasma cholesterol (mmol/l)	6.6 ± 1.5	6.8 ± 1.5
Plasma triglyceride (mmol/l)	2.0 ± 1.0	2.0 ± 1.3

Values are mean ± SD; normal range (95% confidence interval): creatinine, 0.04–0.13 mmol/l, cholesterol, 3.72–8.25 mmol/l, triglyceride, 0.60–2.20 mmol/l.

Discussion

In this trial, the hitherto lowest dose (50–100 mg) of aspirin as an antiplatelet agent was investigated. It had been suggested that such a low dose might have a more impressive antithrombotic effect than the higher doses used in most studies due to partial preservation of the formation of prostacyclin in the vessel wall. The expectation of a substantial risk

TABLE 3. Reasons for Untimely Cessation of Study Medication in Aspirin and Placebo Groups, Danish Very-Low-Dose Aspirin After Carotid Endarterectomy Trial

Reasons	Aspirin ($n = 150$)	Placebo ($n = 151$)
Anticoagulation	3	5
Treatment with nonsteroidal anti-inflammatory drugs	7	10
Gastrointestinal symptoms	3	4
Other diseases	1	3
Noncompliance	5	7
Other reasons specified for drug discontinuation	5	8
Total	24 (16%)	37 (25%)

Data are number of patients.

TABLE 4. Vascular Events Occurring During Treatment Period, Danish Very-Low-Dose Aspirin After Carotid Endarterectomy Trial

Event	Women		Men	
	Aspirin ($n=51$)	Placebo ($n=55$)	Aspirin ($n=99$)	Placebo ($n=96$)
Transient ischemic attack	8	8	10	12
Stroke	3	5	6	6
Acute myocardial infarction	0	0	0	2
Vascular death	4	0	8	6
All events	15	13	24	26

reduction was reflected in the design of our trial. Eligible patients were limited to those undergoing carotid endarterectomy because they formed a well-examined, fairly homogeneous group with angiographically demonstrated atherosclerotic lesions in whom the likelihood of a causal relation between neurologic symptoms and atherosclerotic disease was high. Further, the risk of thromboembolic events and vascular death had recently been determined in a similar population from one of the same institutions.[23]

The dose of aspirin was selected after titration studies[18,19,27] demonstrated that 80% of patients with cerebrovascular disease obtained satisfactory platelet inhibition with 50 mg/day aspirin, a dose that reduces thromboxane production to <5% of normal values and prolongs bleeding time. To assure that platelet inhibition was obtained in all patients receiving aspirin, platelet aggregation was measured at each follow-up visit. It was thereby demonstrated that platelet inhibition was satisfactory in 95% of the measurements in the aspirin group; 5% of the patients in the aspirin group at some time had insufficient platelet inhibition. However, after instruction and dose correction, all patients receiving aspirin eventually obtained satisfactory platelet inhibition. Only 1.2% of the measurements in the placebo group indicated that the patients had taken platelet-inhibiting drugs. The excellent patient compliance in our trial may to some extent reflect that the patients were aware of our monitoring of their treatment.

The event rate in the placebo group corresponded to that expected from a previous study of the postoperative course after carotid surgery.[23] The preconditions of our trial were fulfilled although the number of person-years observed during treatment was approximately 12% less than intended. For the intention-to-treat analysis, the planned number of person-years was obtained.

The 11% risk reduction in the aspirin group compared with the placebo group was not significant. The true effect of aspirin might be somewhere between a 43% risk reduction and a 38% risk increase; the expectation of a strengthening of the antithrombotic effect by using very-low-dose aspirin was not met. One of our goals was to not overlook a

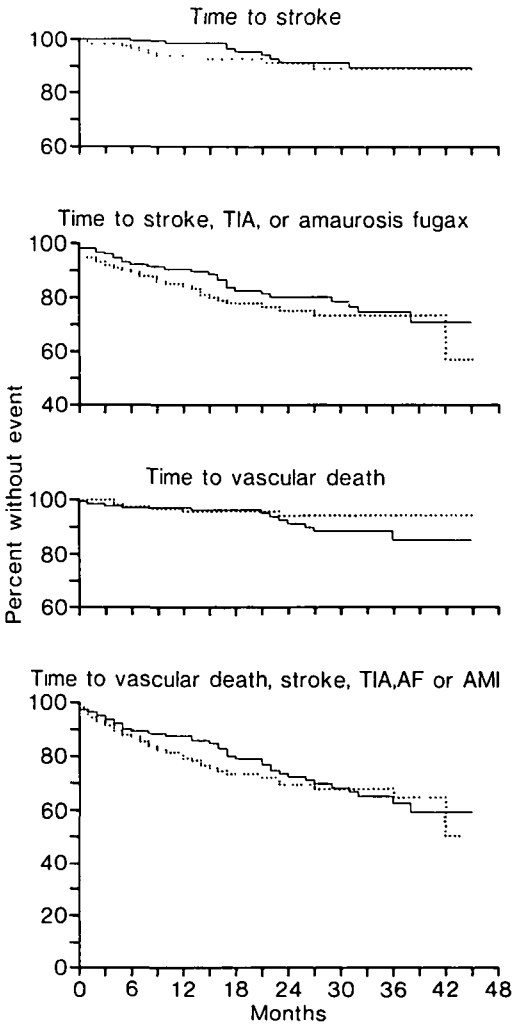

FIGURE 1. *Cumulative probability of survival free of events in 150 patients receiving very-low-dose aspirin (solid lines) and 151 patients receiving placebo (dotted lines) after having undergone carotid endarterectomy, Danish Very-Low-Dose Aspirin Trial. TIA, transient ischemic attack; AF, amaurosis fugax; AMI, acute myocardial infarction.*

risk reduction of 50%, and it may be concluded that a reduction of such magnitude was not obtained.

The platelet-inhibiting effect of aspirin was documented during the treatment period, and there was no waning of the effect with time. The antiplatelet effect of higher doses of aspirin is assumed to be due to the same mechanisms as those we documented, and there are no measurable factors or theoretical arguments to suggest that doses of ≥300 mg should be more effective than a titrated low dose. It is likely that the different dose regimens are equally active but that our sample was too small to demonstrate a significant effect. If the other low-dose aspirin studies that are underway in Denmark, Sweden, and Holland can demonstrate a significant effect, there will be reason to choose the low-dose regimen due to the minimal side effects. From dose-finding studies[18,19] it is known that aspirin at

50–100 mg/day does not cause gastric irritation. In our trial the side effects were minimal, and the fact that we told our patients not to expect any side effects from either the active drug or the placebo may have played a role.

The most severe event, vascular death, was not favorably influenced by aspirin in our trial. The survival curves were identical until 2 years, whereafter more deaths occurred in the aspirin group than in the placebo group; the difference was not significant. There were no fatal strokes; the majority of vascular deaths were due to AMI. The absence of a prophylactic effect against AMI is in contrast to the recently published primary prevention study[28] in which 325 mg aspirin every other day significantly reduced the incidence of fatal and nonfatal AMI.

Among the less severe events (TIA and stroke), Figure 1 shows a tendency to a favorable effect of aspirin in the beginning of the treatment period, but the effect was not significant. This tendency was attributable to men only, which is in concert with the Canadian Cooperative Study[4] and the UK-TIA Aspirin Trial[10] but at variance with the French AICLA Controlled Trial.[5] In the overview study,[3] differentiation between sexes was not documented, but it is urgent to answer the question of whether aspirin at any dose has a prophylactic effect in women.

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