Acetylsalicylic Acid in the Prevention of Stroke in Patients with Reversible Cerebral Ischemic Attacks. A Danish Cooperative Study

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SUMMARY Two hundred and three patients, 148 males and 55 females, who during the last month before admission had experienced at least one reversible cerebral ischemic attack of less than 72 hours duration, were randomly assigned to treatment with either acetylsalicylic acid (ASA) 1000 mg daily (101 patients) or placebo (102 patients). The average follow-up period was 25 months. The two treatment groups were comparable with respect to age, sex, associated diseases, risk factors, number and duration of cerebral ischemic attacks.

No statistically significant differences were found between the treatment groups as to the primary end point: stroke or death (ASA group 20.8%, placebo group 16.7%). Occurrence of transient ischemic attacks during the treatment period was not reduced by ASA treatment, whereas there was a trend suggesting fewer myocardial infarctions in the ASA group (5.9%) than in the placebo group (13.7%). The difference, however, was not statistically significant (p = 0.10).

We were thus unable to demonstrate any favorable influence of ASA 1000 mg daily in patients with reversible ischemic attacks. This study does not, of course, prove that ASA treatment is ineffective in stroke prevention.

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PLATELET-FIBRIN EMBOLI originating from arteriosclerotic lesions in the precerebral arteries are acknowledged to be responsible for a major part of reversible ischemic cerebral attacks. The recognition of the key-role played by platelets in thrombus formation in arteriosclerotic arteries has increased the interest in the use of platelet function inhibiting drugs in the prophylaxis of ischemic cerebrovascular and cardiovascular diseases.

The results of small scale studies and two large cooperative studies suggest a beneficial effect of acetylsalicylic acid (ASA) and other platelet function inhibiting drugs in patients with transient cerebral ischemic attacks.

The present study was begun in 1976, the main objective being to determine if ASA would reduce stroke frequency and mortality in patients with reversible cerebral ischemic attacks. The study was conducted as a cooperative, multicenter, double-blind, randomized clinical trial.

Methods

Participating Institutions

Four neurological departments in Greater Copenhagen (Gentofte Hospital, Glostrup Hospital, Frederiksberg Hospital and Bispebjerg Hospital) and the neurological department of Aalborg Hospital participated in the study. The coagulation laboratory, Municipal Hospital, Copenhagen, was associated in the study. The patients entered the trial from June 1976 through October 1979, and the study was terminated on November 1, 1980.

Eligibility

Eligible for admission to the study were patients who were under the age of 75 and who within one month before admission had experienced at least one reversible cerebral or retinal ischemic attack of less than 72 hours duration. The study group thus comprises cases of transient ischemic attacks (TIA) and reversible ischemic neurologic deficit (RIND). Eligibility was restricted to patients who, according to the Classification of Cerebrovascular Disease, had well-defined carotid or vertebral-basilar attacks. Patients with ill-defined episodes of vertigo, drop-attacks, transient amnesia and loss of consciousness were not accepted.

Exclusions

Reasons for exclusion from the study were: severe residual symptoms from a previous stroke, bad physical condition due to other illness, a history of bleeding peptic ulcer or active peptic ulcer, and hypersensitivity to ASA. Further, we excluded patients who for other medical reasons were given ASA or platelet inhibiting drugs, and those who were referred to carotid surgery.

Randomization and Treatment Regimens

After giving informed consent, patients eligible for admission to the study were randomly assigned to treatment with acetylsalicylic acid (ASA) 1000 mg daily or placebo. ASA was administered once daily as 2 film-coated tablets, each containing 500 mg ASA, to be swallowed whole; and placebo as 2 identically appearing tablets. Randomization, by computer, was de-
signed in such a way that out of every ten consecutive patients in a participating department, five were allocated to ASA and five to placebo. Blindness of doctors and patients was maintained throughout the study period.

Base Line Studies
Patients who were found eligible and accepted participation were interviewed and examined by a neurologist. Information was obtained about the number and dates of ischemic attacks, the presumed vascular territory, as well as the presence of associated medical conditions: hypertension, cardiac disease, peripheral vascular disease, diabetes mellitus, and hematomatous disorders. Patients were questioned about smoking habits and the use of drugs, including oral contraceptives.

A number of laboratory examinations were made including: hemoglobin, hematocrit and blood-cell count. In centers where platelet function studies were accessible, platelet aggregation was examined turbidometrically in vitro by determining the lowest adenosinediphosphate (ADP) concentration that could produce secondary aggregation.11

Cardiovascular examination comprised cardiac auscultation, daily blood pressure recording, electrocardiography and x-ray examination of the chest. Angiography was not mandatory, but aortoc arch angiography and/or direct carotid arteriography were carried out in younger patients in accordance with the usual practice of each participating department.

Before being discharged from the hospital each patient was supplied with a list of platelet-inhibiting drugs to be avoided; this list was also sent to the family physician together with suggestions of analgesics without interference with platelet function. Finally the patient was given a form designed for filling in dates and details of possible ischemic episodes during the trial.

Follow-up Examinations
Follow-up visits took place every month and later at intervals up to six months. Each visit included an interview and examination by the same neurologist, a pill count on left-over medicine as a check on compliance, and questioning about any adverse effect of the drug. Platelet studies were repeated after six months and before the last follow-up visit as a further check of adherence to the study protocol.

Events
The primary end point was stroke or death. A stroke was defined as any episode with neurological deficits lasting more than 72 hours. We distinguished between non-disabling and disabling stroke, depending on the absence or presence of permanent disability that might interfere with clinical evaluation of possible new ischemic attacks. Disabling stroke and death terminated the patients' participation in the trial. Other events as recurrent TIA or RIND and non-fatal myocardial infarction were also monitored.

Withdrawals
Patients who left the study before the scheduled time without having experienced one of the terminating end points were listed as withdrawals.

Statistical Analysis
Comparison of the ASA and placebo group regarding baseline study variables, drug compliance, events during the treatment period, withdrawals and drug side effects was carried out using the Chi-square test and Fischer's exact test. Additional analysis of outcome regarding the end points was performed using life-table methods12 based on Gehan's nonparametric test of difference between survival functions of two groups.13 The risk of stroke or death in untreated patients was estimated to 20% during an average follow-up period of 24 months.14

Results
Admissions
A total of 306 patients were eligible for admission to the study. Ninety-nine of these were excluded for the following reasons: 14 had severe residual symptoms from a previous stroke, 9 were considered unable to participate due to bad physical condition caused by other illness, 8 had a history of bleeding peptic ulcer or symptoms of an active peptic ulcer, 1 patient was known to be allergic to ASA, 15 patients had carotid surgery, 17 were treated with anticoagulants and 7 patients were taking platelet inhibiting drugs for other medical reasons; 10 patients refused randomization, and 18 were not included for various other reasons. Four patients were excluded after randomization because the original diagnosis had to be reconsidered.

After these exclusions, the study group comprised 203 patients: 148 males and 55 females. The mean age was 59 years and the age range 34 to 75 years.

Baseline Comparability of Treatment Groups
Randomization assigned 101 patients to treatment with ASA and 102 to placebo. In the ASA group the mean age was 59 years, the median age 62 years, and the age range 35 to 75 years; in the placebo group the corresponding values were 59, 60 and 34–75 years. The random allocation had produced comparable groups with respect to age, sex, associated diseases and risk factors. A selected number of patient characteristics by treatment groups are presented in table 1.

Six patients in the ASA group and 5 patients in the placebo group gave a history of a previous stroke, but only one of the patients had minor residual symptoms on examination.

About half of the patients in both treatment groups had experienced only one ischemic attack (table 2), 20% had had 2 attacks, 20% from 3 to 10 attacks and 10% more than 10 attacks. Regarding the duration of the attacks about 75% had only experienced TIA, while the remaining 25% had a history of RIND of up to 72 hours duration. The time elapsed from the first attack to admission and the time between the last attack and enrollment were also balanced between the treat-
TABLE 1 Characteristics of the Patients: Age, Sex, Associated Diseases, Smoking Habits and Oral Contraceptives by Treatment Group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ASA (N = 101)</th>
<th>Placebo (N = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>43 (42.6)</td>
<td>48 (47.1)</td>
</tr>
<tr>
<td>60–75 years</td>
<td>58 (57.4)</td>
<td>54 (52.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>77 (76.2)</td>
<td>71 (69.6)</td>
</tr>
<tr>
<td>females</td>
<td>24 (23.8)</td>
<td>31 (30.4)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>11 (10.9)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>History of intermittent claudication</td>
<td>18 (17.8)</td>
<td>12 (11.8)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>28 (27.7)</td>
<td>27 (26.5)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-smokers</td>
<td>23 (24.7)</td>
<td>31 (33.7)</td>
</tr>
<tr>
<td>&gt;15 cigarettes daily</td>
<td>19 (20.4)</td>
<td>25 (27.2)</td>
</tr>
<tr>
<td>Oral contraceptives (females)</td>
<td>9 (37.5)</td>
<td>9 (29.0)</td>
</tr>
</tbody>
</table>

TABLE 2 Characteristics of Ischemic Attacks before Entry: Number, Duration, Time from First Attack to Entry, Time from Last Attack to Entry, Vascular Territory by Treatment Group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ASA (N = 101)</th>
<th>Placebo (N = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of attacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single attack</td>
<td>48 (47.5)</td>
<td>49 (48.0)</td>
</tr>
<tr>
<td>multiple attacks</td>
<td>53 (52.5)</td>
<td>53 (52.0)</td>
</tr>
<tr>
<td>Duration of longest lasting attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA (&lt;15 min)</td>
<td>18 (17.8)</td>
<td>29 (28.4)</td>
</tr>
<tr>
<td>TIA (15–60 min)</td>
<td>22 (21.8)</td>
<td>13 (12.7)</td>
</tr>
<tr>
<td>TIA (1–24 h)</td>
<td>28 (27.7)</td>
<td>36 (35.3)</td>
</tr>
<tr>
<td>RIND (24–72 h)</td>
<td>30 (29.7)</td>
<td>23 (22.5)</td>
</tr>
<tr>
<td>duration uncertain</td>
<td>3 (3.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Time from first attack to entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>70 (69.3)</td>
<td>73 (71.6)</td>
</tr>
<tr>
<td>1–12 months</td>
<td>19 (18.8)</td>
<td>17 (16.7)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>12 (11.9)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>time interval uncertain</td>
<td>0 (0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Time from last attack to entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 week</td>
<td>86 (85.1)</td>
<td>87 (85.3)</td>
</tr>
<tr>
<td>1 week–1 month</td>
<td>14 (13.9)</td>
<td>10 (9.8)</td>
</tr>
<tr>
<td>time interval uncertain</td>
<td>1 (1.0)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Vascular territory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carotid attacks only</td>
<td>82 (81.2)</td>
<td>74 (72.5)</td>
</tr>
<tr>
<td>vertebral-basilar attacks only</td>
<td>13 (12.9)</td>
<td>22 (21.6)</td>
</tr>
<tr>
<td>both carotid and vertebral-basilar attacks</td>
<td>6 (5.9)</td>
<td>6 (5.9)</td>
</tr>
</tbody>
</table>

Follow-up, Compliance, Side-effects and Withdrawals

The median follow-up period in the ASA group was 25 months (range: 1 to 43 months). In the placebo group the median follow-up period was 25 months (range: 0 to 46 months). No patient was lost to follow-up.

Adherence to the study prescription was assessed at each follow-up visit by pill count and calculation of compliance rate for the time interval since last visit.
defined as the number of tablets actually taken by the patient in percentage of the number prescribed. At the final follow-up visit the average discrepancy from 100% was 6% (0–48%) in the ASA group and 5% (0–70%) in the placebo group.

As a further check on compliance platelet aggregation was studied in about half of the patients after six months and at the end of the follow-up period. In the ASA group none of the patients showed platelet hyper-aggregability, 8% had aggregability within the normal range, while 92% revealed inhibition of platelet aggregation consistent with ASA therapy. The pattern of platelet aggregability among the placebo treated patients corresponded to the values found in the baseline studies.

Side effects were reported by 15 patients (14.9%) in the ASA group and 16 patients (15.7%) in the placebo group. Surprisingly, gastrointestinal complaints, including pain, nausea, vomiting and gastrointestinal irritation, were of equal frequency in the two groups: Nine patients (8.9%) in the ASA group and 7 patients (6.9%) in the placebo group. Other side effects reported were exanthema, cutaneous ecchymoses, dizziness, headache and burning feet. Exanthema was seen in 4 patients (4.0%) in both groups, while the remaining side effects were reported by 3 patients (3.0%) in the ASA group and 16 patients (15.7%) in the placebo group.

Fifty-five patients (27.1%) discontinued the trial without having experienced one of the terminating end points: disabling stroke or death. The withdrawals in the ASA group were 20 men and 4 women, with a mean age of 60 years. In the placebo group 17 men and 14 women, with a mean age of 55 years, withdrew from the study. Table 4 presents reasons for withdrawal by treatment groups. At the end of the study the status of patients who withdrew from the trial was evaluated with respect to occurrence of TIA, stroke, myocardial infarction and death.

### TABLE 4: Reasons for Withdrawal from the Trial by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>ASA (N = 101)</th>
<th>Placebo (N = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants added</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Referred for carotid surgery</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bad physical condition due to other illness</td>
<td>2 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelet inhibiting drugs for other medical reason</td>
<td>3 (3.0)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Gastrointestinal side-effects</td>
<td>5 (5.0)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Other side-effects</td>
<td>2 (2.0)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Moved outside study area</td>
<td>0 (0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Failing cooperation</td>
<td>6 (5.9)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Other causes</td>
<td>3 (3.0)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>All causes</td>
<td>24 (23.8)</td>
<td>31 (30.4)</td>
</tr>
</tbody>
</table>

A total of 13 patients (12.9%) in the ASA group and 14 (13.7%) in the placebo group left the study after having experienced one of the terminating end points, disabling stroke or death. The overall percentages for the end points stroke and death are given for both treatment groups in table 5. No statistically significant differences were found in any of the variables. Four patients suffered a fatal cerebrovascular accident; post mortem examination revealed cerebral hemorrhage in 2 patients (one in each treatment group) and cerebral infarction in 2 patients (both in the ASA group). Details of the 38 patients who suffered a stroke or died during the trial are presented in table 6.

Life-table analysis of the occurrence of stroke or death gave results consistent with those of overall percentages (fig. 1 and fig. 2). The highlights of the trial are presented diagrammatically in figure 3.

Recurrent TIA or RIND during the study period were registered with the same frequency in patients allocated to ASA treatment (37.6%) and patients treated with placebo (39.2%) (Chi-square: N.S.; p = 0.93).

Myocardial infarction (fatal and non-fatal) occurred more frequently in the placebo group (13.7%) than in the ASA group (5.9%), but the difference was not statistically significant (Chi-square: N.S.; p = 0.10).

No subgroup analyses were planned from the beginning of the study but the end points stroke or death were analyzed for differences among men and women, patients above and under the age of 60, and patients with one and multiple ischemic attacks (table 7). No statistically significant differences were found.

![Figure 1. Cumulative probability of not having a stroke. Acetylsalicylic acid (ASA) group: N = 101. Placebo group: N = 102. Overall comparison statistics for ASA-placebo difference: p = 0.08.](http://stroke.ahajournals.org/DownloadedFrom)
### Table 5 Occurrence of Stroke and Death by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>ASA (N = 101)</th>
<th>Placebo (N = 102)</th>
<th>Significance for ASA-placebo difference: Chi-square test (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients with non-disabling stroke</td>
<td>12 (11.9)</td>
<td>4 (3.9)</td>
<td></td>
</tr>
<tr>
<td>patients with disabling, non-fatal stroke*</td>
<td>6 (5.9)</td>
<td>7 (6.9)</td>
<td></td>
</tr>
<tr>
<td>patients with fatal stroke*</td>
<td>3 (3.0)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>patients with stroke at all</td>
<td>17 (16.8)</td>
<td>11 (10.8)</td>
<td>0.29 NS</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke deaths</td>
<td>3 (3.0)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>cardiovascular deaths</td>
<td>3 (3.0)</td>
<td>5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>deaths from other causes</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>all deaths</td>
<td>7 (6.9)</td>
<td>7 (6.9)</td>
<td></td>
</tr>
<tr>
<td>patients with stroke or death at all</td>
<td>21 (20.8)</td>
<td>17 (16.7)</td>
<td>0.56 NS</td>
</tr>
</tbody>
</table>

*With or without prior non-disabling stroke during study period.

### Table 6 Characteristics of 38 Patients, Who Suffered Stroke or Death by Treatment Group and Sex

<table>
<thead>
<tr>
<th></th>
<th>ASA males (N = 18)</th>
<th>ASA females (N = 3)</th>
<th>Placebo males (N = 13)</th>
<th>Placebo females (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predisposing factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>history of myocardial infarction</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>history of hypertension</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>cigarette smokers</td>
<td>12</td>
<td>3</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Ischemic attacks before entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carotid attacks</td>
<td>18</td>
<td>3</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>last attack &lt;72 h before entry</td>
<td>18</td>
<td>2</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>longest lasting attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 h</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>1–24 h</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>duration uncertain</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carotid stenosis on angiography</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

At the end of the study a follow-up status was made in the 55 patients who withdrew from the trial. Two patients, both of whom were known to be alive, did not accept the invitation to a follow-up. Five patients reported recurrent TIA, 3 patients had had myocardial infarction, one fatal, and 7 patients had died from other causes. The primary end point stroke or death occurred in six (25%) of the 24 patients who withdrew from the ASA group, and in 5 (16%) of the 31 withdrawals from the placebo group.

**Discussion**

In this study of patients with recent TIA or RIND, prophylactic treatment with ASA 1000 mg daily for an average of 25 months did not reduce the frequencies of stroke and death, when compared with placebo treatment. In fact, these events occurred in 20.8% of the treated patients and in 16.7% of the controls, i.e. a difference of 4.1% in favor of placebo. This does of course not prove that ASA treatment is ineffective. The 95% confidence limits for the above difference (stroke/death rate in placebo group minus the rate in the ASA group) are 6.6% and — 14.8%. This means that, on the basis of our results, it is possible that ASA treatment, given over a two-year period, will prevent stroke or death in a maximum of 6.6% of patients with transient ischemia. The 95% confidence limits can also be expressed in terms of relative risk: when calculations are based on Fieller's theorem, the data are compatible with a maximum risk reduction of 60% for stroke or death, but equally well with a risk increase as high as 110% in such patients.

The failure to demonstrate any benefit of ASA can not be explained by selective factors. The two thera-
stroke or death

Cumulative probability of surviving without event

0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00

• ASA
○ Placebo

Months after entry

0 5 10 15 20 25 30 35


The number of strokes observed in both the ASA

carotid arteries was higher in the ASA group (36%) than in the placebo group (12%). Further, the proportion of patients with normal carotid arteries were higher than that reported in other studies. According to Marshall & Wilkinson, however, the prognosis of patients with normal angiograms is similar to that of patients with demonstrable carotid lesions.

The number of strokes observed in both the ASA

TABLE 7 Sex, Age at Entry, and Number of Attacks by Occurrence of Stroke or Death by Treatment Groups

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Stroke or death group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>placebo</td>
</tr>
<tr>
<td>males (N = 148)</td>
<td>18 (23.4%)</td>
</tr>
<tr>
<td>(N = 77)</td>
<td>13 (18.3%)</td>
</tr>
<tr>
<td>female (N = 55)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>(N = 24)</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>Age at entry</td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>8 (18.6%)</td>
</tr>
<tr>
<td>(N = 91)</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>60–75 years</td>
<td>13 (22.4%)</td>
</tr>
<tr>
<td>(N = 112)</td>
<td>11 (20.4%)</td>
</tr>
<tr>
<td>Number of attacks</td>
<td></td>
</tr>
<tr>
<td>single attack</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>(N = 97)</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>multiple attacks</td>
<td>11 (20.8)</td>
</tr>
<tr>
<td>(N = 106)</td>
<td>11 (20.8)</td>
</tr>
</tbody>
</table>

Total patient population

306 (5 centres)

Total number of patients in trial

207

Ineligible

3

Ineligible

1

ASA 101

Placebo 102

Number of patients in different groups

Withdrawn
Continued
Continued
Withdrawn

Stroke:
Number of patients
17
11

Stroke: % of patients
16.8
10.8

Stroke or death:
Number of patients
21
17

Stroke or death: % of patients
20.8
16.7

FIGURE 3. Result of a randomized trial comparing acetylsalicylic acid (ASA) and placebo in the treatment of patients with reversible ischiatric attacks.
group (17%) and in the placebo group (11%) during a
25 months follow-up period represents an average an-
ual stroke incidence of approximately 7%. This fig-
ure is comparable with those given in several studies of
the natural history of TIA.\(^1\),\(^2\),\(^3\)\(^-\)\(^6\)\(^2\) The mortality in both
treatment groups was nearly 4% per year, which is a
little lower than the mortality for TIA patients found in
a previous retrospective follow-up study carried out in
the same hospitals participating in the present investi-
gation.\(^3\) Cerebrovascular accidents were responsible
for 27% of the deaths and heart diseases for 53%,
figures similar to those found in other series of TIA
patients.\(^2\),\(^2\)

The Canadian cooperative study\(^8\) reported a reduc-
tion of stroke and/or death by 31% in patients treated
with ASA. The frequency of stroke and/or death was
15.9% in patients given an ASA containing study
medicine (ASA — sulfinpyrazone or ASA alone) and
23.1% in the no-ASA treatment groups (sulfinpyra-
zone or placebo). Comparison of the group treated
solely with ASA with the placebo treated group, how-
ever, gives frequencies for stroke and/or death of
18.1% and 21.6% respectively, and this difference of
3.5% is not statistically significant (Chi-square = 0.354, \(p > 0.50\)). We found a stroke and/or death fre-
dency of 20.8% in the ASA group and 16.7% in
the placebo group in a trial of comparable treatment
group sizes and follow-up period. In the Canadian
study the effect of ASA could be demonstrated only in
males, whereas our results did not show any sex dif-
cence. Using a contingency table, we have compared
the stroke or death frequency in our two treatment
groups and in the four treatment groups in the Canadi-
an study, the result being that the frequency seems to
be unrelated to type of treatment and trial (Chi-square
6.714 (5 d.f.; \(p = 0.24\)).

A double-blind trial of ASA 1300 mg daily for the
treatment of cerebral ischemia (the AITI-study) con-
ducted in the United States\(^9\) indicated a favorable influ-
ence of ASA compared with placebo, but the findings
of a trend toward a decrease in stroke or death were not
statistically significant. However, significance in fa-
favor of ASA treatment was found in patients with a
history of multiple (i.e. more than one) TIA. In the
present study we found no such difference.

It appears from several reports that TIA patients
have a higher risk of myocardial infarction than the
population at large, and that cardiovascular disease is
the predominant cause of death in TIA patients.\(^2\),\(^2\),\(^2\)\(^-\)\(^2\)\(^2\)\(^6\)\(^2\) We found a trend toward a reduction of myocardial infarc-
tion in ASA treated patients, although the difference
was not statistically significant. Some large-scale con-
trolled trials of ASA in patients who had recovered
from myocardial infarction have shown the same trend
indicating a favorable influence of ASA, although the
findings were not conclusive;\(^2\),\(^2\)\(^5\)\(^-\)\(^6\)\(^2\)\(^5\) one study showed no
reduction in mortality among patients treated with
ASA.\(^2\)

The dosages of ASA used in previous clinical trials
of ASA in cerebral ischemic attacks, being of the same
magnitude as those used in our study, have been criti-
cized for being too large.\(^2\) ASA influences platelet
aggregability in two ways working in opposite direc-
tions. Firstly, ASA affects platelet cyclo-oxygenase,
thereby preventing generation of the proaggregating
thromboxane \(A_2\). This inhibition is irreversible and
probably lasting for the platelet survival time.\(^3\) Sec-
ondly ASA inhibits the vessel-wall cyclo-oxygenase,
thus countering the formation of prostacyclin, a po-
tent inhibitor of platelet aggregation.\(^2\) It seems, how-
ever, that platelet cyclo-oxygenase is more sensitive to
ASA than vessel-wall cyclo-oxygenase,\(^2\) and that the
recovery of platelet cyclo-oxygenase after ASA treat-
ment is slower than that of the vessel-wall cyclo-oxy-
genase.\(^3\) Burch et al.\(^2\) measured the degree of inacti-
vation of platelet cyclo-oxygenase in 22 volunteers
taking ASA for various periods. Daily doses between
80 and 650 mg resulted in 85% to 95% inhibition of the
enzyme activity measured 24 hours after the last dose.
Therefore, in order not to reduce the effect of vessel-
wall prostacyclin, ASA should be given as antithrom-
botic treatment in the lowest dose needed to inactivate
the platelet cyclo-oxygenase. The many inconclusive
studies of ASA treatment in cerebrovascular and car-
diovascular ischemic disease might have been influ-
enced by the relatively large doses of ASA used in
these trials. In new prospective trials it might be re-
warding to use ASA dosages based on measurements
of the individual dose of ASA needed to inactivate the
platelet cyclo-oxygenase.

Although it might be concluded that ASA adminis-
tered to a heterogenous group of patients with revers-
able ischemic attacks does not reduce the risk of stroke
or death, it is still possible that ASA in smaller dosages
or in combination with other drugs could have a favor-
able influence at least in selected groups of patients
with cerebral ischemic attacks.

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Flow and Neuronal Density in Tissue Surrounding Chronic Infarction

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SUMMARY In 6 cats, cerebral infarction was produced by transorbital occlusion of the left middle cerebral artery (MCA). Five animals developed typical cortical infarcts. Eight weeks later, cerebral blood flow (CBF) was determined by $^{14}$C-iodoantipyrine autoradiography and the number of intact neurons was counted histologically. Two non-operated cats served as controls. Cortical blood flow in the infarcted hemisphere was reduced by 24.6–74.4% when compared to the flow in the contralateral cortex and in controls. Averaged white matter flow was decreased by 39.1%. Regional cortical flow was gradually reduced from parasagittal regions towards the infarct. In the surrounding of the infarct, cortical perfusion was decreased to 24.8 ± 9.7 ml/100 g/min, i.e. 19.7% of contralateral flow. Although the infarcts were circumscribed, hypoperfused regions have been described in the surrounding of an ischemic lesion. A significant linear correlation was found between absolute CBF-values and the number of neurons in areas of the infarcted hemisphere. The homolateral gyrus lateralis had normal neuronal density but flow was reduced by 20%. These findings suggest that the blood flow reduction in tissue surrounding chronic infarcts is due to neuronal cell loss and to functional inactivation caused by damage of afferent fibers.

Reversibility of neurological deficits and extension of the persisting brain damage is dependent on the collateral flow, by which transiently impaired perfusion may be improved and tissue necrosis avoided. The resulting infarcts appear as morphologically well-demarcated necrotic areas with surrounding tissue of preserved structure.

In the acute and subacute stage of focal ischemia, disturbed blood flow has been observed in the center and in the surrounding of an ischemic lesion. A circumscribed hypoperfused region has been described...
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