Controlled Trial of Aspirin in Cerebral Ischemia.
Part II: Surgical Group

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SUMMARY Patients (125) who had carotid transient ischemic attacks (TIAs) and one or more accessible carotid lesions visualized angiographically had reconstructive operations of the carotid artery and were then randomly assigned to aspirin or placebo treatment. They were followed to determine the incidence of subsequent TIAs, death, cerebral infarction, or retinal infarction.

Life table analysis (for 24 months follow up) that eliminated deaths which were not stroke-related revealed a significant difference in favor of aspirin. Because of the small number of patients and the short period of follow up, these results should be interpreted only as consistent with those reported in the initial publication but not conclusive of an aspirin effect in preventing cerebral infarction.

THE FOLLOWING report is the second to be published from the Aspirin in Transient Ischemic Attacks (AITIA) Study, a cooperative clinical trial designed to test the effectiveness of aspirin in vivo in the treatment of cerebral arterial thromboembolism and its consequences. The 2 main objectives of the AITIA study were to determine 1) whether oral administration of aspirin would result in the reduction or prevention of transient cerebral ischemic attacks (TIAs) of the hemispheric type and of transient monocular blindness or partial blindness (amaurosis fugax) and 2) whether oral administration of aspirin would result in a reduction of cerebral infarction and stroke-related mortality.

In the initial publication, details of the study design, criteria for selection of patients, follow up surveillance, and study results for nonsurgical patients were described. This report presents the results of a study of patients who had reconstructive operations of the carotid artery before being randomly allocated to either aspirin or placebo.

Design and Methods

The major design features of the AITIA trial are outlined below.

1. Ten institutions throughout the United States plus a Central Registry-Drug Distribution Center* participated in the study.
2. The drugs compared were aspirin and an indistinguishable placebo, administered at a daily fixed dose.
3. Only subjects having episodes of monocular blindness or cerebral hemispheric type of TIA were eligible for admission to the study. Subjects with ill-defined symptoms, severe neurological deficits, or nonlateralized symptoms only were excluded. It was also a requirement that the patient’s most recent TIA occurred not more than 3 months prior to randomization.
4. Following baseline clinical and laboratory evaluation of the patient, including arteriography, a decision was made by the responsible physician regarding surgical intervention, thereby determining the group into which the patient would be assigned — either medical or surgical. In general, criteria used in selection of patients for surgical treatment varied from institution to institution. The majority of institutions selected for surgery those patients with 1) isolated carotid stenosis on the side appropriate to the symptoms in a patient considered a good surgical risk; 2) ulcerated internal carotid artery atherosclerotic plaques on the side appropriate to the symptoms.

Patients excluded from surgery generally had multiple atherosclerotic lesions in cerebral or cervical arteries.
5. A double-blind randomization took place independently within each group (medical or surgical) and allocation made to either aspirin or placebo. In the surgical group, the study medication (aspirin or placebo) was scheduled to begin 5 days after surgery.
6. Overall mortality, stroke-related mortality, retinal infarction, and nonfatal cerebral infarction were considered as end points. Also, TIA experience, prerandomization and postrandomization, was used for end point construction.
7. Follow up visits were scheduled at 4-week intervals during the first 6 months following dismissal from the hospital and thereafter at 3-month intervals for the duration of the study.
8. Follow up evaluations were done in a “blind” fashion. Drug adherence was monitored by the Central Registry in cooperation with a “control officer” at each participating institution.
9. The first patients were admitted in October 1972; admissions continued until June 1, 1975. The study was terminated formally on November 1, 1975.
10. Each participating institution required an independent review to ensure adequate safeguards for the rights and welfare of the subjects at risk.

*See Appendix

Prepared for the study: Aspirin in Transient Ischemic Attacks. (Participants are listed in the Appendix).
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Results

Study Population

The study protocol defined a surgical candidate as "a patient with 1 or more accessible carotid lesions visualized angiographically, who meets all the other criteria for admission to the study and who has agreed to surgery as the clinical treatment of choice." A nonsurgical candidate was "a patient for whom the clinical decision was made not to operate for at least 1 of the following reasons: 1) the lesion, although in the carotid system on the side appropriate to the symptoms, was surgically inaccessible; 2) the patient refused surgery but agreed to enter the controlled clinical drug trial; or 3) the clinician felt that surgery was not appropriate for reasons which did not exclude the patient from the study." The decision regarding the assignment of a patient to either the medical or the surgical group was strictly based on the clinical judgment of the attending physician. In fact, over half of the patients in the nonoperated (medical) group had lesions that in many centers would have been considered suitable for operation. Study results for the nonoperated individuals were reported in the initial AITIA publication.

Table 1 presents the 2 randomized series (medical and surgical) by "percentage surgical" and institution. Two of the 10 institutions had more patients clinically and surgical) by "percentage surgical" and institution. Variations in "percentage surgical" reflect local judgment, referral patterns, and patient consent.

Random allocation to drug therapy (aspirin or placebo) was done postoperatively in the surgical group. The original design intended that randomization would take place about 5 days after surgery. Randomization following surgery was done because of the suspicion that preoperative administration of aspirin might interfere with intraoperative hemostasis and this observation might indicate whether the subject was receiving aspirin or placebo.

Baseline Comparisons

A total of 130 surgically treated patients from 10 institutions were randomly allocated to either aspirin (650 mg) or placebo tablets twice daily after meals.

Five patients (3 aspirin, 2 placebo) were excluded from the study after undergoing randomization. Two of these individuals had findings suggestive of a brain tumor, 2 had not had a carotid TIA in the 3 months prior to randomization, and 1 patient had an unclassified platelet abnormality which caused him to show inhibition of aggregation on repeated tests even though he was on no drugs. In each instance, the Central Registry made the decision to exclude the patient after consultation with the principal investigator who had admitted the patient.

Table 2 presents (by treatment category) the numbers and percentages of patients with selected baseline findings. In the surgical group, there were 65 persons assigned to aspirin and 60 to placebo. Randomization produced approximate comparability for all relevant variables. Definitions of each of the variables may be found in the initial AITIA report.

The study groups can be demographically characterized as age 55 years or older, white, and male. Symptoms of cerebrovascular disease were of relatively recent origin and characterized by multiple TIAs with a history (proximate to randomization) of hemispheric events and cardiovascular disease.

Not all of the patients were randomized to the study drugs exactly 5 days after surgery; however, 60 to 70% were randomized within 1 week of surgery.

Variable 20 (table 2) indicates the number of patients who had been on platelet antiaggregant drugs prior to admission to the study. As mentioned in the previous report, this variable was interpreted differently among the participating institutions. Some investigators checked this item "yes" if the patient took aspirin for an occasional headache or if the patient had taken 1 or 2 aspirin just before entering the hospital. The Central Registry requested details of doubtful cases and included only those individuals who were taking a platelet antiaggregant on a regular basis before admission to the study. This reduced the numbers to 6 in the aspirin group and 9 in the placebo group.

The only variable in table 2 with any tendency toward imbalance was variable 12, History of Peripheral Vascular Disease. However, the difference in distribution between the aspirin and placebo groups is not statistically significant at the 5% level (0.05 < P < 0.10), and this trait is a concomitant of the other cardiovascular categories. The remaining variables were well balanced between the 2 drug groups, indicating that the randomization process had produced roughly homogeneous groups for comparison.

Carotid Lesions

A radiologist at each institution reviewed the arteriograms and classified each lesion according to degree of stenosis (less than 50%, 50 to 99%, or occlusion) and the appearance of the atheromatous lesion as smooth or ulcerated. Following surgery, the pathological specimen was described according to 1 or more of the following characteristics: appearance of the lesion (smooth plaque, ulcerated plaque, atherothrombotic plaque, intimal fold, or ulcer with cholesterol material only) and the nature of the throm-
aspirin, if present (white thrombus, red thrombus, or aminated mixed thrombus).

In the aspirin group, 70 carotid operations were performed on the 65 patients (5 had bilateral surgery). In 54 instances (77%), there was agreement between the radiologist's assessment of the lesion and that of the surgical pathologist. In most of the 16 cases where there was disagreement, there were ulcerated lesions described by the pathologist which the radiologist had categorized as "smooth." Such a discrepancy may occur when an ulcer is covered by a thrombus, resulting in a smooth appearance on the X-ray.

In the placebo group, 68 carotid operations were performed on the 60 patients (8 had bilateral surgery). In 41 instances (91%), there was agreement between the radiologist's assessment of the lesion and that of the surgical pathologist. Again, in 5 of the 6 cases where there was disagreement, the pathological specimens were noted to be roughened or ulcerated although the radiologist had classified them as "smooth."

**End Point Results**

The absolute end points were mortality, cerebral infarction, and retinal infarction. If a retinal infarction or a nonfatal cerebral infarction occurred, the patient was withdrawn from the study so that therapy of the physician's choice could be considered. Nonfatal cardiovascular events, such as myocardial infarction, were not considered as end points. Specific clinical details for each patient reaching an absolute end point within 24 months after randomization are presented in tables 3 and 4. Table 3 gives a description of each patient (8 aspirin, 8 placebo) by sex, race, age, type of end point event, time of occurrence of event, and follow up life table methods. Table 4 presents a complete 24-month life table for each treatment group. This table provides actuarial estimates of the cumulative probability, Q, of the occurrence of an absolute end point at the end of 6, 12, 18, and 24 months following randomization. The ratio (placebo/aspirin) of the cumulative probabilities decreased from 2.24 at 6 months to 0.83 at 24 months. The differences observed between the aspirin and placebo groups are not statistically significant at the 5% level.
It is of interest to examine the type of end point events reported in the aspirin and placebo groups (table 3). There were 8 patients who reached an absolute end point within 24 months in the aspirin group and also 8 in the placebo group. All 8 of the end points among the placebo patients were brain infarcts and 6 of these occurred within 10 months after randomization. Among the aspirin treated patients, 6 of the 8 end points were cardiovascular deaths and these tended to occur during a later time period (4 of them between 11 and 24 months of follow up).

The reason for this difference is not known. It can be postulated that aspirin has an effect on cerebrovascular disease and that those individuals taking aspirin did not suffer strokes but succumbed (at a later time) to their cardiac problems, perhaps as a consequence of arrhythmia which one would not expect to be affected by aspirin.

Several observations may help to explain the unusual split of cardiovascular mortality (6 aspirin, 0 placebo) in the surgical group. At baseline, the 2 treatment groups were balanced on percentages of the patient population with histories of angina, myocardial infarction, and peripheral vascular disease. However, on comparing the treatment groups by cardiovascular risk factors at 12 months postrandomization, it was apparent that the 2 groups were no longer balanced.

More placebo patients with risk factors had experienced end point or withdrawal. This left the aspirin group with a higher percentage of persons with cardiovascular risk factors. For example, at 12 months follow up, 29.3% of the remaining aspirin patients had a history of peripheral vascular disease versus 12.5% of placebo patients. A history of angina was 24.2% versus 10.3%; previous myocardial infarction was 17.1% versus 10.3%. Because of this disproportion, the aspirin group would be expected to have more cardiovascular deaths during the later months of the study.

Also, there was an imbalance in the numbers of cases at risk beginning at month 12 in the life table. At that point there were 41 aspirin cases and 32 placebo cases still at risk. This differential could also be a factor contributing to the observed mortality split.

Third, correlated to the use of absolute end points (which included both fatal and nonfatal events), the exact number of cardiovascular deaths within 24 months of randomization cannot be ascertained. There was no study requirement for follow up beyond withdrawal. (See section on Withdrawals for details.) In spite of a priori efforts to obtain additional follow up after end
### Table 4: Further Information on Same Patients Listed in Table 3

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Placebo</th>
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<td><strong>Bilateral ulcerated</strong></td>
<td><strong>Bilateral ulcerated</strong></td>
</tr>
<tr>
<td>1. B ♂ 48</td>
<td>1. W ♂ 52</td>
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<td>2. W ♂ 54</td>
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<td>3. W ♂ 43</td>
<td>3. W ♂ 69</td>
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<td>4. W ♂ 67</td>
<td>4. W ♂ 77</td>
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<td>5. B ♂ 56</td>
<td>5. W ♂ 97</td>
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<td>7. W ♂ 63</td>
</tr>
<tr>
<td>8. W ♂ 66</td>
<td>8. W ♂ 63</td>
</tr>
</tbody>
</table>

**Aspirin**
- Only on side appropriate to symptoms
- Left hemisphere infarct. Bilateral symptoms originally
- Side opposite surgery. No lesion of carotid on side of retinal infarct.

**Placebo**
- Bilateral ulcerated
- Left hemisphere infarct. Bilateral symptoms originally
- Side opposite surgery. No lesion of carotid on side of stroke.
- Side opposite surgery. Had old stroke on this side.

### Notes
- *Appropriate* refers to carotid artery ipsilateral to the hemisphere or eye from which the symptoms on admission are presumed to originate.

### Table 5: Total Mortality, Nonfatal Cerebral and Retinal Infarction for 185 Patients by Treatment Modality Summarized in an Actuarial Life Table

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<th>Months post-randomization</th>
<th>At risk at start of interval</th>
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<th>Placebo</th>
<th>Events during interval</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Proportion having event during interval</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Cumulative proportion surviving event-free</th>
<th>Aspirin</th>
<th>Placebo</th>
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Total: 8, 8
point or withdrawal on all cases, the data remain incomplete. The vital status at 24 months is definitely known for 34 (52%) of the original 65 aspirin patients and for 28 (47%) of the 60 placebo patients.

It was documented that 2 additional patients from the placebo group and 1 from the aspirin group died of cardiovascular causes within the 2-year period. These deaths occurred 2, 11, and 14 months after reaching an end point or withdrawal from the study.

These 3 factors discussed above are evidence consistent with the hypothesis of no real difference in the risk of cardiovascular mortality between the treatment groups.

If we reconstruct a life table of absolute end points by eliminating deaths from causes other than cerebral or retinal infarction, then a significant difference in favor of aspirin emerges. Table 7 presents such an analysis. The ratio (placebo/aspirin) of the cumulative probabilities of a fatal or nonfatal cerebrovascular event decreases from 4.75 at 6 months to 3.03 at 24 months. The cerebrovascular end points are unequivocal and the majority of withdrawals were for reasons unrelated to cerebrovascular disease. The small numbers of patients and the short time of follow up require that the results be interpreted as not conclusive of an aspirin effect in preventing cerebral infarction.

Since the primary objective of this investigation was to determine whether the oral administration of aspirin would result in a reduction of carotid transient ischemic attacks, a second class of end points was used to evaluate the patient's experience postrandomization. Each patient's experience during the first six months of follow up was categorized as "favorable" or "unfavorable" depending upon (1) the number of TIAs reported (2) the occurrence of either cerebral or retinal infarction, and (3) mortality.

<table>
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<th>Time in months</th>
<th>Treatment group</th>
<th>Q</th>
<th>Standard error</th>
<th>Q</th>
<th>Standard error</th>
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<td>Aspirin N = 65</td>
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<td>0.075</td>
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Chi-square test of association over all intervals.

\[ \chi^2 = 4.74, \, 1 \, \text{d.f.,} \, P = 0.03. \]

An outcome was considered "unfavorable" if: 1) the patient died during the first 6 months of follow up, or 2) the patient survived the first 6 months but experienced a cerebral or retinal infarction during that time period, or 3) the patient survived and did not have a cerebral or retinal infarction during the first 6 months but the number of TIAs during that time was greater than or equal to the number of TIAs reported in the 3 months prior to randomization. All the remaining patients who completed 6 months of follow up were classified as "favorable." Subjects who did not complete the full 6 months of observation were labeled "less than 6 months follow up."

The 6-month versus 3-month period was used for classification purposes for the following reasons: 1) the patients were seen monthly each of the first 6 months and, thus, this period provided a uniform reporting interval for both the aspirin and placebo treatment groups; 2) a 50% reduction in TIAs within 6 months is required to judge a treatment successful; and 3) the analysis is easily reproducible for comparison with similar studies. The classification scheme described above is also attractive since in it each patient serves as his own control. The classification of

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Treatment group</th>
<th>Q</th>
<th>Standard error</th>
<th>Q</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Aspirin N = 65</td>
<td>0.016</td>
<td>0.018</td>
<td>0.076</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Placebo N = 60</td>
<td>0.016</td>
<td>0.016</td>
<td>0.123</td>
<td>0.048</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>0.016</td>
<td>0.016</td>
<td>0.185</td>
<td>0.061</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>0.061</td>
<td>0.047</td>
<td>0.185</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Chi-square test of association over all intervals.

\[ \chi^2 = 4.74, \, 1 \, \text{d.f.,} \, P = 0.03. \]
patients into favorable or unfavorable clinical outcomes was accomplished by a consulting physician at the Central Registry.

Table 8 presents the results of the clinical classification procedure. As observed in the life tables, there was an excess of absolute end points reported within the placebo group during the first six months. However, the use of a 6-month reporting period minimizes the influence of cardiovascular deaths on the total aspirin-placebo comparison. (There was only 1 cardiovascular death in the aspirin group during the first 6 months.) There is a difference of cases (8 placebo versus 4 aspirin) classified as unfavorable by the criterion of excessive ratio of TIAs. Table 9 gives the specific numbers of TIAs for the 8 placebo and the 4 aspirin patients who experienced sufficient TIAs to be labeled as unfavorable. As indicated in table 8, not all of the individuals could be observed for the complete 6-month reporting period or to the occurrence of a clinical end point. There were 13 of 65 patients (20.0%) in the aspirin group and 11 of 60 patients (18.3%) in the placebo group who did not complete 6 months of follow up. Excluding those who did not have 6 months of follow up, the clinical outcomes indicated that 6 of 52 (11.5%) cases in the aspirin group and 12 of 49 (24.5%) in the placebo group were classified as unfavorable. Although the observed difference is not statistically significant at the 5% level, the result is consistent with the earlier finding reported for nonsurgical patients. Among the nonsurgical patients there was a similar differential — the percentage of aspirin treated patients (in both single and multiple attack groups) classified as unfavorable was slightly in excess of half of that reported for the placebo groups. However, in the surgical group, the absolute level of unfavorable outcomes is about half of the percentage of unfavorable cases reported for the nonsurgical group. This differential may reflect the independent effect of surgery. There may also have been other factors, such as patient selection, accounting for the difference. This study was not designed to test the efficacy of surgical versus medical therapy. Each group was randomized independently.

**Drug Compliance**

At each follow up visit, the following steps were taken in order to assess the patient's adherence to the study drug regimen: 1) interview and questioning by a neurologist, 2) review of patient's daily diary for other drugs taken concurrently, 3) platelet aggregation test.

### Table 10: Clinical Outcomes by Institution and Treatment Group

<table>
<thead>
<tr>
<th>Institution number</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favorable</td>
<td>Unfavorable</td>
<td>Other (Percentage unfavorable)</td>
</tr>
<tr>
<td>01</td>
<td>7</td>
<td>0</td>
<td>4 (0.0)</td>
</tr>
<tr>
<td>02</td>
<td>3</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>03</td>
<td>4</td>
<td>2</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>04</td>
<td>2</td>
<td>0</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>05</td>
<td>8</td>
<td>0</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>06</td>
<td>4</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>07</td>
<td>1</td>
<td>2</td>
<td>0 (66.7)</td>
</tr>
<tr>
<td>08</td>
<td>1</td>
<td>0</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>09</td>
<td>8</td>
<td>1</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>1</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>6</td>
<td>12 (11.3)</td>
</tr>
</tbody>
</table>

1Percentage unfavorable = unfavorable/(favorable + unfavorable) × 100.

Table 11 presents the treatment groups classified by clinical outcome and history of TIA symptomatology. Within both the single and multiple attack groups, the percentage of aspirin treated patients classified as unfavorable is about half of that reported for the placebo groups. Although the results are not statistically significant, they are consistent and support the earlier findings for nonsurgical patients. Among the nonsurgical patients there was a similar differential — the percentage of aspirin treated patients (in both single and multiple attack groups) classified as unfavorable was slightly in excess of half of that reported for the placebo groups. However, in the surgical group, the absolute level of unfavorable outcomes is about half of the percentage of unfavorable cases reported for the nonsurgical group. This differential may reflect the independent effect of surgery. There may also have been other factors, such as patient selection, accounting for the difference. This study was not designed to test the efficacy of surgical versus medical therapy. Each group was randomized independently.

### Table 11: Clinical Outcome 6 Months Following Randomization by Treatment Group and History of Previous TIAs

<table>
<thead>
<tr>
<th>History of TIA attacks</th>
<th>Single attack</th>
<th>Multiple attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td>(15.4)</td>
<td>(33.3)</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>(84.6)</td>
<td>(66.7)</td>
</tr>
<tr>
<td>Less than six months</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>
4) urine or blood serum salicylate level, and 5) pill count of leftover or unused medication.

Since the platelet aggregation test was probably the most reliable check on compliance, the result of each follow up test was recorded at the Central Registry but was not known by the attending physician.

In the aspirin group of 65 patients, a total of 284 platelet aggregation tests were done during the first 6 months of the study. Some subjects reached end points during that period, were lost to follow up or withdrawn for a variety of reasons, so each of the 65 persons did not have a total of 6 tests. Of the 284 tests recorded, 266 showed platelet aggregation inhibition (aspirin response). Three more tests were recorded as "equivocal," indicating some inhibition of platelet aggregation but perhaps not to the extent expected for a patient on a daily intake of 1300 mg of aspirin. However, if these 3 tests are included as showing some aspirin response, 269 tests (of a total of 284 done) revealed that patients were complying by taking their study drug.

In the placebo group of 60 patients, a total of 271 platelet aggregation tests were done during the first 6 months of the study. Of these, 219 tests revealed a normal response, i.e., there was no inhibition of platelet aggregation. The results of the platelet aggregation tests were also related to compliance in the following manner. Table 12 shows the number of patients having an aspirin response 100% of the time. The percentages are graduated down to the zero level, at which point there were 28 patients receiving placebo who never showed any aspirin response and no patients taking aspirin who never showed an aspirin response. The patients (4 aspirin, 3 placebo) not subjected to laboratory examination (listed in table 12 as "not tested") were primarily those who reached an end point or were withdrawn before their first follow up visit. In others where an end point or withdrawal occurred early, follow up laboratory work was accomplished and reported.

There were 51 patients in the aspirin group (78.5%) who always showed an aspirin response. There were 4 patients receiving placebo who always had an aspirin response on platelet aggregation testing. Three of these patients had had only 1 test done before end point or withdrawal and the fourth patient had had 2 tests. Two of these cases showed no urine salicylate and 2 showed urine salicylate present. Three of these patients were taking other medications in addition to the study placebo. None of the concurrent medications was on the list of drugs known to influence platelet aggregation, but future studies may reveal that such an effect exists.

Table 12

<table>
<thead>
<tr>
<th>Percent aspirin response</th>
<th>Aspirin (Percent)</th>
<th>Placebo (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>51 (78.5)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>75–99</td>
<td>8 (12.3)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>50–74</td>
<td>0</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>25–49</td>
<td>2 (3.1)</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>1–24</td>
<td>0</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>Not tested</td>
<td>4 (6.1)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Total</td>
<td>65 (100.0)</td>
<td>60 (100.0)</td>
</tr>
</tbody>
</table>

Reported Adverse Reactions to Medication

Four patients taking aspirin and 1 taking placebo withdrew from the study because they felt ill on the medication. Symptoms included stomach upset, diarrhea, and a "shaky" feeling. None of these cases showed positive stool guaiac tests. Three of these individuals from the aspirin group who had abdominal complaints had a remote history of peptic ulcer on admission to the study.

Among the aspirin group of 65 subjects, a total of 16 patients had positive stool guaiac tests on 1 or more examinations during the follow up period, while 7 persons from the placebo group had at least 1 positive test.

Five patients receiving aspirin had evidence of hemorrhagic complications or the development of a peptic ulcer which, in some cases, appeared to be related to the study medication. The following is a brief description of these individuals:

Case 1. A 56-year-old white male had skin ecchymoses noted during the routine follow up visit at 9 months. The study medication was discontinued for 1 week and then resumed without recurrence of the ecchymoses during an additional 17 months of follow up. His physician felt that the ecchymoses were due to ingestion of a laxative containing phenolphthalein.

Case 2. A 48-year-old white male was withdrawn after 12 months of follow up because of upper gastrointestinal hemorrhage. This was sudden and severe without warning symptoms and required transfusions and hemigastrectomy. There had also been an increase in alcohol intake before the hemorrhage. At 23 months follow up the man was doing well.

Case 3. A 46-year-old white female was withdrawn at 20 months of follow up after admission to a hospital with a stomach ulcer. She gave no history of peptic ulcer when she entered the study, but had had several positive stool guaiac tests. At 30 months follow up she was working and was neurologically intact.

Case 4. A 56-year-old white male was withdrawn at 22 months of follow up because of upper gastrointestinal bleeding. A diagnosis of diffuse gastritis and duodenitis was made and he was advised to avoid aspirin.

Case 5. A 60-year-old black male was withdrawn at 2 months of follow up because he developed a duodenal ulcer. He had given no history of ulcer on admission to the study. He had no further TlAs or other evidence of cerebrovascular disease over 27 months of follow up.

None of the patients allocated to placebo had problems with bleeding or the development of a peptic ulcer.
Withdrawals

In addition to the patients who experienced an absolute morbidity or mortality end point as described previously, other conditions permitted patients to be withdrawn from the study. These conditions are listed below:

1. Excessive TIAs.
2. Possible adverse reaction to study medication.
3. Lost to follow up.
4. Refusal or inability to cooperate by returning for follow up visits.
5. Failure to take study medication for a period of 6 weeks.
6. Other serious intercurrent medical problems.

Patients who did not complete 6 months of observation because an excessive number of TIAs (condition 1, above) necessitated early withdrawal were classified as unfavorable outcome.

Other individuals (13 aspirin, 11 placebo) who were withdrawn before completing 6 months of observation (conditions 2 through 6 above) were considered as being unclassifiable regarding favorable or unfavorable status and were listed on table 8 as “Less Than 6 Months Follow up.”

Patients who experienced recurrent TIAs during the follow up period were not uniformly withdrawn. The decision regarding the advisability of continuing such persons in the study was made by the “blinded” principal investigator at each institution. In most instances, patients were retained in the study. Over the 37 months of the controlled trial, among the surgically treated patients, 1 patient in the aspirin group and 3 patients in the placebo group were withdrawn because of what was considered to be an excessive number of TIAs. In each case, the principal investigator felt that, in the patient’s best interest, he should be withdrawn so that medical or other surgical therapy of the physician’s choice could be considered.

The patient who had been on aspirin was withdrawn at 1 month because of excessive TIAs and put on a coumarin-type anticoagulant. He was still on the anticoagulant at 20 months and was doing well.

Two of the patients who had been taking placebo were put on aspirin after withdrawal because of excessive TIAs. The information after withdrawal is sketchy for the first of these persons, but the second individual took aspirin for 5 months without relief of her TIAs. At that point, aspirin plus dipyridamole was tried and she has been asymptomatic for a period of 18 months. The third placebo patient who was withdrawn from the study because of excessive TIAs had a second carotid operation after withdrawal and was then put on aspirin. He continued on aspirin for 38 months, at which time he suffered a fatal myocardial infarction.

Four patients (2 aspirin, 2 placebo) had nonfatal myocardial infarctions during the study. Three continued uninterrupted on their allocated study medications, and 1 patient was withdrawn because his physician preferred to prescribe coumarin-type anticoagulant therapy.

Conclusions

The results for a group of patients who had reconstructive operations of the carotid artery before being randomly allocated to either aspirin or placebo are reported. The random allocation method produced homogeneous groups of aspirin and placebo (surgical) patients for analysis.

Based on analysis of the surgical group, the following conclusions were reached:

1. Life table analysis of absolute end points (mortality, cerebral infarction, and retinal infarction) for 24 months follow up did not reveal a statistically significant differential between the aspirin and placebo treatments.
2. Life table analysis that eliminated deaths which were not stroke-related revealed a significant difference in favor of aspirin. However, it must not be inferred from this that aspirin prevents stroke. The small numbers of patients and the short period of follow up do not permit the conclusion that aspirin has an effect in preventing cerebral infarction.
3. When the occurrence of carotid transient ischemic attacks during the first 6 months of follow up was also taken into consideration, analysis revealed a trend in favor of aspirin although the observed difference was not statistically significant at the 5% level. This result was consistent with that reported earlier for medically treated patients.
4. Especially interesting was the finding that all 8 placebo patients reaching an absolute end point within 24 months had brain infarcts as end point events. Among aspirin patients, there was 1 cerebral infarct, 1 retinal infarct, and 6 cardiovascular deaths.
5. In the surgical treatment group, the absolute level of cases having an unfavorable outcome was about half of the percentage of unfavorable cases reported for those treated medically only. This differential may reflect the independent effect of surgery. There may also have been other factors involved. (See section on End Point Results).
6. All results and analyses for surgical patients were generally consistent with findings reported earlier for the medical group.

Acknowledgment

This cooperative study was supported by the NHLBI Grant No. HL-14340-03 to the Central Registry and separate grants to the participating institutions. Glenbrook Division of Sterling Drug, Inc., prepared, numbered, and packaged the active drug and placebo in a format suitable for a double-blind, controlled trial.

Reference

Appendix

THE ASPIRIN IN TRANSIENT ISCHEMIC ATTACKS STUDY (AITIA)

Participants

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Surgeons

(continued)
Long Term Changes in Blood Pressure and Risk of Cerebrovascular Disease

SIMON W. RABKIN, M.D., F.R.C.P. (C), FRANCIS A. L. MATHEWSON, M.D., and ROBERT B. TATE, M.SC.

SUMMARY Little attention has been given to assessing risk factors for cerebrovascular disease (CBVD) and less has been given to relating long term changes in blood pressure (BP) to CBVD occurrence. In the Manitoba Study a cohort of 3,983 North American men (predominantly between 25-34 years of age at entry in 1948), measured 5 times during the 26 year observation period from 1948 to 1974, was related to the incidence of CBVD. Used were measurements of age, systolic (SBP) and diastolic (DBP) blood pressure and Body Mass Index-weight/height2 determined at entry and at examination closest to July 1, 1954, 1959, 1964 and 1969. Change was calculated as the difference in these variables between examinations. In order to adjust for age and BP as CBVD risk factors, as well as for the effect both may have on the rate of BP change, the data were analyzed using multivariate as well as univariate methods.

After adjusting for age and SBP, change in SBP was significantly associated with subsequent CBVD, primarily in men middle aged or older. When considering SBP after entry, changes from a measurement 5 years earlier were more important than SBP changes over longer intervals. Thus, in evaluating SBP as a risk factor for CBVD, the rate of change in SBP is also an important factor in the identification of the stroke prone individual.

IDENTIFICATION of persons at high risk for development of a disease, is an important initial step in prevention of that disease. The search for factors which increase the risk of cerebrovascular disease (CBVD) is therefore highly relevant.1-4 The clinical observation that some persons manifest CBVD after a short period of rise in blood pressure to "hypertensive levels"5,6 raises the possibility that BP change may be a CBVD risk factor. To our knowledge this has not been previously investigated. The purpose of this report was to examine, in a prospective cardiovascular study, the hypothesis that the magnitude of BP change over time or the rate of change of BP is a predictor of the occurrence of CBVD.

Methods

Details of this Manitoba Study have been reported previously.6-11 In summary, the cohort consisted of 3,983 healthy men fit for pilot training in World War II. From 1946 to 1948 contact was re-established with the post-war survivors and on July 1, 1948, the Study population was sealed. For each subject measurements of age, blood pressure, body weight and height at the examination closest to June 30th, 1948 (date that population was defined) were selected as the entry examination. The mean age at entry was 30.8 years. Medical information and examinations provided evidence that they were without clinical manifestations of CBVD at entry. Since then, they have been followed by annual mail contact and periodic medical examinations. The observation period was defined from July 1, 1948 until June 30, 1974, an average follow up of 26 years. Annual contact has been lost with only 1 person.

Persons with secondary hypertension were not excluded from analysis because of their small number...
Controlled trial of aspirin in cerebral ischemia. Part II: surgical group.
W S Fields, N A Lemak, R F Frankowski and R J Hardy

Stroke. 1978;9:309-319
doi: 10.1161/01.STR.9.4.309

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/9/4/309