Antiplatelet Agents in the Secondary Prevention of Stroke: Meta-analysis of the Randomized Control Trials

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Randomized control trials of antiplatelet agents in the prevention of stroke following transient ischemic attacks have had conflicting results. The decision to employ aspirin instead of placebo as the control regimen in trials testing newer antiplatelet agents emphasizes the need for an accurate estimate of the efficacy of older drugs. A meta-analysis of seven randomized control trials comparing aspirin and/or sulfinpyrazone or dipyridamole with placebo was performed. For aspirin compared with placebo, a nonsignificant reduction in stroke of 15% (odds ratio 0.85, 95% confidence interval 0.60–1.19; χ² = 0.78, p > 0.30) was found. For aspirin combined with sulfinpyrazone or dipyridamole compared with placebo, a 39% reduction in stroke was observed (odds ratio 0.61, 95% confidence interval 0.39–0.95; χ² = 4.22, p < 0.05); at the same time a 350% increase in gastrointestinal hemorrhage or peptic ulcer was noted (odds ratio 3.5, 95% confidence interval 1.26–9.75; χ² = 4.61, p < 0.05). A trend in reduction of strokes for men was observed (odds ratio 0.58, 95% confidence interval 0.32–1.07; χ² = 2.52, p < 0.15) for any regimen containing aspirin. The significant benefit of aspirin-combination therapy on stroke must be interpreted cautiously because of a number of possible biases. It is still conceivable that aspirin alone may decrease the incidence of stroke by as much as 40%, but a sample of > 13,000 patients would be needed to confirm the benefit observed in our analysis. (Stroke 1988;19:436–442)

Much attention has focused on the prevention of stroke, especially following a transient ischemic attack (TIA). Antiplatelet agent therapy following a TIA is a relatively recent area of stroke prevention research. In theory, these agents, through a variety of mechanisms, prevent platelet aggregation and therefore reduce the probability of continuing thrombotic events leading to stroke and myocardial infarction. Since 1969, randomized control trials (RCTs) have tested the effectiveness of a variety of antiplatelet agents (i.e., aspirin, dipyridamole, and sulfinpyrazone) alone and in combination against placebo, or each other in the secondary prevention of stroke following a TIA. Reviews and a recent editorial have expressed support for only one antiplatelet agent—aspirin. A number of trials, both completed and in progress, testing newer agents (ticlopidine and pentoxifylline) have now replaced placebo with aspirin controls, even though the efficacy of aspirin is still open to question as indicated by two recently published meta-analyses. Concern has also been expressed regarding whether any RCT is large enough to detect a clinically significant benefit from aspirin.

In view of the uncertain efficacy of these agents and because of the relatively small size of the published trials, a meta-analysis and quality assessment of the published RCTs of all antiplatelet agents including aspirin is appropriate and timely. Meta-analysis is a retrospective technique of pooling data from multiple trials, which can increase statistical power. However, to avoid the many biases of retrospective research, the selection of papers should be determined in duplicate and in a blinded manner. Quality should be assessed, within- and between-study variability measured, and the impact of publication bias considered.

Subjects and Methods

Selection of Trials

RCTs in the English-language literature were gathered through weekly review of Current Contents, a search of the Medline computer data base of the National Library of Medicine from 1966 to June 1987, and a scan of references from review articles, editorials, and RCTs obtained from the first two methods. RCTs using antiplatelet agent therapy in the prevention of stroke following TIAs only or TIAs in addition to ischemic cerebrovascular events with continuing neurologic deficit (e.g., reversible ischemic neurologic deficit [RIND] or completed stroke) were included for analysis. RCTs that did not include placebo controls or that entered only patients with completed stroke were not included.

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Quality Assessment of Trials

RCTs were evaluated for study design, statistical analysis, and presentation of data based on a previously developed quantitative scoring system. Numerical scores ranged from 0 to 1, with a score of 1 satisfying all criteria examined. Trials were selected and scored independently by two reviewers who were blinded to the results as well as to the identity of the trials; interreviewer differences were resolved in conference.

Definition of Treatment Comparisons and End Points

We compared the effects of a variety of antiplatelet treatment regimens, aspirin in particular, with placebo. Data were pooled based on the following nonmutually exclusive groups: 1) all antiplatelet agents, 2) aspirin only, 3) nonaspirin antiplatelet agents, 4) all regimens combining aspirin with another antiplatelet agent (aspirin combinations), and 5) any regimen containing aspirin. Each of these treatment groups was compared with a placebo group for the following nonmutually exclusive end points: 1) total mortality (death from any cause), 2) total strokes (including fatal and nonfatal cerebral and retinal infarct and cerebral hemorrhage), 3) nonfatal stroke and death, and 4) serious side effects (gastrointestinal hemorrhage and peptic ulcer). Outcomes by sex were also analyzed. In all cases in which data were available, intention-to-treat analyses were performed, which included all patients in the groups to which they were originally randomized. Occurrence of further TIA s was not included as an end point. In the single crossover trial, data on end points were collected from only the first phase, before the crossover, and it was assumed that of the 50 patients included in the trial, half were allocated to each group. Data was extracted by two independent investigators, blinded with respect to authors and source of the study, with differences resolved in conference.

Statistical Methods

For each RCT, 2×2 contingency tables were constructed for the various treatment and placebo groups for each individual end point. Data were then combined using the Yusuf-Peto modification of the Mantel-Haenszel χ² test. This method yields an odds ratio (OR) of an effect of control compared with treatment, with a 95% confidence interval (CI); it also tests for statistical heterogeneity. To permit proper calculation of OR, 0.5 was added to each cell of the 2×2 table when any cell contained a 0.

A significance level of 5% was established. It was recognized that a more stringent level of significance might have been applicable due to the multiple comparisons performed. However, it was not clear which correction factor could be appropriately applied, especially as the multiple tests were not independent.

Results

Selection, Description, and Findings of Randomized Control Trials

A search of the literature yielded a total of 19 RCTs published in English. Of these, 12 were excluded. Eight studies were rejected because placebo control groups were not included. Of these eight trials, three tested the effectiveness of aspirin versus anticoagulant therapy, whereas five others compared various antiplatelet therapies against each other. One trial did not present adequate numerical data for analysis. Another trial, requiring that surgical intervention precede antiplatelet therapy, was excluded because it represented a different population from those studied in the other trials. Two trials tested agents (clofibrate and Calmic 131A) with questionable antiplatelet properties in vivo.

Table 1 lists selected features of the seven RCTs included in the meta-analysis. Patient selection criteria varied, with some trials including only those with TIA s, whereas in others a majority of patients had completed strokes. Approximately 70% of the study participants were men, and a majority were older than 55 years of age. Five RCTs tested aspirin at daily doses ranging from 990 to 1,500 mg, with two trials testing multiagent regimens consisting of aspirin and either sulfinpyrazone or dipyridamole. Two of the seven trials tested sulfinpyrazone at a daily dose of 800 mg, and one trial tested dipyridamole first at 400 and then at 800 mg/day. The maximum time allowable between an acceptable neurologic event and randomization into a study ranged between 3 weeks and 3 months for five trials and was 1 year for another. One trial did not specify a time limit, but 65% of the sample had experienced an event within the previous year. Follow-up for most studies was 2 years, with a range of 4–36 months.

A summary of the results as reported in the individual trials is shown in Table 1. End points,
TABLE 1. Selected Study Characteristics and Results of Seven Randomized Control Trials as Analyzed in Original Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Diagnosis (%)</th>
<th>Interval</th>
<th>Sex</th>
<th>Age</th>
<th>Follow-up (mo)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Cooperative Study Group (1978)</td>
<td>TIA (62) Stroke (38)</td>
<td>&lt;3 mo</td>
<td>M  69</td>
<td>F  31</td>
<td>—</td>
<td>26 (mean)</td>
</tr>
<tr>
<td>Fields et al (1977)</td>
<td>TIA (100)</td>
<td>&lt;3 mo</td>
<td>M  66</td>
<td>F  34</td>
<td>85% 45-74</td>
<td>24 (total)</td>
</tr>
<tr>
<td>Sorenson et al (1983)</td>
<td>TIA (75)</td>
<td>&lt;1 mo</td>
<td>M  73</td>
<td>F  27</td>
<td>59, 34-75</td>
<td>25 (median)</td>
</tr>
<tr>
<td>Bousser et al (1983)</td>
<td>TIA (16)</td>
<td>&lt;1 yr</td>
<td>M  70</td>
<td>F  30</td>
<td>63 ± 10</td>
<td>36 (total)</td>
</tr>
<tr>
<td>Reuther and Dorndorff (1978)</td>
<td>TIA/RIND (100)</td>
<td>&lt;3 mo</td>
<td>M  66</td>
<td>F  34</td>
<td>69% &gt;55</td>
<td>24 (total)</td>
</tr>
<tr>
<td>Acheson et al (1969)</td>
<td>TIA (37)</td>
<td>Unknown</td>
<td>M  69</td>
<td>F  31</td>
<td>58 (mean)</td>
<td>14/11 (mean)</td>
</tr>
<tr>
<td>Roden et al (1981)</td>
<td>TIA/AF (100)</td>
<td>3 wk</td>
<td>M  70</td>
<td>F  30</td>
<td>63 ± 10 (mean ± SD)</td>
<td>4 (total)</td>
</tr>
</tbody>
</table>

Trials listed in descending order of overall quality score. Interval, time from diagnosis to randomization; TIA, transient ischemic attack; AF, amaurosis fugax; RIND, reversible ischemic neurologic deficit; M, multiple strokes; S, single stroke; RI, retinal infarct; Sulf, sulfinpyrazone; ASA, aspirin; Dip, dipyridamole; NS, not significant.

*All sulfinpyrazone (Sulf and ASA + Sulf) vs. no sulfinpyrazone (Placebo and ASA); only "all sulfinpyrazone" results shown.
†All aspirin (ASA and ASA + Sulf) vs. no aspirin (Placebo and Sulf); only "all aspirin" results shown.
‡Two periods of treatment, first period: mean of 14 months with 400 mg, second period: mean of 11 months with 800 mg; only results from first period are shown.
§Crossover study design; 25 assumed to be in each group, with only results from first half of the crossover shown.

Findings of Meta-Analysis

Data as analyzed using the intention-to-treat method are shown in Table 2.

No significant reductions or trends in mortality were found for any of the five treatment regimens compared with placebo (Figure 2).

A significant reduction, 39%, in stroke was found for the aspirin-combination regimens (OR = 0.61, 95% CI 0.39-0.95; χ² = 4.22, p < 0.05) (Figure 3). A 15% reduction was found for aspirin, but the result was not significant (OR = 0.85, 95% CI 0.60-1.19; χ² = 0.78, p > 0.30). None of the other regimens was significant for preventing stroke. Similar results were found for the combined end point of nonfatal stroke and death, with a strong trend observed favoring any regimen containing aspirin (OR = 0.76, 95% CI 0.58-1.00; χ² = 3.59, p < 0.10).

Occurrence of serious side effects was reported in six of the seven studies. A 350% increase in these side effects was noted for aspirin combinations, yielding a significant OR of 3.5 (95% CI 1.26-9.75; χ² = 4.61, p < 0.05) (Figure 4). Results of the other four regimens, including aspirin only, were not significant.

Where possible, analyses of end points by sex were conducted for aspirin only and for any regimen containing aspirin. Only three trials gave results by sex.
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Patients randomized</th>
<th>Patients analyzed</th>
<th>End points</th>
<th>Number of events/patients analyzed</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>173</td>
<td>156</td>
<td>Death or stroke</td>
<td>58/302*</td>
<td>NS</td>
</tr>
<tr>
<td>1300</td>
<td>156</td>
<td>144</td>
<td>Death or stroke</td>
<td>46/290†</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>800 + 1300</td>
<td>156</td>
<td>146</td>
<td>Death or stroke</td>
<td>30/139</td>
<td></td>
</tr>
<tr>
<td>1300</td>
<td>94</td>
<td>88</td>
<td>Death or RI or stroke</td>
<td>13/88</td>
<td>NS</td>
</tr>
<tr>
<td>1000</td>
<td>104</td>
<td>101</td>
<td>Death or stroke</td>
<td>21/101</td>
<td>NS</td>
</tr>
<tr>
<td>990</td>
<td>198</td>
<td>198</td>
<td>Fatal or nonfatal stroke</td>
<td>17/198</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>990 + 225</td>
<td>202</td>
<td>202</td>
<td>Fatal or nonfatal stroke</td>
<td>18/202</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>1500</td>
<td>30</td>
<td>29</td>
<td>Stroke or TIA</td>
<td>6/29</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>400/800</td>
<td>85</td>
<td>85</td>
<td>Stroke or TIA</td>
<td>34/85</td>
<td>NS</td>
</tr>
<tr>
<td>800</td>
<td>25</td>
<td>16</td>
<td>Stroke or TIA</td>
<td>7/16</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results as reported in original trials

<table>
<thead>
<tr>
<th>End points in meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Canadian Cooperative Study Group (1978)(^4)</td>
</tr>
<tr>
<td>ASA</td>
</tr>
<tr>
<td>ASA + Sulf</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Fields et al (1977)(^3)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Sorenson et al (1983)(^8)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Bousser et al (1983)(^7)†</td>
</tr>
<tr>
<td>ASA + Dip</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Reuther and Dornhoff (1978)(^2)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Acheson et al (1969)(^9)†</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Roden et al (1981)(^3)†</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

Trials listed in descending order of overall quality score. Sulf, sufipryrazone; ASA, aspirin; Dip, dipyridamole.

*Most withdrawals expressed as nonfatal strokes or deaths.
†Data unavailable to analyze by intention-to-treat.
For any regimen containing aspirin, there was a trend for preventing stroke in men (OR = 0.58, 95% CI 0.32–1.07; \( \chi^2 = 2.52, p < 0.15 \)), while for women no discernible effect was found (Figure 5). CIs for the two sexes overlapped appreciably. No benefit was apparent for aspirin only.

Tests of heterogeneity were performed for the various pooled comparisons; none was found to be significant at the 5% level.

**Discussion**

None of the pooled analyses for single-agent antiplatelet drugs, including aspirin, showed a significant benefit in the prevention of stroke and/or death. After inclusion of > 1,100 patients, the 95% CI for the observed effect of aspirin therapy includes a decrease in stroke of 40%. However, a sample of approximately 13,000 would be needed to detect with 90% power the observed reduction of 15%.

Only aspirin combinations appeared to significantly reduce the occurrence of stroke and stroke or death. At the same time, this analysis also showed a significant increase in serious side effects. A synergistic effect of treatments combining aspirin with nonaspirin antiplatelet agents is possible. Alternatively, these results may represent a Type I error. However, reanalysis of the data by the more conservative DerSimonian and Laird method, which takes into account between-study heterogeneity, has revealed essentially the same results (J. Berlin, unpublished data).

One of the most publicized subgroup findings was the benefit of aspirin in preventing stroke or death in men but not women from the Canadian Cooperative Study. Results from two other trials with data on sex comparing aspirin with placebo did not confirm those findings. Likewise, in our analysis, no significant advantage of aspirin over placebo was found for either sex, based on our defined end points, although a trend favoring a reduction of strokes in men was noted for any regimen containing aspirin. Because of the limited data available for analysis, the possibility that there is a beneficial effect in men cannot be ruled out. Dyken, using data from the Hospital Frequency Study, a retrospective cohort, has claimed a reduction in stroke with aspirin therapy for men older than 60 but no effect for those younger than 60.

The mean quality score of the RCTs included in our study compared favorably with those for RCTs testing other therapeutic regimens, with the second highest mean score among 18 subject areas (D. Reitman, unpublished data). These trials have incorporated more elements in study design and analysis that minimize the likelihood of bias and increase the validity of the results. Still, it is important to comment on areas in which bias might have been introduced into the individual trials and during our analyses.

Our analysis of the data was based on the intention-to-treat principle, a method that avoids bias resulting from discarding exclusions or withdrawals.
Events were recorded, when available, for all patients who were randomized, not just for those completing the studies. Of seven trials, four obtained follow-up data on withdrawals. Except for the Heidelberg Study, which found no further events among the withdrawals, only the Canadian Cooperative Study combined withdrawal data on stroke or death with those of patients remaining in the trial, despite the fact that four of seven trials had a withdrawal rate of >15%.

Second, since only a few trials published life tables with timing of events specifying when patients withdrew from a study or reached an end point, combining data at specific times to form a pooled life table was not possible. Calculations were based instead on the number of overall events, usually compiled at the end of each trial. This may introduce some error or bias, depending on whether the timing of events differed between the two groups. It is thus important that individual trials provide information in life tables on timing of events so that a more accurate life table pooling technique can be applied in future meta-analyses.

Publication bias is an important consideration whenever a conclusion is borderline, as in this case. Its existence in the clinical trial field has been documented, but at present it is impossible to measure its exact impact on the conclusions of a meta-analysis. It is reasonable to speculate, however, that completed trials that have never been published are not likely to be significant in either direction.

While statistical evaluations found the data to be comparable and not heterogeneous, clinical interpretation of the results may be more difficult. Differences in selection criteria, such as the inclusion of patients having either TIAs or mostly completed strokes within a trial, may limit the conclusions that can be drawn. More uniform selection criteria within trials might lead to greater clinical applicability in the interpretation of results.

A comparison of the results from two previously published meta-analyses with our own suggests that certain differences in findings can be attributed to differences in selection criteria (Table 3) or possibly techniques of meta-analysis.

For aspirin versus no aspirin, Warlow has estimated 28% and 25% overall reductions in risk for stroke and death compared with 14% and 13% in our comparisons. The greater reductions are attributable to the inclusion of two trials by Warlow, one without placebo controls and another that we excluded from our analysis because all patients had prior surgery.

The Swedish Cooperative Study found no significant effect of aspirin combinations in secondarily preventing stroke or death. This is in contrast to our findings, even though the same two trials were analyzed. Differences in methods of analysis (intention-to-treat vs. efficacy analysis) did not appear to account for all the differences in findings. After reanalyzing the data as published in the Swedish Cooperative Study using the Yusuf-Peto method, we still noted a significant effect.

Other potential causes of between-meta-analysis variability involve the unresolved issue of inclusion of unpublished trials or unpublished outcome data from published trials, which apparently neither Warlow nor the Swedish Cooperative Study included. This is a potential source of bias that should be considered in any meta-analysis. There is also potential confusion in how one includes data from a 2 x 2 factorial study, such as that of the Canadian Cooperative Study. Finally, it should be recognized that different methods of analysis may be variably responsive to differences in sample size and heterogeneity of results (J. Berlin, unpublished data).

In an attempt to answer the same question, the variations in findings raise concerns regarding the reliability of meta-analysis. A moderate lack of replicability has been demonstrated among 46 meta-analyses of RCTs that included two or more attempts to answer the same question out of a total of 91 discovered meta-analyses. It is essential that the aims and procedures of the meta-analysis be clearly defined and reported so as to maximize information about reproducibility. Measures to prevent bias should be undertaken. For example, the selection of articles and the extraction of data should be performed blinded and in duplicate in adherence to criteria determined a priori. In spite of these potential defects we still believe that meta-analysis, if performed scientifically, is a useful technique with an important role in clinical decision-making.

In spite of the publication of seven RCTs comparing antiplatelet agents with a placebo, the benefit of antiplatelet agents has yet to be clearly shown. Until that time, it is not appropriate to replace placebo with aspirin controls. Whereas there may be a benefit with aspirin combinations, an increased occurrence of side effects diminishes that advantage. More investigation is indicated to determine whether there is indeed a positive risk/benefit ratio, and if so, to pinpoint the patients most likely to benefit. Finally, if accurate and meaningful results are to be obtained through the pooling of data, it is important that the original trials be exemplary and that unbiased methods of analysis be employed.

### References


Key Words • aspirin • cerebrovascular disorders • clinical trials • dipryidamole • sulfinpyrazone • meta-analysis
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P C Sze, D Reitman, M M Pincus, H S Sacks and T C Chalmers

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