Failure of Aspirin Treatment After Stroke

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Background and Purpose Despite its low efficacy, aspirin is the most widely used drug for secondary stroke prevention. The reasons why stroke recurs while patients are on aspirin are unknown. We have analyzed a series of patients who had recurrent strokes while on aspirin.

Methods Out of 2231 consecutive patients who were admitted to the Tel Aviv Medical Center from May 1988 through December 1992 with the diagnosis of ischemic stroke, 129 admissions were due to recurrent ischemic strokes while the patients were already on aspirin, and these were defined as aspirin failures. The clinical characteristics of those patients in whom aspirin treatment failed were compared with three control groups, each comprising 129 patients who had had only a single ischemic stroke and were then taking aspirin. One control group was matched for aspirin dose and date of first stroke; another control group was matched for age, sex, and date of first stroke; and a third control group was matched for age, sex, date of first stroke, and aspirin dose. Statistical analysis was carried out by two-tailed Student's t test and χ² test.

Results The average period until stroke was longer for patients on higher aspirin doses. Patients matched for aspirin dose and date of first stroke did not differ significantly in age (72.4 years in aspirin failures versus 74.2 years in the first control group) and sex (89 versus 94 men, respectively). Matching for age, sex, and date of first stroke but not for aspirin dose demonstrated a trend toward high frequency of aspirin failure in patients taking lower doses of aspirin (χ² test for trend=3.5; P=.06). Comparison of aspirin-failure patients with a control group matched for age, sex, date of first ischemic stroke, and aspirin dose demonstrated that these patients more commonly had statistically significant hyperlipidemia (odds ratio, 2.6; 95% confidence interval, 1.0 to 6.8; P=.04) and ischemic heart disease (odds ratio, 2.3; 95% confidence interval, 1.3 to 3.9; P=.002).

Conclusions We conclude that age and sex do not influence the efficacy of aspirin. Lower aspirin dose in patients with stroke recurrence suggests that aspirin doses of 500 mg daily or more should be used in secondary stroke prevention. Hyperlipidemia and ischemic heart disease are risk factors for stroke recurrence despite aspirin treatment, which requires further clinical and laboratory evaluation. (Stroke. 1994;25:275-277.)

Key Words • aspirin • cerebral infarction • epidemiology • stroke prevention
until the qualifying recurrence was 14.8 ± 3.7 months. The aspirin doses used were variable; 7 patients took 100 mg, 68 patients were on 250 mg, 21 patients used 325 mg, and 33 patients took 500 mg aspirin daily. The average period to recurrence according to aspirin doses, shown in Table 1, shows a significant trend toward longer intervals in patients on higher aspirin doses.

**ASAF Group Versus a Control Group Matched for Aspirin Dose and Date of First-Ever IS**

ASAF patients were younger (72.4 ± 7.4 versus 74.2 ± 7.7 years) and were less often male (89 versus 94 men) than control subjects in whom stroke had not recurred. These differences were small and not statistically significant.

**ASAF Group Versus a Control Group Matched for Age, Sex, and Date of First-Ever IS**

The distribution of aspirin doses in patients with ASAF and in control subjects is shown in Table 2. There was a trend toward higher frequency of lower doses of aspirin in patients with ASAF ($\chi^2$ for trend, 3.5; $P = .06$).

**ASAF Group Versus a Control Group Matched for Age, Sex, Date of First Stroke, and Aspirin Dose**

The relative frequencies of the risk factors for stroke showed that the ASAF group had an excess of almost all stroke risk factors. The results of the statistical analysis are shown in Table 3. The differences between ASAF and control groups were statistically significant only for ischemic heart disease and hyperlipidemia.

**Discussion**

In the Stroke Prevention in Atrial Fibrillation 1 Study, it was shown that older patients were often "aspirin nonresponders." However, Sivenius concluded that age (above or below 65 years) does not influence the effectiveness of aspirin therapy. We also found that age does not influence the efficacy of aspirin. The proportion of women was greater in the ASAF group than in the control group. Although the difference was not statistically significant, it is consistent with some but not all previous studies suggesting that aspirin may be less efficacious for secondary stroke prevention in women.

Our study showed a significant trend toward high frequency of ASAF in patients under lower doses of aspirin and a longer period until stroke recurrence in those treated with higher aspirin doses (Table 1). It is consistent with a laboratory study in which it was shown that there was a progressive increase in the number of patients with platelet hyperactivity as the aspirin dose decreased.

### Table 1. Average Period Between the First and Recurrent Stroke According to Aspirin Dose

<table>
<thead>
<tr>
<th>Daily Aspirin Dose, mg</th>
<th>No. of Patients</th>
<th>Mean Time ± SD, mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>7</td>
<td>10.0 ± 2.9</td>
</tr>
<tr>
<td>250</td>
<td>68</td>
<td>11.1 ± 3.3</td>
</tr>
<tr>
<td>325</td>
<td>21</td>
<td>14.0 ± 2.7</td>
</tr>
<tr>
<td>500</td>
<td>33</td>
<td>24.1 ± 5.3</td>
</tr>
<tr>
<td>Mean</td>
<td>129</td>
<td>14.8 ± 3.7</td>
</tr>
</tbody>
</table>

*The comparison of mean duration between the first and recurrent stroke in patients with different doses of aspirin, ANOVA, $F = 6.8$, $P = .002$.

### Table 2. Differences in Aspirin Dose: Aspirin Failure Group Versus Control Group*

<table>
<thead>
<tr>
<th>Daily Aspirin Dose, mg</th>
<th>Aspirin Failure Group (n=129)</th>
<th>Control Group (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>5.4</td>
</tr>
<tr>
<td>250</td>
<td>68</td>
<td>52.7</td>
</tr>
<tr>
<td>325</td>
<td>21</td>
<td>16.3</td>
</tr>
<tr>
<td>500</td>
<td>33</td>
<td>25.6</td>
</tr>
</tbody>
</table>

* $\chi^2$ for trend, $\chi^2 (1) = 3.5$, $P = .06$. The aspirin failure group consisted of patients with recurrent ischemic strokes while on aspirin; control group consisted of patients with nonrecurrent ischemic strokes while on aspirin.

### Table 3. Relative Frequency of Risk Factors in Aspirin Failure and Control Groups

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Aspirin Failure Group (n=129)</th>
<th>Control Group (n=129)</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>82</td>
<td>73</td>
<td>1.34</td>
<td>0.79-2.28</td>
<td>.310</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>65</td>
<td>40</td>
<td>2.26</td>
<td>1.32-3.88</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44</td>
<td>38</td>
<td>1.24</td>
<td>0.71-2.17</td>
<td>.500</td>
</tr>
<tr>
<td>Smoking</td>
<td>39</td>
<td>34</td>
<td>1.21</td>
<td>0.68-2.16</td>
<td>.583</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>20</td>
<td>18</td>
<td>1.13</td>
<td>0.54-2.38</td>
<td>.861</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>19</td>
<td>8</td>
<td>2.61</td>
<td>1.03-6.80</td>
<td>.041</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14</td>
<td>15</td>
<td>0.93</td>
<td>0.40-2.14</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8</td>
<td>6</td>
<td>1.36</td>
<td>0.41-4.56</td>
<td>.784</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Risk factors with statistically significant differences between aspirin failure and control groups by $\chi^2$ test.
As expected, hypertension, ischemic heart disease, smoking, diabetes mellitus, and peripheral vascular disease were prevalent both in patients followed after a single stroke without a recurrence and in those with recurrent IS. The control and treatment of these risk factors might influence the success of primary and secondary stroke prevention. Although hyperlipidemia and ischemic heart disease were more common among ASAF patients, it cannot be concluded that these well-known risk factors necessarily affect the efficacy of aspirin. However, the results do demonstrate that aspirin does not obliterate the excess risk for stroke recurrence associated with ischemic heart disease and hyperlipidemia. These results correspond with previous studies; therefore, patients with ischemic heart disease and hyperlipidemia should be considered for more aggressive forms of therapy, as already suggested by Chyatte and Chen. We conclude that neither sex nor age but other unknown causes could influence the efficacy of aspirin; these causes require further clinical and laboratory evaluation.

References
Failure of aspirin treatment after stroke.
N M Bornstein, V G Karepov, B D Aronovich, A Y Gorbulev, T A Treves and A D Korczyn

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