Effect of Prior Aspirin Use on Stroke Severity in the Trial of Org 10172 in Acute Stroke Treatment (TOAST)

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Background and Purpose—Although the efficacy of aspirin in reducing stroke incidence is clear, its role in reducing stroke severity is disputed. This study compares stroke severity between patients who did or did not take aspirin in the week before stroke and enrollment in the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

Methods—Of 1275 patients randomized, 509 reported aspirin use in the week before stroke; 766 did not. Clinical stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) and the Supplementary Motor Examination (SME) at trial entry and at 3 months. Using these scales, we compared the categorization of stroke severity (mild, moderate, and severe) and mean scores between aspirin users and nonusers.

Results—The difference in distribution of baseline NIHSS scores was statistically significant between aspirin users and nonusers (P=0.006), with a greater percentage of milder strokes among aspirin users. The difference in mean baseline NIHSS scores was also significantly lower in aspirin users (8.2) and nonusers (9.3) (P=0.003). The distribution of baseline SME scores and mean SME scores also showed lower stroke severity in aspirin users than in nonusers (P=0.048 and P=0.004, respectively). At 3 months, differences in stroke severity measured by the SME but not the NIHSS remained statistically significant. Seven-day and 3-month mortality did not differ significantly.

Conclusions—In this study aspirin use is associated with milder clinical deficits at stroke onset. These deficits may affect prognosis and influence response to treatment. Future clinical trials should ensure that prestroke aspirin use is comparable in study groups. (Stroke. 2001;32:2836-2840.)

Key Words: aspirin ■ stroke outcome ■ stroke prevention

A

spirin and other antiplatelet drugs have well-established efficacy in secondary prevention of ischemic stroke. This efficacy is generally measured by reduction in incidence of ischemic stroke. However, this may provide an incomplete measure of efficacy if stroke severity as well as stroke incidence is diminished.

Several groups have investigated this question, some finding a reduction in stroke severity among aspirin users,1–4 others not.5–10 However, these studies may have been inconclusive because of small sample size, particularly in the aspirin-treated groups.1,3,6,7,9,10 Another limitation of many previous studies was the use of low-resolution stroke severity measures, such as “fatal versus nonfatal” or the 6-point modified Rankin Scale, which may be unable to detect relatively small differences in stroke severity between groups.1,2,4,5,8

In the Trial of Org 10172 in Acute Stroke Treatment (TOAST), patients were rigorously evaluated for stroke severity with the use of well-validated scales, including the National Institutes of Health Stroke Scale (NIHSS) and the Supplementary Motor Examination (SME), which measure stroke severity on a 42- and 40-point scale, respectively.11,12 The purpose of this study was to compare stroke severity with the use of these measures among users and nonusers of aspirin.

Subjects and Methods

TOAST was a multicenter, randomized, placebo-controlled, double-blind clinical trial that tested the usefulness of early (<24 hours) intravenously administered antithrombotic therapy in the treatment of patients with acute ischemic stroke.13,14 Patients with acute ischemic stroke symptoms of ≤24 hours in duration were randomized at 37 centers in the United States. The study population for this analysis included all 1275 intent-to-treat patients randomized in TOAST. Patients and families were questioned as to their use of aspirin (any) in the 7 days before their stroke. Patients having unknown aspirin use (n=21) during this period were categorized as nonusers. No information was collected as to daily use or dose of aspirin used during this period; aspirin use was not confirmed by blood or urine levels, nor was information collected about other antiplatelet therapy or warfarin use, although patients with “therapeutic” international normalized ratios secondary to warfarin were...
Aspirin use comparisons for categorical variables were also compared between (atherothromboembolic, cardioembolic, lacunar, other, or unknown), aspirin nonusers were compared. Categories of stroke subtypes

\[ \text{Baseline NIHSS score} \]

\[ \text{Baseline SME score} \]

\[ \text{Mean baseline NIHSS score} \]

\[ \text{Mean baseline SME score} \]

\[ \text{Median baseline NIHSS score} \]

\[ \text{Median baseline SME score} \]

\[ \text{Aspirin use (n=509)} \]

\[ 256 (50.3\%) \]

\[ 204 (40.1\%) \]

\[ 49 (9.6\%) \]

\[ 8.2 \pm 5.6 \text{ points} \]

\[ 6 \text{ points} \]

\[ \text{No aspirin use (n=766)} \]

\[ 329 (43.0\%) \]

\[ 324 (42.3\%) \]

\[ 113 (14.8\%) \]

\[ 9.3 \pm 6.3 \text{ points} \]

\[ 7 \text{ points} \]

\[ \text{*Distribution of scores: } P=0.006; \text{ controlling for covariates, } P=0.007. \]

\[ \dagger P=0.003; \text{ controlling for covariates, } P=0.029. \]


not included because prolonged coagulation time was an exclusion for entry in TOAST.

All patients were examined by investigators who were experienced and certified in the application of the NIHSS and SME.\(^{13}\) The SME grades strength in the proximal and distal upper and lower extremities on a scale of 1 to 5.\(^{16}\) Baseline examination occurred on admission into the study, within 24 hours of stroke onset. Patients were also examined daily for the first 7 days and then again at 3 months. Patients who died received the maximum score. All the data were also examined daily for the first 7 days and then again at 3 months and were verified against source documentation. All data entered in a studywide database at the University of Iowa. We categorized stroke severity as mild (NIHSS 0 to 6, SME 0 to 6), moderate (NIHSS 7 to 15, SME 7 to 14), and severe (NIHSS >16, SME >15). Aspirin users were compared with nonusers by Fisher’s exact test or the Freeman-Halton extension to Fisher’s exact test for \(R \times C\) tables. The 2 groups were also compared on continuous baseline NIHSS score and baseline SME score with the use of the Wilcoxon rank sum test.

To assess the role of possible confounding factors, various demographic and clinical characteristics of the aspirin users and aspirin nonusers were compared. Categories of stroke subtypes (atherothromboembolic, cardioembolic, lacunar, other, or unknown), as defined by prespecified criteria, were also compared between groups.\(^{15}\) Aspirin use comparisons for categorical variables were made with Fisher’s exact test or the Freeman-Halton extension to Fisher’s exact test for \(R \times C\) tables. Aspirin use comparisons for continuous variables were made with the Wilcoxon rank sum test. The Cochran-Mantel-Haenszel row mean score test using ranks, adjusted for sex, race, categorized age, peripheral vascular history, atherosclerosis risk factors, cardiac history, and cardiovascular history, was used to control for differences in NIHSS and SME scores between aspirin users and nonusers.

**Results**

Almost 40% of subjects (509 of 1275 patients) had used aspirin at least once (aspirin users) in the 7 days preceding current stroke, while 766 had no or unknown aspirin use (aspirin nonusers). Categorization of NIHSS scores, mean NIHSS scores, categorization of SME scores, and mean SME scores at baseline (within 24 hours of stroke onset) are presented in Tables 1 and 2. All measures showed a statistically significantly lower stroke severity among aspirin users than among nonusers.

Categorization of NIHSS scores, mean NIHSS scores, categorization of SME scores, and mean SME scores at 3 months are presented in Tables 3 and 4. At 3 months, aspirin users continued to have milder motor deficits (as measured by the SME), but the trend toward milder strokes in patients taking aspirin as measured by the NIHSS, while present, was no longer statistically significant.

Differences in 7-day mortality (1.9%) and 3-month mortality (6.3%) were not statistically significant between aspirin users and nonusers. The size of infarction, estimated by local investigators’ review of 90-day CT scans as small (<0.5 cm), intermediate (0.5 to 1 cm), moderate (1 to 3 cm), large (>3 cm), and massive (multilobar), was not significantly different between aspirin users and nonusers.

This was not a randomized treatment trial of aspirin use versus no aspirin use, and therefore the role of potential confounding factors in the observed effect of aspirin on stroke severity may be great. To assess this, various characteristics of the aspirin users and aspirin nonusers were compared (Table 5). Expectedly, aspirin users had a higher preponderance of patients who had atherosclerosis risk factors (except diabetes) and other manifestations of atherosclerotic vascular disease in the cerebral, coronary, or peripheral circulations. Aspirin users were also more likely to be white than nonwhite. After we controlled for these factors using the Cochran-Mantel-Haenszel row mean score test using ranks adjusted for sex, race, categorized age, peripheral vascular history, atherosclerosis risk factors, cardiac history, and cardiovascular history, the difference between aspirin users and nonusers for baseline NIHSS remained significant \((P=0.029)\), but the difference for baseline SME was no longer significant \((P=0.384)\).

Because aspirin use was believed to have a potential effect on stroke mechanism, another factor that might play a confounding role in stroke severity, the distribution of stroke

**TABLE 1. Categorization of Baseline Stroke Severity by Aspirin Use: NIHSS Score**

<table>
<thead>
<tr>
<th>Baseline NIHSS Score, n*</th>
<th>Mean Baseline NIHSS Score†</th>
<th>Median Baseline NIHSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin use (n=509)</td>
<td>256 (50.3%)</td>
<td>8.2 ± 5.6 points</td>
</tr>
<tr>
<td>No aspirin use (n=766)</td>
<td>329 (43.0%)</td>
<td>9.3 ± 6.3 points</td>
</tr>
</tbody>
</table>

*Distribution of scores: \(P=0.006\); controlling for covariates, \(P=0.007\).

†\(P=0.003\); controlling for covariates, \(P=0.029\).

**TABLE 2. Categorization of Baseline Stroke Severity by Aspirin Use: SME Score**

<table>
<thead>
<tr>
<th>Baseline SME Score, n*</th>
<th>Mean Baseline SME Score†</th>
<th>Median Baseline SME Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin use (n=509)</td>
<td>283 (55.6%)</td>
<td>7.3 ± 6.9 points</td>
</tr>
<tr>
<td>No aspirin use (n=766)</td>
<td>373 (48.7%)</td>
<td>8.8 ± 7.0 points</td>
</tr>
</tbody>
</table>

*Distribution of scores: \(P=0.048\); controlling for covariates, \(P=0.364\).

†\(P=0.004\); controlling for covariates, \(P=0.384\).
There was no interaction between danaparoid/placebo treatment and aspirin use. There was no difference between aspirin users and nonusers with regard to baseline glucose, initial temperature, elevated white blood cell count, or time to first neurological examination.

Discussion

The results of this study suggest that aspirin may reduce clinical stroke severity. We found that both overall deficit and motor impairments were less severe in patients who had recently used aspirin compared with those who had not. Several different potential mechanisms provide a rational basis for antiplatelet therapy to have this effect. Platelets play a critical role in initiating the thrombotic process and are believed to constitute a large proportion of the thrombus volume, perhaps 50%.18 Interference with this process by aspirin may derive from its antioxidant properties. Aspirin inhibits cyclo-oxygenase, which contributes to the generation of oxygen free radicals during arachidonic acid metabolism. Additionally, salicylic acid (an aspirin metabolite) is a free radical scavenger, providing another mechanism by which one study of patients with small subcortical strokes, those with asymptomatic reinfarction had measurable inhibition of platelet aggregability, while those with symptomatic reinfarction did not.24 Because the symptomatic nature of the secondary infarction may be a measure of stroke severity, this suggests that the degree of platelet activation may contribute to stroke severity. Finally, using excretion of a thromboxane metabolite as a measure of platelet activation, van Kooten et al25 found an association between the apparent extent and duration of platelet activation and stroke severity as measured by the modified Rankin Scale on admission.

Other studies suggest that the efficacy of aspirin in this regard may be distinct from its antiplatelet effect. Joseph and colleagues4 found that of 45 consecutive ischemic stroke patients, those taking aspirin had less severe strokes, whether measured by clinical scales or infarction size on CT, than those not taking aspirin. However, stroke severity did not correlate with increased levels of platelet ionized calcium, a measure of platelet activity. Thus, they questioned whether the beneficial effect of aspirin is solely through platelet inhibition and postulated an anti-inflammatory effect whereby aspirin decreases leukocyte migration and the attendant release of prostaglandins and lysosomal enzymes deleterious to ischemic tissue.18 In vitro studies have since supported a neuroprotective role of aspirin independent of its antiplatelet effect.26,27 Grilli et al26 found that both aspirin and its metabolite sodium salicylate appear to reduce glutamate-mediated excitotoxicity. Relatively high concentrations of aspirin in these cell cultures, more similar to plasma concentrations in patients receiving aspirin for rheumatoid arthritis than is usual for vascular disease, have led some to question what the optimal neuroprotective dose of aspirin might be.

Alternatively, the putative neuroprotective effect of aspirin may derive from its antioxidant properties. Aspirin inhibits cyclo-oxygenase, which contributes to the generation of oxygen free radicals during arachidonic acid metabolism. Additionally, salicylic acid (an aspirin metabolite) is a free radical scavenger, providing another mechanism by which

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**TABLE 3. Categorization of 3-Month Stroke Severity by Aspirin Use: NIHSS Score**

<table>
<thead>
<tr>
<th>3-Month NIHSS Score, n*</th>
<th>Mean 3-Month NIHSS Score†</th>
<th>Median 3-Month NIHSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (0–6 Points)</td>
<td>Moderate (7–15 Points)</td>
<td>Severe (16–42 Points)</td>
</tr>
<tr>
<td>Aspirin use (n=509)</td>
<td>389 (76.4%)</td>
<td>54 (10.6%)</td>
</tr>
<tr>
<td>No aspirin use (n=764)</td>
<td>558 (73.0%)</td>
<td>113 (14.8%)</td>
</tr>
</tbody>
</table>

*Distribution of scores: P=0.409; controlling for covariates, P=0.107.
†P=0.145; controlling for covariates, P=0.107.

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**TABLE 4. Categorization of 3-Month Stroke Severity by Aspirin Use: SME Score**

<table>
<thead>
<tr>
<th>3-Month SME Score, n*</th>
<th>Mean 3-Month SME Score†</th>
<th>Median 3-Month SME Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (0–6 Points)</td>
<td>Moderate (7–14 Points)</td>
<td>Severe (15–40 Points)</td>
</tr>
<tr>
<td>Aspirin use (n=509)</td>
<td>369 (72.5%)</td>
<td>84 (16.5%)</td>
</tr>
<tr>
<td>No aspirin use (n=764)</td>
<td>510 (66.8%)</td>
<td>150 (19.6%)</td>
</tr>
</tbody>
</table>

*Distribution of scores: P=0.094; controlling for covariates, P=0.167.
†P=0.033; controlling for covariates, P=0.095.
TABLE 5. Demographic and Clinical Characteristics of Aspirin Users and Nonusers

<table>
<thead>
<tr>
<th></th>
<th>No Aspirin Use</th>
<th>Aspirin Use</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>766</td>
<td>509</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>64.4</td>
<td>66.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>59.1</td>
<td>62.9</td>
<td>0.198</td>
</tr>
<tr>
<td>Nonwhite, %</td>
<td>42.6</td>
<td>29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.1</td>
<td>71.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.4</td>
<td>31.6</td>
<td>0.116</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17.5</td>
<td>30.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10.3</td>
<td>30.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina</td>
<td>11.2</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6.9</td>
<td>12.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.6</td>
<td>12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2.5</td>
<td>4.3</td>
<td>0.075</td>
</tr>
<tr>
<td>Leg claudication</td>
<td>4.8</td>
<td>9.4</td>
<td>0.002</td>
</tr>
<tr>
<td>EC/IC surgery</td>
<td>0.1</td>
<td>0.2</td>
<td>1.000</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>0.4</td>
<td>3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>3.0</td>
<td>17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>41.9</td>
<td>34.6</td>
<td>0.010</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>11.1</td>
<td>28.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>9.9</td>
<td>20.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atherosclerosis risk factors</td>
<td>87.3</td>
<td>91.0</td>
<td>0.046</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>24.9</td>
<td>52.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>20.0</td>
<td>44.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EC/IC indicates extracranial/intracranial; TIA, transient ischemic attack.

oxidative tissue damage may be reduced by aspirin therapy. Aspirin might be dose related in some individuals. Aspirin has known efficacy in the prevention of cardioembolic strokes but has been demonstrably inferior to warfarin for most of these conditions. Interestingly, in contrast to this study, Chimowitz et al concluded that prior aspirin use did not clearly influence stroke subtype; 47 consecutive patients who suffered a stroke while on aspirin seemed to have a distribution of stroke etiologies similar to those reported in larger stroke data banks. Definitions of stroke subtypes in this study did not seem to differ significantly from those used in TOAST, but the series is quite small.

This study did not elicit information on the dose of prior aspirin use. Therefore, its effect on clinical stroke severity cannot be assessed. While informal surveys of clinical practice reveal that most neurologists use a dose of 325 mg per day, patients may have been prescribed aspirin by non-neurologists or have been taking it without specific physician recommendations. Thus, it seems likely that a broad range of aspirin doses is represented in the aspirin users. In addition, aspirin users were those who responded that they had used aspirin in the preceding 7 days. Such patients may merely have taken 1 aspirin tablet during that week or may have been on regular daily treatment. These issues may be important because, while thromboxane A2 inhibition may be maximal with low-dose aspirin, other important aspirin effects, including its potential neuroprotective effects, may require higher doses and more frequent administration to maximize efficacy. Others question whether even the antiaggregant effect of aspirin might be dose related in some individuals. Aspirin nonusers may also have been on other antithrombotic or

Another limitation of nonrandomization is that stroke subtypes were unevenly distributed among treatment groups. One would expect, however, that the preponderance of cardioembolic strokes in the aspirin users might bias the results toward more severe strokes in this group. Therefore, these factors may have limited our ability to see larger differences and more persistent differences between the groups. Alternatively, it is possible that the presence of these factors premorbidly may imply that such patients were receiving a greater degree of medical attention and engaging in more aggressive risk factor reduction than were those who did not carry these diagnoses. Even the presence of aspirin use among such patients may represent that more active preventative measures were being pursued. It is possible that these may be equally responsible to aspirin in achieving the lower stroke severity that was observed. While only a prospective randomized study of aspirin versus placebo, which thereby eliminates confounding bias, will be able to better assess this question, it is impossible that such a study will be done.

The strengths of this study include the fact that these data were prospectively collected about aspirin use in a large, multicenter trial whose patients are representative of Americans who have ischemic stroke. All patients were evaluated within 24 hours by validated, clinically relevant rating instruments.

A problem with the comparison between aspirin users and nonusers in this study is that this is a post hoc analysis from data collected for a clinical trial. Patients were not random-
antiplatelet treatments such as ticlopidine. While this may have minimized the magnitude of the apparent effect of aspirin on stroke severity, ticlopidine use is unlikely to have been particularly prevalent. At the time that patients were entered into this study (1990–1996), no other antiplatelet therapies were approved for stroke prevention.

The influence of aspirin use on stroke severity has several implications. It suggests that future clinical trials studying stroke prevention should include some measure of stroke severity as well as stroke incidence to best determine the efficacy of treatment. Additionally, because the severity of neurological impairment affects outcome after stroke, prior aspirin use could influence response to acute treatment. Therefore, future clinical trials testing treatments for acute ischemic stroke should ensure that use of aspirin before stroke is comparable in all study groups.

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References
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for the TOAST Investigators

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