Previous Use of Aspirin and Baseline Stroke Severity
An Analysis of 17 850 Patients in the International Stroke Trial

Stefano Ricci, MD; Steff Lewis, PhD; Peter Sandercock, MA, DM, FRCPE, FMedSci; on behalf of the IST Collaborative Group

Background and Purpose—Some studies suggest that taking aspirin regularly at the time of the onset of stroke reduces stroke severity. Other studies suggest the converse (ie, that previous aspirin therapy is associated with greater stroke severity). We sought to examine this question among the patients enrolled in the International Stroke Trial (IST).

Methods—Analysis of the associations of reported use of aspirin in the 3 days before randomization in IST with baseline stroke severity (as assessed by stroke clinical syndrome, predicted outcome at 6 months, and observed outcome at 6 months). We adjusted analyses for confounding factors.

Results—We excluded those patients who were first scanned after trial entry and were found to have an intracerebral hemorrhage as the cause of the stroke leading to randomization. We performed analyses for all treatment groups combined. For the 17 850 patients with ischemic stroke, data at baseline and follow-up were available for 100% and 99%, respectively. Among these patients, 3820 (21.4%) reported previous aspirin use. Previous aspirin use appeared, in univariate analyses, to be associated with greater baseline stroke severity, more severe stroke syndrome, and, in control subjects, worse observed outcome at 6 months. However, after adjustment, these associations were no longer significant.

Conclusions—In this large prospective and complete data set, we found no evidence of any association of previous aspirin use with baseline stroke severity. The analyses suggest that previously reported positive and negative associations may well have been attributable to the play of chance in small samples, confounding or other biases, rather than a biological effect of aspirin.

Key Words: aspirin • outcome • stroke, ischemic

Several reports have suggested that patients who have an ischemic stroke while taking aspirin have less severe strokes than those not on such pretreatment,1–5 whereas others have suggested either no effect or an increase of stroke severity.6–9 The apparent variations in the effect of previous aspirin use on severity may be real or merely attributable to extreme results occurring in small samples, “confounding by indication” or other methodological factors. First, a variety of methods were used in previous studies to assess stroke severity: neurological scales, disability scales, imaging, and mortality. The type of patients included varied; some studied patients with first-ever stroke, whereas others included recurrent strokes. The proportion of patients reporting previous use of antiplatelet drugs varied from 6% to 55%. If pretreatment with aspirin or other antiplatelet drugs does in fact reduce the cerebral damage from a cerebral ischemic event, this is potentially important. The International Stroke Trial (IST) was a randomized trial among patients with acute ischemic stroke, of whom about one fifth reported previous aspirin use at the time of randomization.10 This study provided a large, complete, prospective data set, which was therefore unlikely to be prone to random error or any bias related to incomplete follow-up.

Materials and Methods

Patients Included in These Analyses
The IST methods have been described previously in detail.10 Briefly, 19 435 patients with a presumed ischemic stroke, with symptoms lasting <48 hours, were randomly allocated to aspirin, subcutaneous heparin, both, or neither. A computed tomography (CT) scan was to be performed before randomization if at all possible but could be done afterward if, in the clinical opinion of the physician in charge, hemorrhagic stroke was highly improbable. After the pilot phase of the study, involving 984 patients, data collected at randomization were extended to include information on several variables, including use of aspirin in the 3 days before the randomization. Of the 18 451 patients in the main trial, data on previous use of aspirin were available for 100%. Of these, the initial event leading to randomization proved, in 569 patients, to be attributable to an intracerebral hemorrhage; we therefore restricted our analysis to the remaining 17 850 patients. To describe the characteristics of the included patients, we compared the frequency of the following variables among those with and without previous aspirin use: male gender, the presence of atrial fibrillation (AF), Oxfordshire Community Stroke Project (OCSP) stroke syndrome,11 and the presence of visible

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From the UOCD Neurologia e Ictus (S.R.), USL 2, Via Cestellini, Perugia, Italy; and Department of Clinical Neurosciences (S.L., P.S.), Western General Hospital, Edinburgh, UK.
Correspondence to Dr Stefano Ricci, UOCD Neurologia e Ictus, Centro di Salute, Via Cestellini, Perugia, Italy 06087. E-mail istitaly@unipg.it
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infarction on the baseline CT. We also compared the mean age and time from stroke onset to randomization in the 2 groups.

Measures Used to Assess Stroke Severity

We used 3 methods to assess baseline stroke severity: OCSP syndrome, baseline-predicted poor outcome, and observed poor outcome. The OCSP syndrome provides a simple assessment of stroke severity, with total anterior circulation syndrome having the worst prognosis. The second type of measure, the predicted probabilities (calculated at baseline) of death within 14 days and of death or dependency at 6 months, was calculated by means of 2 validated prognostic models. The models calculated the probabilities from variables collected at baseline before randomization (the randomization computer did not generate a treatment allocation for the patient in question until all the baseline variables had been entered and validated). The third method of assessing severity (the observed outcome at 14 days and 6 months) was applied to all treatment groups combined and in an analysis restricted to the patients who were allocated to control. The latter patients were to avoid both aspirin and heparin, and this group enabled us to assess the impact of previous aspirin uncomplicated, as far as possible, by the effects of antithrombotic therapy during the acute phase of stroke.

Analysis

We first performed an analysis in the 17 850 patients with ischemic stroke for all treatment groups combined. The relative frequency of dichotomous baseline characteristics among patients with and without previous aspirin use were compared with odds ratios (ORs) and their 95% CIs. We compared the means of continuous variables and tested for differences with a t test (the large numbers precluded the need for nonparametric tests). With OCSP stroke syndrome as the dependent variable, we adjusted for the following potential confounding factors: age, sex, and the presence of AF.

<table>
<thead>
<tr>
<th>Characteristics at Baseline</th>
<th>Previous Aspirin Use</th>
<th>No Previous Aspirin Use</th>
<th>Statistical Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2147 (56.2%)</td>
<td>7382 (52.6%)</td>
<td>OR, 1.16 (1.08–1.24)</td>
</tr>
<tr>
<td>AF</td>
<td>706 (18.5%)</td>
<td>2379 (17.0)</td>
<td>OR, 1.11 (1.01–1.22)</td>
</tr>
<tr>
<td>Clinical syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LACS</td>
<td>862 (22.6%)</td>
<td>3425 (24.4%)</td>
<td>(\chi^2) test</td>
</tr>
<tr>
<td>PACS</td>
<td>1567 (41.0%)</td>
<td>5685 (40.5%)</td>
<td>(P=0.185)</td>
</tr>
<tr>
<td>TACS</td>
<td>938 (24.6%)</td>
<td>3286 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>POCS</td>
<td>443 (11.6%)</td>
<td>1598 (11.4%)</td>
<td>Multinomial regression</td>
</tr>
<tr>
<td>OTHER</td>
<td>10 (2.3%)</td>
<td>36 (2.3%)</td>
<td>(P=0.67)</td>
</tr>
<tr>
<td>Infarct visible on CT</td>
<td>1265 (33.1%)</td>
<td>4737 (33.8%)</td>
<td>OR, 0.97 (0.9–1.05)</td>
</tr>
<tr>
<td>Mean age</td>
<td>73</td>
<td>71</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>Time to randomization</td>
<td>21 h</td>
<td>20 h</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>Severity score (predicted probability of death or dependency at 6 mo) for all patients</td>
<td>0.64</td>
<td>0.63</td>
<td>(P=0.057)</td>
</tr>
<tr>
<td>Severity score (predicted probability of death or dependency at 6 mo) among control group</td>
<td>0.65</td>
<td>0.62</td>
<td>(P=0.004)</td>
</tr>
<tr>
<td>Observed severity (No. dead or dependent at 6 mo) among control group</td>
<td>301/925</td>
<td>1373/3541</td>
<td>OR, 1.33 (1.13–1.57)</td>
</tr>
</tbody>
</table>

LACS indicates lacunar syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; Other, syndrome not classifiable.

Results

Of the 17 850 patients with ischemic stroke eligible for these analyses, 3820 (21.4%) reported taking aspirin in the 3 days before randomization (Table). Previous aspirin users were more often male (OR, 1.16; 95% CI, 1.08 to 1.24), in AF (OR, 1.11; 95% CI, 1.01 to 1.22), older (mean age 73 versus 71; \(P<0.0001\)), and to have been randomized with slightly greater delay from onset (21 hours versus 20 hours; \(P<0.0001\)). There was no significant difference in previous aspirin use in the proportion with visible infarction on the baseline CT scan (OR, 0.97; 95% CI, 0.9 to 1.05). When all these factors were examined in a logistic model, sex, age, and time to randomization remained significantly different between the 2 groups, with \(P<0.0001\), whereas the difference in AF was no longer significant.

OCSP Syndrome As the Measure of Baseline Severity

When we compared the distribution of OCSP stroke syndromes among previous aspirin users and nonusers, we did not find any significant difference (\(P=0.185\)). A multinomial logistic regression, adjusting for age, sex, and AF, again gave a nonsignificant result for previous aspirin use (\(P=0.67\)), whereas the other factors were, as expected, significant predictors of the OCSP ischemic stroke subtype.

“Baseline Predicted Probability of Poor Outcome” As the Measure of Baseline Severity

We then tested the impact of previous aspirin use on severity assessed by “baseline-predicted probability of predicted poor
outcome” (Table); there was no significant effect: $P=0.057$ either on predicted probability of death within 14 days and $P=0.624$ for death or dependency at 6 months. However, when limiting the analysis to the control group (4466 patients, of whom 925 [20.7%] reported previous aspirin use), previous aspirin was highly significantly associated with a higher predicted probability of death or dependency at 6 months ($P=0.004$).

“Observed Poor Outcome” As the Measure of Baseline Severity

We next analyzed the impact of previous aspirin on baseline severity, as measured by “observed outcome (death or dependency at 6 months),” in the control group. Again, previous aspirin use was significantly associated with higher odds of being dead or dependent (OR, 1.31; 95% CI, 1.13 to 1.53), most likely because of greater stroke severity at baseline. However, in a logistic regression with outcome at 6 months as dependent variable and previous use of aspirin as independent predictor, adjusting for age, sex, AF, and stroke type, the result was no longer significant (Table).

Discussion

Is it now possible to conclude reliably that previous aspirin use has no material effect on stroke severity and that any observed effects are attributable to methodological factors and not a biological effect of aspirin? Compared with the published literature on the effect of previous antiplatelet (mostly aspirin) use on stroke severity, the present study certainly has several strengths: the sample size was large (larger than all the other studies together), limiting the possibility of random error and the likelihood of extreme effects in small samples; we collected data prospectively, and data were very complete, limiting data collection and attrition biases; and we included different types of ischemic stroke from a large number of centers in several countries, thus increasing the generalizability of the results. On the other hand, the study design also had some weaknesses: we relied on self-reported aspirin use; we could not analyze either the duration of aspirin pretreatment or the dose, which may well be relevant; or the reasons for that because data on previous myocardial infarction, TIA, or other vascular events were not collected in IST; and the comparison of severity between users and nonusers was not based on random allocation of previous use, and therefore the factors that influenced previous aspirin use were not evenly distributed.

To determine whether any association (either positive or negative) found in an observational study between previous aspirin use and stroke severity is causal, the first step must be to correct for confounding factors. For example, if aspirin users were taking the drug because they already had symptomatic vascular disease at stroke onset, as in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study, the association could be positive (ie, previous aspirin use would be associated with more severe strokes [confounding by indication]). If, on the other hand, previous aspirin use was associated with compliance with treatment and health-seeking behaviors, the association might be negative. The study with the results in most striking contrast to the present study is the TOAST study. The design of the comparison of severity among previous users and nonusers was similar to the present study in that it was a post hoc analysis of prospectively registered data from a randomized trial. The rather different result could be explained in several ways. First, TOAST had a time “window” of eligibility of 24 hours from stroke onset compared with 48 hours in IST. Second, we only asked for use of aspirin in the previous 3 days, whereas in TOAST, the question was “have you used aspirin in the last 7 days?” thus possibly picking up more patients who had been on treatment but omitted their medication in the previous 3 days. Third, the way the severity of stroke was measured was very different, a neurological scale in TOAST compared with the 3 different methods used in these analyses (clinical syndromes, which can predict the outcome even when diagnosed in the acute phase,13 prognostic models obtained from variables collected in the acute phase, and observed outcome at 6 months). Furthermore, the TOAST study was based on just 1 country, whereas our study involved 20 different countries. Finally, the proportion reporting previous aspirin use was very different: 40% in TOAST compared with 21% in IST. However, none of these differences would be expected necessarily to introduce bias into the assessment of the effect of aspirin; the key is in the method used to adjust for confounding factors. In TOAST, 2 different measures of severity were used: the National Institutes of Health Stroke Scale (NIHSS) and the Supplementary Motor Examination (SME) at trial entry. In the adjusted analyses, the association between previous antiplatelet use and severity (NIHSS) persisted but disappeared when severity was assessed by the SME.4

We must also stress the fact that the differences found in the univariate analyses in IST, although statistically highly significant because of the large number of patients, were probably of limited clinical significance. The ORs were close to unity and the difference of means similarly small. Furthermore, the fact that the association disappeared after adjusting for confounding factors confirmed that any apparent relationship of previous aspirin treatment with greater stroke severity was probably not a biological effect but merely attributable to confounding. In summary, we found no evidence that previous aspirin use has any effect on the type and severity of ischemic stroke at baseline or on the outcome at 6 months.

Addendum

After the preparation of this article, a new study appeared online (Sanossian et al: Premorbid antiplatelet use and ischemic stroke outcomes. Neurology. December 28, 2005), which reported data on 260 patients of whom 35% were treated with antiplatelet drugs before the index stroke. The authors (AA) found a lower NIHSS in those on antiplatelets (AP) but included in the “no AP” group a significant number (26 of 168) on warfarin, probably because of AF, which is related to more severe strokes. The duration of AP treatment is not reported, nor is the long-term outcome, because the AAs just concentrate on Rankin at discharge. The mean age of this population was rather young (70 years), and the number who reached an almost complete recovery at discharge (Rankin 0 to 1) was very high (51%), suggesting a particular selection of the population sample. We do not think that these results change our conclusions.
Acknowledgments
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Disclosures
The trial was designed, conducted, analyzed, and reported independently of all sponsors. P.S. and S.R. have received honoraria and travel expenses to lecture at conferences and pharmaceutical advisory meetings, but neither holds any consultancy with, or financial interest in, a pharmaceutical company, nor are they aware of any other potential conflict of interest. S.L. has no conflict of interest to declare.

References
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