Early Deterioration After Thrombolysis Plus Aspirin in Acute Stroke
A Post Hoc Analysis of the Antiplatelet Therapy in Combination With Recombinant t-PA Thrombolysis in Ischemic Stroke Trial

Sanne M. Zinkstok, MD; Ludo F. Beenen, MD; Charles B. Majoie, MD, PhD; Henk A. Marquering, PhD; Rob J. de Haan, PhD; Yvo B. Roos, MD, PhD

Background and Purpose—Aspirin early after intravenous thrombolysis in acute ischemic stroke increases the risk of symptomatic intracranial hemorrhage (SICH), without influencing functional outcome at 3 months. The effect of aspirin on early neurological deterioration (END) was explored as a post hoc analysis of the randomized Antiplatelet Therapy in Combination With Recombinant t-PA Thrombolysis in Ischemic Stroke (ARTIS) trial.

Methods—END, defined as a ≥4 points National Institutes of Health Stroke Scale worsening ≤24 hours after intravenous thrombolysis, was categorized into SICH (END SICH) and cerebral ischemia (END CI). Multinomial logistic regression was used to assess the effect of aspirin on END.

Results—Of the 640 patients, 31 patients (4.8%) experienced END (14 END SICH, 17 END CI). Aspirin increased the risk of END SICH (odds ratio, 3.73; 95% confidence interval, 1.03–13.49) but not of END CI (odds ratio, 1.14; 95% confidence interval, 0.44–3.00). After adjustment for other explanatory variables, the association between aspirin and END SICH remained significant.

Conclusions—In this trial, there is no evidence of an early antithrombotic effect from the addition of aspirin to intravenous thrombolysis in acute ischemic stroke. (Stroke. 2014;45:3080-3082.)

Key Words: aspirin ■ safety ■ stroke ■ thrombolytic therapy
Table 1. Baseline Characteristics (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=322)</th>
<th>Standard Treatment (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.1±13.8</td>
<td>66.7±13.5</td>
</tr>
<tr>
<td>Men</td>
<td>163 (50.6)</td>
<td>160 (50.0)</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>140 (43.5)</td>
<td>129 (40.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (11.8)</td>
<td>26 (8.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>36 (11.2)</td>
<td>35 (10.9)</td>
</tr>
<tr>
<td>Prestroke mRS ≥1</td>
<td>38 (11.8)</td>
<td>42 (13.1)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>9 (5–15)</td>
<td>9 (5–14)</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>45 (15.6)</td>
<td>63 (21.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>156 (22)</td>
<td>156 (22)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83 (13)</td>
<td>84 (14)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.3±2.8</td>
<td>7.0±1.8</td>
</tr>
<tr>
<td>Onset to IVT time, min</td>
<td>113 (85–150)</td>
<td>115 (85–165)</td>
</tr>
</tbody>
</table>

Data are number, n (%), mean (SD), or median (interquartile range). ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; HCMAS, hyperdense middle cerebral artery sign; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Not scored for patients with posterior circulation stroke.

Table 2. Univariate Multinomial Logistic Regression: Impact of Potential Explanatory Variables on Early Neurological Deterioration (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th></th>
<th>No END (n=609)</th>
<th>END (n=31)</th>
<th>OR (95% CI)</th>
<th>Value</th>
<th>END (n=14)</th>
<th>OR (95% CI)</th>
<th>Value</th>
<th>END (n=17)</th>
<th>OR (95% CI)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early aspirin*</td>
<td>302 (49.6)</td>
<td>20 (64.5)</td>
<td>1.85 (0.87–3.92)</td>
<td>0.11</td>
<td>11 (78.6)</td>
<td>3.73 (1.03–13.49)</td>
<td>0.03</td>
<td>8 (47.1)</td>
<td>1.14 (0.44–3.00)</td>
<td>0.79</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.7 (13.5)</td>
<td>71.1 (12.4)</td>
<td>1.03 (1.00–1.06)</td>
<td>0.08</td>
<td>76.4 (7.7)</td>
<td>1.07 (1.02–1.12)</td>
<td>0.01</td>
<td>66.7 (13.9)</td>
<td>1.00 (0.96–1.04)</td>
<td>0.99</td>
</tr>
<tr>
<td>Men*</td>
<td>303 (49.8)</td>
<td>19 (61.3)</td>
<td>1.60 (0.76–3.35)</td>
<td>0.21</td>
<td>6 (42.9)</td>
<td>0.76 (0.26–2.21)</td>
<td>0.61</td>
<td>13 (76.5)</td>
<td>3.28 (1.06–10.18)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are number, n (%), mean (SD), or median (interquartile range). ASPECTS indicates Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; END, early neurological deterioration due to cerebral ischemia; ENDCI, early neurological deterioration due to symptomatic intracranial hemorrhage; END_SICH, early neurological deterioration due to symptomatic intracranial hemorrhage; HCMAS, hyperdense middle cerebral artery sign; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Variable included in the multivariate model.
†No observations to estimate the effect size.
‡Not scored for patients with posterior circulation stroke.

Discussion

This post hoc analysis shows that aspirin early after IVT in ischemic stroke is related to END_SICH without evidence of a beneficial effect on ENDCI. These results are consistent with the only other trial that investigated aspirin concomitant with IVT, which showed that patients treated with aspirin and streptokinase had higher rates of in-hospital cerebral death with ICH compared with patients receiving streptokinase only, whereas proportions of cerebral death without an ICH were similar between the groups.6 The hypothesis of ARTIS was based on the observation that antiplatelet therapy before IVT has a beneficial effect,5,9 whereas more recent studies could not confirm this association.16 Hence, from this hypothesis-testing analysis, there is no reason to assume that aspirin early after IVT has a compensatory antithrombotic effect in the acute phase. Because only 2 small transcranial Doppler studies investigated the effect of prior antiplatelet therapy on recanalization after IVT showing conflicting results,11,12 more studies are needed to further unravel the effects of antiplatelet therapy in combination with IVT.

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Disclosures
None.

References
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