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_{C,I}). 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_{C,I}). Aspirin increased the risk of END_{SICH} (odds ratio, 3.73; 95% confidence interval, 1.03–13.49) but not of END_{C,I} (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

The randomized Antiplatelet in Combination With Recombinant t-PA Thrombolysis in Ischemic Stroke (ARTIS) trial demonstrated that early addition of aspirin after intravenous thrombolysis (IVT) increased the risk of symptomatic intracranial hemorrhage (SICH), without influencing functional outcome at 3 months.1 This apparent lack of effect can be interpreted in 3 ways: either the trial results were falsely negative, or the hypothesized antithrombotic effect has not become manifest in the long-term end point, or the hypothesis was incorrect. Early neurological deterioration (END) after IVT is related to stroke progression and recurrence, in addition to SICH,2,3 and has been attributed to the inability to achieve or sustain vessel patency4 and occurred less likely while on aspirin.5 The aim of this post hoc analysis was to explore the effect of aspirin on END.

Methods
Methodology of ARTIS has been described before.1 Briefly, 642 aspirin-naïve ischemic stroke patients were randomized to aspirin ≤90 minutes after IVT or IVT alone. END was defined as a ≥4 points National Institutes of Health Stroke Scale worsening ≤24 hours after IVT, categorized into SICH (END_{SICH}) and cerebral ischemia (END_{C,I}). Patients with END because of other causes were excluded. Anonymized admission computed tomographic scans were evaluated by a blinded neuroradiologist and an emergency radiologist independently for Alberta Stroke Program Early CT Score,6,7 the presence of a hyperdense middle cerebral artery sign, old (lacunar) infarction, and leukoaraiosis. In case of disagreement, computed tomographic scans were reviewed until consensus was reached.

Statistical analyses were done in both the intention-to-treat and per-protocol population. Potential explanatory variables that were significantly (P≤0.20) associated with END_{SICH} or END_{C,I} in the univariate multinomial logistic regression analyses were entered into a multivariate model with forced entry of aspirin. Effect sizes were presented in (adjusted) odds ratios (ORs). Statistical uncertainty was expressed in 95% confidence intervals (CIs).

Results
Baseline characteristics were similar between the treatment groups (Table 1). After exclusion of 2 patients with END because of a seizure and pneumonia (standard treatment), 31 of 640 patients (4.8%) experienced END (14 END_{SICH}, 17 END_{C,I}). Unvariably, aspirin tended to increase END (OR, 1.85; 95% CI, 0.87–3.92), which was attributed to END_{SICH} (OR, 3.73; 95% CI, 1.03–13.49) but not to END_{C,I} (OR, 1.14; 95% CI, 0.44–3.00; Table 2). After adjustment for explanatory variables, aspirin remained associated with END_{SICH} (adjusted OR, 5.38; 95% CI, 1.05–27.48) but...
not with all END (adjusted OR, 1.69; 95% CI, 0.70–4.11) or END<sub>C</sub> (adjusted OR, 0.75; 95% CI, 0.24–2.39). Results were similar in the per-protocol population.

**Discussion**

This post hoc analysis shows that aspirin early after IVT in ischemic stroke is related to END<sub>SCt</sub> without evidence of a beneficial effect on END<sub>C</sub>. 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. The hypothesis of ARTIS was based on the observation that antiplatelet therapy before IVT has a beneficial effect, whereas more recent studies could not confirm this association. 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, more studies are needed to further unravel the effects of antiplatelet therapy in combination with IVT.

**Acknowledgments**

We thank Janneke Schut, medical student, who contributed to the collection of computed tomographic scans and the radiological assessment.

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**Table 1. Baseline Characteristics (Intention-to-Treat Population)**

<table>
<thead>
<tr>
<th>History</th>
<th>Aspirin (n=322)</th>
<th>Standard Treatment (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>67±13.8</td>
<td>66.7±13.5</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>163 (50.6)</td>
<td>160 (50.0)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>140 (43.5)</td>
<td>129 (40.3)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>38 (11.8)</td>
<td>26 (8.1)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>36 (11.2)</td>
<td>35 (10.9)</td>
</tr>
<tr>
<td><strong>Premortem mRS ≥1</strong></td>
<td>38 (11.8)</td>
<td>42 (13.1)</td>
</tr>
<tr>
<td><strong>NIHSS</strong></td>
<td>9 (5–15)</td>
<td>9 (5–14)</td>
</tr>
<tr>
<td><strong>Cardioembolic stroke</strong></td>
<td>45 (15.6)</td>
<td>63 (21.7)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td>156 (22)</td>
<td>156 (22)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>83 (13)</td>
<td>84 (14)</td>
</tr>
<tr>
<td><strong>Glucose, mmol/L</strong></td>
<td>7.3±2.8</td>
<td>7.0±1.8</td>
</tr>
<tr>
<td><strong>Onset to IVT time, min</strong></td>
<td>113 (85–150)</td>
<td>115 (85–165)</td>
</tr>
</tbody>
</table>

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

<table>
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<tr>
<th>No END (n=609)</th>
<th>END (n=31)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>END&lt;sub&gt;SCt&lt;/sub&gt; (n=14)</th>
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<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 (76.6)</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>
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<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>
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<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>
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**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.**

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Disclosures
None.

References
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