Factors Associated With Intracerebral Hemorrhage After Thrombolytic Therapy for Ischemic Stroke

Pooled Analysis of Placebo Data From the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II Trials

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Background and Purpose—A number of factors have been associated with postthrombolysis intracerebral hemorrhage, but these have varied across studies.

Methods—We examined patients with acute ischemic stroke treated with intravenous tissue plasminogen activator within 3 hours of symptom onset who were enrolled in the placebo arms of 2 trials (Stroke-Acute Ischemic NXY Treatment [SAINT] I and II Trials) of a putative neuroprotectant. Early CT changes were graded using the Alberta Stroke Program Early CT Score (ASPECTS). Post–tissue plasminogen activator symptomatic intracerebral hemorrhage was defined as a worsening in National Institutes of Health Stroke Scale of ≥4 points within 36 hours with evidence of hemorrhage on follow-up neuroimaging. Good clinical outcome was defined as a modified Rankin scale of 0 to 2 at 90 days.

Results—Symptomatic intracerebral hemorrhage occurred in 5.6% of 965 patients treated with tissue plasminogen activator. In multivariable analysis, symptomatic intracerebral hemorrhage was increased with baseline antiplatelet use (single antiplatelet: OR, 2.04, 95% CI, 1.07 to 3.87, P = 0.03; double antiplatelet: OR, 9.29, 3.28 to 26.32, P < 0.001), higher National Institutes of Health Stroke Scale score (OR, 1.09 per point, 1.03 to 1.15, P = 0.002), and CT changes defined by ASPECTS (ASPECTS 8 to 9: OR, 2.26, 0.63 to 8.10, P = 0.21; ASPECTS ≤7: OR, 5.63, 1.66 to 19.10, P = 0.006). Higher National Institutes of Health Stroke Scale was associated with decreased odds of good clinical outcome (OR, 0.82 per point, 0.79 to 0.85, P < 0.001). There was no relationship between baseline antiplatelet use or CT changes and clinical outcome.

Conclusions—Along with higher National Institutes of Health Stroke Scale and extensive early CT changes, baseline antiplatelet use (particularly double antiplatelet therapy) was associated with an increased risk of post–tissue plasminogen activator symptomatic intracerebral hemorrhage. Of these factors, only National Institutes of Health Stroke Scale was associated with clinical outcome. (Stroke. 2009;40:3067-3072.)

Key Words: acute ischemic stroke ■ intracerebral hemorrhage ■ prognosis ■ thrombolysis

Symptomatic intracerebral hemorrhage (ICH) complicates thrombolytic therapy for acute ischemic stroke in approximately 6% of patients and is associated with very poor outcome.1–3 A number of factors have been associated with an increased risk of postthrombolysis ICH. In a recent systematic review, the presence of early hypodensity on CT, elevated serum glucose, and history of diabetes were most consistently associated with increased risk.4 Increasing stroke severity, longer time to treatment, higher pretreatment blood pressure, lower platelet count, history of cardiac disease, history of congestive heart failure, prior antiplatelet therapy, use of antiplatelet agents other than aspirin, advanced age, and nonsmoking status have also been associated with increased risk in some studies.3–9 We examined factors associated with postthrombolysis ICH in the placebo arm of 2 large companion acute stroke neuroprotectant trials (Stroke-Acute Ischemic NXY Treatment [SAINT] I and SAINT II Trials). We also examined the impact of these factors on final clinical outcome.

Methods

Detailed descriptions of the SAINT I and SAINT II trials have been published previously.10,11 These trials enrolled patients from May...
2003 to June 2006 and involved 520 centers in multiple countries worldwide. Briefly, the trials were companion randomized trials with similar design and inclusion/exclusion designed to test the efficacy of the putative neuroprotectant NXY-059 compared with placebo in acute ischemic stroke. Patients treated with intravenous tissue plasminogen activator (tPA) within 3 hours of symptom onset according to local treatment practices were eligible for enrollment in both SAINT trials. Given the possibility of an interaction between NXY-059 and postthrombolysis hemorrhage, we included in our analysis only patients randomized to placebo in the 2 trials. Given the similar designs of SAINT I and SAINT II, data were pooled. All study procedures were approved by local Institutional Review Boards as appropriate.

**Patients**

Patients were eligible for enrollment in the SAINT trials if they had a clinical diagnosis of acute ischemic stroke, a National Institutes of Health Stroke Scale (NIHSS) score ≥6 of which 2 points had to be for limb weakness, were ≥18 years of age, were not in a coma, and had no history of severe renal disease. Written informed consent was obtained from patients or legally acceptable surrogates. For this analysis, only enrolled patients treated with tPA were included.

**Procedures**

As part of the SAINT protocols, formal clinical assessments with the NIHSS occurred at baseline and 24 and 72 hours after enrollment and were done by personnel trained and certified in its performance. Antiplatelet use was defined as a patient or family report that the patient took aspirin, ticlopidine, clopidogrel, triflusil, cilostazol, or dipyridamole within the 3 days immediately before the stroke for which they were enrolled. Early CT changes were graded using the Alberta Stroke Program Early CT Score (ASPECTS). ASPECTS is a semiquantitative grading scheme that assesses hypoattenuation on CT in 10 brain regions supplied by the middle cerebral artery. Scores range from 0 to 10, with 10 being a normal CT and 0 representing extensive, complete middle cerebral artery territory hypoattenuation. All patients treated with thrombolytic therapy underwent systematic follow-up neuroimaging at 72 hours after enrollment. Earlier repeat neuroimaging was mandated if neurologic deterioration occurred. Post-tPA symptomatic ICH (sICH) was defined as a worsening in NIHSS score of ≥4 points within 36 hours with evidence of any hemorrhage on follow-up neuroimaging. Asymptomatic ICH (aICH) was defined as the presence of any hemorrhage without neurological worsening. Interpretation of all neuroimaging studies was performed by a central reader blinded to treatment. Final clinical outcome was categorized based on modified Rankin scale (mRS) assessment at 90 day follow-up by trained and certified personnel.

**Statistical Analysis**

Initial univariable analysis compared baseline factors between those with sICH, aICH, and no ICH. Our selection of baseline factors for testing paralleled the analysis in the Multicenter rt-PA Acute Stroke Survey, a large observational study of hemorrhage risk after thrombolytic therapy, with several modifications. First, we analyzed NIHSS and onset to treatment time as continuous variables given that these data were available in our data set, whereas in the Multicenter Stroke Survey, these were collected and therefore analyzed only as categorical variables. Second, we divided antiplatelet therapy into use of single versus double antiplatelet agents as opposed to aspirin versus “other antiplatelets” because this seemed biologically to be more sensible in terms of potential hemorrhage risk. Third, we used ASPECTS grading to assess CT hypodensity as opposed to the local assessment of more than one third versus less than one third middle cerebral artery territory involvement. This reflects the fact that assessment of early hypodensity was only performed systematically with ASPECTS in our data set and is supported by the greater interrater reliability of ASPECTS. Fourth, we additionally tested the specific factors ischemic heart disease and congestive heart failure in lieu of “other cardiac disease,” the category used in the Multicenter Stroke Survey. We felt this was appropriate because of the increased precision of these factors and because data from European Cooperative Acute Stroke Study (ECASS II) suggested that congestive heart failure was an independent predictor of sICH.

Multivariable analysis was performed using logistic regression, including variables significant at \( P < 0.10 \), in the univariable analysis. We used similar methods to test the role of these factors on clinical outcome with good outcome defined as a mRS of 0 to 2 at 3 months poststroke.

**Results**

A total of 965 subjects were enrolled with intravenous tPA and in the SAINT trials. The mean age was 68 ± 13 years, 57% of subjects were male, and 92% were white. The median time from symptom onset to treatment with tPA was 145 ± 33 minutes. The median and mean NIHSS at enrollment was 14. sICH occurred in 5.6% (95% CI, 4.1% to 7.0%) and aICH in 17.3% (95% CI, 14.9% to 19.7%). Follow-up neuroimaging was performed with CT in 91% of patients and MRI in 9%. There was no difference in the rate of sICH or aICH based on the type of follow-up neuroimaging. Characteristics of enrolled patients by ICH status are shown in Table 1. For purposes of comparison with prior studies, absolute hemorrhage rates associated with various factors are presented in the Figure.

Multivariable analysis showed that risk of sICH was increased with antiplatelet use at the time of enrollment, particularly with double antiplatelet therapy (single antiplatelet: OR, 2.04, 1.07 to 3.87, \( P < 0.03 \); double antiplatelet: OR, 9.29, 3.28 to 26.32, \( P < 0.001 \)), higher NIHSS score (OR, 1.09 per point, 1.03 to 1.15, \( P = 0.002 \)), and lower ASPECTS (ASPECTS 8 to 9: OR, 2.26, 0.63 to 8.10, \( P = 0.21 \); ASPECTS ≤7: OR, 5.63, 1.66 to 19.10, \( P = 0.006 \)) (Table 2). There was an inverse relationship between risk of sICH and history of stroke (OR, 0.13, 0.03 to 0.60, \( P = 0.009 \)).

Risk of aICH was increased with older age (OR, 1.03 per year, 1.02 to 1.05, \( P < 0.001 \)), higher NIHSS (OR, 1.07 per point, 1.03 to 1.10, \( P < 0.001 \)), and lower ASPECTS (ASPECTS 8 to 9: OR, 1.05, 0.42 to 2.64, \( P = 0.92 \); ASPECTS ≤7: OR, 4.43, 1.72 to 11.38, \( P = 0.002 \)) (Table 3). Risk of aICH was lower with antiplatelet use (single antiplatelet: OR, 0.59, 0.38 to 0.93, \( P = 0.02 \); double antiplatelet: OR, 0.76, 0.28 to 2.07, \( P = 0.59 \)).

Risk of any ICH was increased with greater age (OR, 1.03 per year, 1.02 to 1.05, \( P < 0.001 \)), higher NIHSS (OR, 1.07 per point, 1.04 to 1.11, \( P < 0.001 \)), and lower ASPECTS (ASPECTS 8 to 9: OR, 1.36, 0.62 to 3.01, \( P = 0.45 \); ASPECTS ≤7: OR, 4.82, 2.0 to 11.5, \( P < 0.001 \)) (Table 4).

To further characterize the relationship between double antiplatelet therapy and risk of sICH, we analyzed the specific antiplatelet regimen for the 43 patients found to be on double antiplatelet therapy. This included 34 patients on aspirin plus clopidogrel, 5 on aspirin plus dipyridamole, 2 on aspirin plus ticlopidine, and one each on aspirin plus triflusil and aspirin plus cilostazol. All sICH in the double antiplatelet group occurred in patients on combination aspirin and clopidogrel.

An additional exploratory analysis assessing the relationship between serum glucose measured at 24 hours after enrollment and risk of sICH was performed. This was done in response to observations from the ECASS II trial, which
Factors Associated With Clinical Outcome

Overall, 46% of patients treated with tPA had a good outcome (defined as mRS 0 to 2) and 14% of patients died. Only 6% of those with sICH had a good outcome, and 61% died.

In multivariable analysis, a good outcome was less likely in older patients (OR, 0.96 per year, 0.95 to 0.98, \( P < 0.001 \)), those with a history of congestive heart failure (OR, 0.47, 0.25 to 0.87, \( P = 0.02 \)), those with higher systolic blood pressure (OR, 0.91 per 10 mm Hg, 0.84 to 0.99, \( P = 0.03 \)), and higher NIHSS (OR, 0.82, 0.79 to 0.85, \( P < 0.001 \)) (Table 5). Good outcome was more likely with higher diastolic blood pressure (OR, 1.13 per 10 mm Hg, 1.00 to 1.27, \( P = 0.05 \)). Notably, there was no relationship between antiplatelet use and outcome (single antiplatelet: OR, 0.98, 0.68 to 1.43, \( P = 0.93 \); double antiplatelet: OR, 0.74, 0.32 to 1.73, \( P = 0.49 \)).

Discussion

In this analysis of a prospective cohort of carefully monitored patients treated with intravenous tPA, we found an increased risk of sICH associated with greater stroke severity, as measured by the NIHSS, and major, extensive early infarct changes on CT scan, as defined by ASPECTS \( \leq 7 \). We also found a significant relationship between baseline antiplatelet use, particularly involving double antiplatelet therapy, and risk of sICH. Interestingly, there was no increased risk of overall ICH associated with antiplatelet use, largely because the risk of asICH was actually lower in the antiplatelet group. One possible explanation for these findings is that antiplatelet use does not increase the risk of hemorrhage itself, but if hemorrhage occurs, it is more likely to become clinically significant, presumably due to continued bleeding related to the antiplatelet-induced coagulopathy. To our knowledge, the finding of a particularly increased risk of postthrombolysis sICH associated with prior double antiplatelet therapy has not been previously described, although it is perhaps not surpris-
ing given evidence of increased bleeding complications with double antiplatelet therapy in stroke prevention trials. This observation should be considered preliminary, however, given the small number of patients in our cohort on double antiplatelet therapy.

Several previous studies have suggested an increased risk of sICH in patients on antiplatelet therapy, although this has not been shown to influence overall clinical outcome in patients treated with thrombolytic therapy. In tPA-treated

### Table 2. Multivariable Logistic Regression Model for sICH Versus No ICH

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>1.02 (0.99–1.05)</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.49 (0.18–1.36)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.13 (0.03–0.60)</td>
<td>0.009</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2.04 (1.07–3.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>Double</td>
<td>9.29 (3.28–26.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS per point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2.04 (1.07–3.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>Double</td>
<td>9.29 (3.28–26.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–9</td>
<td>2.26 (0.63–8.10)</td>
<td>0.21</td>
</tr>
<tr>
<td>≤7</td>
<td>5.63 (1.66–19.10)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Note. Analysis incorporated all factors significant in univariable analysis at P<0.10. N=784.

### Table 3. Multivariable Logistic Regression Model for asICH Versus No ICH

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>1.03 (1.02–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.59 (0.38–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Double</td>
<td>0.76 (0.28–2.07)</td>
<td>0.59</td>
</tr>
<tr>
<td>NIHSS, per point</td>
<td>1.07 (1.03–1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–9</td>
<td>1.05 (0.42–2.64)</td>
<td>0.92</td>
</tr>
<tr>
<td>≤7</td>
<td>4.43 (1.72–11.38)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glucose per 10 mg/dL</td>
<td>1.03 (1.0–1.07)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Note. Analysis incorporated all factors significant in univariable analysis at P<0.10 except for platelet count, which was missing for a substantial no. of subjects. Analysis, including platelet count in the multivariable model, did not substantially alter any of the results. N=784.
patients in ECASS II, sICH occurred in 18.9% of patients on aspirin compared with 6.2% of those not on aspirin. Our results indicate a less substantial differential risk with sICH occurring in 8.2% of patients on a single antiplatelet agent compared with 3.7% on no antiplatelet agent. In our study, final clinical outcome was not modified by antiplatelet use despite the increased risk of sICH. This raises the possibility that the increased risk of bleeding with antiplatelet medication in some patients is balanced by beneficial effects in other patients, perhaps mediated by increased reperfusion or a decreased risk of vessel reocclusion. In the National Institute of Neurological Diseases (NINDS) and Stroke tPA trial, patients with prior aspirin use had a lower rate of early clinical deterioration, although the mechanism underlying this finding was unclear.15 On the other hand, animal models examining the interaction between antiplatelet agents and tPA have shown complex and contradictory results with aspirin counterintuitively attenuating thrombolysis and reducing hemorrhage in some models and increasing hemorrhage without substantially altering thrombolytic efficacy in others.16–18

In our cohort, we did not find a relationship between either baseline serum glucose or history of diabetes and risk of sICH. Several other large clinical trials of intravenous thrombolysis, including ECASS II, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), and an initial analysis of the NINDS trial, also failed to find an independent association between baseline glucose and sICH, although a subsequent reanalysis of NINDS incorporating the placebo-treated patients and using a different statistical approach did report an increased risk of sICH with hyperglycemia.6,7,19 In contrast, large observational studies in clinical practice such as the Multicenter tPA Stroke Survey Group, Canadian Alteplase Stroke Effectiveness Study, and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) have consistently demonstrated an association between sICH and hyperglycemia.2,3,8

In the ECASS II trial, the relationship between hyperglycemia and parenchymal ICH varied significantly based on the timing of glucose measurement.13 For subjects with elevated baseline glucose but normal 24-hour glucose, there was no increased risk of parenchymal hemorrhage. In contrast, non-diabetic subjects with hyperglycemia at 24-hour measurement (with or without baseline hyperglycemia) had a very substantial increased risk of parenchymal hemorrhage. The findings of our analysis largely confirm these observations from the ECASS II study. Therefore, it appears that timing of glucose measurement may be critical to its association with sICH. This also raises the important question of the cause-and-effect relationship between hyperglycemia and sICH. Given that most sICH after thrombolysis occurs within the first 24 hours,6 and that hyperglycemia may represent a reactive “stress response” to critical illness, it is plausible that hyperglycemia at the 24-hour time point is actually precipitated by sICH as opposed to being predictive of it, thus accounting for the observed association.

In this respect, the discrepancy between data from clinical trials and from observational studies in clinical practice is intriguing. It could be speculated that glucose measurements recorded in clinical trials might occur more reliably pre-enrollment and therefore truly at baseline, whereas those collected in observational studies in clinical practice might often reflect measurements at somewhat later time points, introducing a potential important bias confounding the perceived relationship between hyperglycemia and sICH. The role of hyperglycemia in promoting sICH after thrombolytic therapy remains to be clarified, and future studies should closely examine the relationship between sICH and glucose levels at baseline and later time points.

An inverse relationship between the risk of sICH and history of stroke was identified in our study, a finding that was unexpected and has not been found in previous studies. Patients with pre-existing significant disability, defined as a mRS of ≥2, were excluded from enrollment in the SAINT trials and thus not represented in our cohort. It is possible that

### Table 5. Multivariable Logistic Regression Model for Good Outcome

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>1.03 (1.02–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.77 (0.52–1.14)</td>
<td>0.19</td>
</tr>
<tr>
<td>Double</td>
<td>1.56 (0.75–3.27)</td>
<td>0.24</td>
</tr>
<tr>
<td>NIHSS, per point</td>
<td>1.07 (1.04–1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–9</td>
<td>1.36 (0.62–2.01)</td>
<td>0.45</td>
</tr>
<tr>
<td>≤7</td>
<td>4.82 (2.02–11.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose per 10 mg/dL</td>
<td>1.03 (1.01–1.06)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Note. Analysis included factors significantly associated with good outcome in univariable analysis at P<0.10. Good outcome defined as mRS 0 to 2. N=798.
the exclusion of patients with prior stroke associated with major disability could account for the discrepant risk of sICH seen in our cohort. Alternatively, and probably most likely, this observation is spurious.

A final important observation in our study relates to the risk of postthrombolysis hemorrhage associated with increasing age. Marketing authorization for recombinant tPA does not extend to patients aged >80 years in Europe, and concerns about safety in this population are frequently expressed. Although we found an association between age and asICH, there was no association between age and sICH in multivariate analysis in our cohort. Given that almost 20% of our total patient population was aged >80 years old, this provides important reassuring safety data supporting thrombolytic therapy in this demographic group. These findings are in agreement with other reports that have assessed the risk of sICH after thrombolysis in the elderly.20,21

Our study has a number of strengths, including prospective data collection using a standardized case report form across study sites, central analysis of all imaging studies, and use of trained and certified personnel to determine NIHSS and mRS scores. However, there are also limitations based on the analysis being post hoc and focused mainly on factors previously suggested to be related to post-tPA hemorrhage. Confounding by alternative unmeasured factors associated with post-tPA hemorrhage is certainly possible. Furthermore, because data were collected in the setting of a clinical trial, the enrolled population was highly selected and may not be representative of the stroke population in clinical practice, limiting generalizability. In particular, patients with prior disabling stroke, severe renal disease, or multiple comorbidities limiting life expectancy were excluded.

In conclusion, we found that patients with higher NIHSS scores, baseline antiplatelet use (particularly double antiplatelet therapy), and major, extensive early CT findings were at increased risk of sICH after intravenous tPA. The finding of a particularly increased risk of sICH with double antiplatelet therapy is novel and requires further confirmation in future studies. Of these factors, only NIHSS score was associated with final clinical outcome. Given the lack of an association between prior use of antiplatelet therapy and clinical outcome, our data do not support using this factor to withhold thrombolytic treatment.

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The SAINT trials were sponsored by AstraZeneca.

Disclosures
None.

References
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