Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated With Intravenous Alteplase

Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score

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Background and Purpose—Symptomatic intracerebral hemorrhage (SICH) is a serious complication in patients with acute ischemic stroke treated with intravenous thrombolysis. We aimed to develop a clinical score that can easily be applied to predict the risk of SICH.

Methods—We analyzed data from 31 627 patients treated with intravenous alteplase enrolled in the Safe Implementation of Treatments in Stroke (SITS) International Stroke Thrombolysis Register. The outcome measure was SICH per the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition: a Type 2 parenchymal hemorrhage with deterioration in National Institutes of Health Stroke Scale score of ≥4 points or death. Univariate risk factors associated with the outcome were entered into a logistic regression model after stratification of continuous variables. Adjusted ORs for the independent risk factors were converted into points, which were summed to produce a risk score.

Results—We identified 9 independent risk factors for SICH: baseline National Institutes of Health Stroke Scale, serum glucose, systolic blood pressure, age, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and history of hypertension. The overall rate of SICH was 1.8%. The risk score ranged from 0 to 12 points and showed a >70-fold graded increase in the rate of SICH for patients with a score ≥10 points (14.3%) compared with a score of 0 point (0.2%). The prognostic discriminating capability by C statistic was 0.70.

Conclusions—The SITS SICH risk score predicts large cerebral parenchymal hemorrhages associated with severe clinical deterioration. The score could aid clinicians to identify patients at high as well as low risk of SICH after intravenous alteplase. (Stroke. 2012;43:00-00.)

Key Words: cerebral infarct ■ database ■ hemorrhag ■ intrac ■ prognosis ■ stroke management ■ thrombolysis

Intravenous thrombolysis with alteplase improves functional neurological outcome and reduces mortality in acute ischemic stroke. After numerous randomized controlled trials and safety monitoring studies, alteplase is now approved within 3 hours and recommended by major professional organizations within 4.5 hours of symptom onset. The proportion of patients who benefit from thrombolysis by at least 1 point on the modified Rankin Scale has been calculated to 32%, whereas 3% sustain worsened outcome by any degree of the modified Rankin Scale compared with placebo. However, alteplase has the potential to cause life-threatening intracerebral hemorrhage. Several clinical, radiological, and pharmacological factors have
been implicated in raising the risk for different varieties of thrombolysis-related cerebral hemorrhage.\(^{17,18}\) Not all types and amounts of cerebral blood extravasation have been found to cause symptoms superimposed on those caused by the acute ischemia itself or by edema or to worsen long-term functional outcome.\(^{19–22}\) Truly symptomatic intracerebral hemorrhage (SICH) caused by thrombolysis can be conceptualized as a homogenous blood clot large enough to exert a mass effect on brain tissue outside the infarct. Furthermore, it must be associated with distinct deterioration in neurological status occurring within a timeframe when an effect of alteplase is pharmacologically plausible. Previously published models of risk stratification in thrombolysis were designed for a less specific outcome definition, that is, any type and size of hemorrhage plus any level of neurological decline within a variable timeframe.\(^{23,24}\) There is currently a lack of risk scores that predict true SICH.

To be clinically practical, a risk score should be easy to apply at the bedside using information available in the emergency situation. To perform accurately, it should use variables that confer independent prognostic information and must take into account the complex profile of patients with multiple risk factors. Such a score could be useful in adjusting for baseline risk and patient selection in future trials of reperfusion therapy and could be combined with future radiological methods and biomarkers predicting thrombolytic complications.

In the present study, we aimed to develop a risk score for SICH derived from a comprehensive multivariate analysis in a large prospectively collected cohort of patients treated with intravenous alteplase for acute ischemic stroke enrolled into the Safe Implementation of Treatments in Stroke—International Stroke Thrombolysis Register (SITS-ISTR).

**Methods**

**Study Population**

All patients recorded in the SITS-ISTR between December 25, 2002, and March 1, 2010, were included in this study. Patients were included if they presented with stroke symptoms and were treated with intravenous alteplase (Actilyse; Boehringer-Ingelheim, Ingelheim, Germany) within as well as outside license criteria. The need for ethical approval or patient consent for participation in the SITS-ISTR varied among participating countries, but ethics approval and patient consent were obtained in countries that required this; other countries approved the register for conduct as an anonymized audit. The SITS-Monitoring SStudy (MOST) data \(n=6483\)\(^{16}\) are embedded within the SITS-ISTR. The SITS-MOST was approved by the Ethics Committee of the Karolinska Institutet in Stockholm, Sweden, as well as by the Swedish Medical Products Agency. The SITS International Coordination Office did regular online monitoring of the SITS-ISTR data and checked individual patient data monthly to identify errors or inconsistencies. For a sample of patients included in SITS-MOST, source data were verified on-site by monitors under the supervision of the national coordinator.

**Procedures**

The SITS-ISTR is an ongoing, prospective, Internet-based, academic-driven, multinational, observational monitoring register for clinical centers using thrombolysis for the treatment of acute ischemic stroke. The methodology of the SITS-ISTR, including the procedure for data collection and management, patient identification, and verification of source data, has been described previously.\(^{10}\)

We collected baseline and demographic characteristics, stroke severity per the National Institutes of Health Stroke Scale (NIHSS), risk factors, onset-to-treatment time, medication history, and imaging data on admission and follow-up.

The main outcome measure of this study was SICH per the SITS-MOST definition: a local or remote Type 2 parenchymal hemorrhage on imaging 22 to 36 hours after treatment or earlier if the imaging scan was performed due to clinical deterioration combined with a neurological deterioration of \(\geq 4\) NIHSS points from baseline or from the lowest NIHSS score between baseline and 24 hours or leading to death within 24 hours. A grading of Type 2 parenchymal hemorrhage for intracranial hemorrhage indicates a coagulum exceeding 30% of the infarct with substantial space occupation.

In addition to the SITS-MOST definition, we used 2 other definitions of SICH to enable comparison with previously published data: (1) SICH per the European Cooperative Acute Stroke Study (ECASS) II definition: any type of intracerebral hemorrhage on any posttreatment imaging after the start of thrombolysis and increase of \(\geq 4\) NIHSS points from baseline, or from the lowest value within 7 days, or leading to death; and (2) SICH per the National Institute of Neurological Disorders and Stroke (NINDS) definition: any deterioration in NIHSS score or death within 7 days combined with intracerebral hemorrhage of any type (including petechial) on any posttreatment imaging after the start of thrombolysis.

All assessments of imaging studies and neurological status were done according to clinical routine at centers participating in the SITS-ISTR. A follow-up CT or MR scan at 22 to 36 hours after intravenous tissue-type plasminogen activator treatment was required for all patients. All SICH events (per SITS-MOST, ECASS II, and NINDS definitions) were adjudicated centrally by the SITS International Coordination Office based on submitted imaging and clinical data.

**Statistical Analysis**

We performed descriptive statistics for baseline, imaging, and demographic data, comparing patients with and without SICH per SITS-MOST definition. All baseline variables available in the SITS-ISTR were analyzed. For continuous variables, median and interquartile range values were calculated. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases, as done in previous SITS publications.\(^{10–12}\) For calculation of significance of difference between medians and proportions, we used the Mann-Whitney U test and the Pearson \(\chi^2\) method, respectively. To avoid variable selection caused by spurious correlations, only variables showing an association with SICH at the \(p=0.10\) level in the univariate analysis were included as potential predictors into the multivariate logistic regression model. This analysis, variables significant at \(p<0.05\) were regarded as independent risk factors for SICH. Stratification of continuous variables was necessary for bedside practicality. In an exploratory manner, we obtained the cutoff value for each variable, which resulted in the highest univariate odds ratio for SICH per SITS-MOST in a dichotomization. If several adjacent values showed the same OR at dichotomization, the lowest value was chosen to include all levels of the variable with the highest odds for SICH. Stroke severity by NIHSS was stratified in an explorative manner into 3 levels optimizing the difference between the univariate ORs for SICH of the respective strata. Stratification of the NIHSS into more groups did not result in an improved predictive ability of the score. A new multivariate logistic regression analysis was performed, including the stratified continuous risk factors and the categorical risk factors, obtaining the final adjusted ORs for SICH per SITS-MOST. Point values were assigned to the risk factors based on their adjusted ORs: 1 point for OR \(>1.0\) and \(<1.2\), 2 points for OR \(>1.7\) and \(<2.7\), and 3 points for OR \(>2.7\).

For each patient, the SITS SICH risk score was calculated as the sum of point values assigned to their risk factors with possible total individual scores ranging between 0 and 12. Rates of SICH by all 3 definitions were calculated among patients in each score category. Score categories were collapsed when the prevalence of a given score was <1%, that is, for \(\geq 9\) points. For clinical practicality, we also performed a stratification of the total risk scores for SICH per SITS-MOST into 4 tiers: low, average, moderate, and high risk. The discriminating capacity of the risk score in the derivation cohort was assessed using the area under the receiver operating characteristic curve (C statistic) as an index of model performance. All analyses were performed using STATISTICA 10.0.
Internal Validation
The model was developed on a population of 15,814 patients with odd database entry numbers, a random pick, avoiding potential chronologi-
cal and geographical confounding factors. All statistical methods de-
scribed were performed at this stage. Having obtained the score model,
it was internally validated on the remaining 15,813 patients with even
database entry numbers. In both populations, only patients with com-
plete data for all score variables and outcomes were included in the
analysis. Validation was performed by evaluating the discriminating
capability of the model by receiver operating characteristic analysis as
well as calibration using the Hosmer-Lemeshow goodness-of-fit
method. Both methods were subsequently also applied to the entire
database population with complete data for score variables and
outcomes.

Results
In total, 31,627 patients with ischemic stroke treated with
intravenous thrombolysis were recorded in SITS-ISTR at 669
centers from 34 countries, of whom 93.3% (29,508 of 31,627)
were from Europe. Data were complete for all score variables
and the main outcome in 13,908 (87.9%) patients in the
model derivation cohort, in 13,896 (87.9%) patients in the
internal validation cohort, and in 27,804 patients (87.9%), in
the entire database. Follow-up imaging results at 22 to 36
hours were available in 96.4% of cases.

The time from symptom onset to tissue-type plasminogen
activator treatment ranged between 3 and 4.5 hours in 10.3%
(3,257 of 31,627 patients), whereas 1.5% (459 of 31,627 patients)
were recorded as treated /H11022
270 minutes after stroke onset.

In the entire population, the rate of SICH per SITS-MOST
was 1.8%, the rate of SICH per ECASS II was 5.1%, and the
rate of SICH per NINDS was 7.4%.

Table 1 shows the baseline characteristics of patients with
SICH per the SITS-MOST definition compared with those
without SICH. Multivariate logistic regression analysis re-
sulted in 9 risk factors independently associated with SICH
per SITS-MOST. These are reported in Table 2 together with
the attributed score points for each risk factor.

The SITS SICH Risk Score
The SITS SICH risk score showed a strong association with
SICH per the SITS-MOST definition with a >70-fold increase

Table 1. Univariate Analysis of Baseline Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>SICH SITS-MOST</th>
<th>No SICH SITS-MOST</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to treatment, min</td>
<td>558 (150 (120–176)</td>
<td>30,072 (145 (117–170)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age, y</td>
<td>568 (74 (66–78)</td>
<td>30,349 (69 (60–76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>546 (127 (106–162)</td>
<td>29,018 (118 (103–142)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rtPA dose, mg</td>
<td>560 (70 (60–80)</td>
<td>30,171 (68 (60–77)</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>559 (79 (70–90)</td>
<td>30,163 (75 (67–85)</td>
<td>0.002</td>
</tr>
<tr>
<td>NIHSS at baseline</td>
<td>558 (14 (9–19)</td>
<td>30,009 (12 (7–17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>557 (160 (145–170)</td>
<td>29,728 (150 (137–167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>555 (82 (75–91)</td>
<td>29,708 (81 (74–90)</td>
<td>0.561</td>
</tr>
<tr>
<td>Sex, female</td>
<td>224/558 (40%)</td>
<td>12,782/30,352 (42%)</td>
<td>0.201</td>
</tr>
<tr>
<td>Hypertension</td>
<td>430/555 (77%)</td>
<td>18,684/29,772 (63%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>142/555 (26%)</td>
<td>5,019/29,918 (17%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>207/493 (42%)</td>
<td>9,501/27,001 (35%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking–never</td>
<td>300/471 (64%)</td>
<td>16,466/28,111 (59%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking–current</td>
<td>79/471 (17%)</td>
<td>6,528/28,111 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking–previous</td>
<td>93/471 (20%)</td>
<td>5,117/28,111 (18%)</td>
<td>0.912</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>111/525 (21%)</td>
<td>3,951/29,929 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>188/553 (34%)</td>
<td>7,466/29,602 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>69/547 (13%)</td>
<td>2,548/29,701 (9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>276/554 (50%)</td>
<td>9,392/30,035 (31%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>19/560 (3%)</td>
<td>701/30,144 (2%)</td>
<td>0.098</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>30/560 (5%)</td>
<td>1,087/30,166 (4%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Oral anticoagulant, INR N/A</td>
<td>6/566 (1%)</td>
<td>299/30,222 (1%)</td>
<td>0.862</td>
</tr>
<tr>
<td>Oral anticoagulant, INR ≥1.7</td>
<td>10/566 (2%)</td>
<td>473/30,222 (2%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Oral antihypertensive</td>
<td>332/556 (60%)</td>
<td>14,018/30,097 (47%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Signs of infarct on CT/MRI</td>
<td>138/373 (27%)</td>
<td>6,181/28,230 (22%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables: median with interquartile range (IQR) and P values per the Mann-Whitney U test. Categorical variables: proportions (%) and
P values per the Pearson $\chi^2$ test.

SICH indicates symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; rtPA, recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; INR, international normalized ratio, N/A, not available or unreported.
in SICH between patients with a score of 0 and those with a score ≥10 (Figure 1). The overall rate of SICH was 1.8% for the entire population. The median total score was 4 points. Eleven percent of patients scored ≥7 points, showing a rate of SICH of ≥3.7%, that is, at least double the population average. With a score ≥10 points (0.2% of all patients), the rate of SICH increased 8-fold from the average to 14.3%. In Figures 1 to 3, due to the low prevalence, patients with ≥10 points have been pooled together with those scoring 9 points. Conversely, among the 500 patients with a score of 0 points, there was only a single case of SICH per SITS-MOST. In addition to presenting the SICH rates for all score levels in Figure 1, we have also shown the total risk score levels as 4 tiers: low, average, moderate, and high risk (Table 2).

For purposes of comparability with published results, the ability of the score to predict SICH per ECASS II and NINDS definitions was also assessed (Figures 2 and 3). The association between rising score and increasing SICH rates was evident here as well. A doubled rate of both SICH per ECASS II and NINDS was seen in patients with a score ≥7 who comprise 11% of the population. Compared with the average rates, a score ≥10 was associated with a 6-fold increase in SICH per ECASS II to 31% and a 4-fold increase in SICH per NINDS to 29%.

The index of predictive capability of the score for SICH per SITS-MOST in the model derivation cohort, internal validation cohort, and entire database population was calculated using the area under the receiver operating characteristic curve (C statistic). The C statistic in the derivation cohort was 0.71. The C statistic in the internal validation cohort was 0.70. The C statistic in the pooled total population was 0.70. In the entire material, the C statistic for the predictive capability of the score for SICH per ECASS II was 0.67 and 0.66 for SICH per NINDS. The Hosmer-Lemeshow test statistic was 8.0 (P=0.09) in the validation cohort and 7.5 (P=0.19) in the entire population.

Discussion

We have designed a clinical risk score with good discriminatory ability to identify patients with acute stroke at high risk of SICH when treated with IV alteplase. Previous studies of other hemorrhage risk scores have been performed on smaller data sets of a few hundred patients.23-24 The present study is based on 31,627 patients. We have identified and incorporated several independent risk factors for SICH into a risk score, which demonstrates a strong association between the risk for SICH and an accumulating burden of risk factors. The rate of SICH increases >70-fold in patients with a score ≥10 points (14.3%) compared with those with a score of 0 (0.2%). The predictive ability of the score is acceptable with a C statistic of 0.70 in the entire population. Internal validation depicted nearly identical performance among the model derivation, validation, and total study cohorts. The Hosmer-Lemeshow goodness-of-fit test comparing predicted and observed rates of SICH showed good calibration of the score model in the validation cohort.

Identifying patients at low risk of SICH may facilitate treatment by nonspecialists. In a survey of American emergency physicians, 26% of 1105 respondents were reluctant to use thrombolysis in acute ischemic stroke for fear of SICH.25 Among this physician population, the highest acceptable rate of SICH was 3.4%, which is approximately double the average rate of SICH per SITS-MOST (1.8%) in the SITS-ISTR registry. Our risk score shows that 11% of thrombolysed patients have a risk for SICH of this magnitude or higher (≥3.7% with ≥7 points). Still, any decision whether to withhold thrombolysis because of an increased risk of SICH needs to weigh this against the potential benefit to the patient.

The SITS SICH risk score may be relevant and useful in 3 different contexts: (1) the score may aid clinicians as well as patients and families in the process of decision-making when faced with acute ischemic stroke eligible for thrombolytic treatment; (2) as neuroimaging modalities and biomarkers evolve in their ability to predict SICH, they could be used in conjunction with the SITS SICH risk score; and (3) the risk score may be useful in clinical trials for patient selection and balancing the risk of SICH between randomized groups.

Risk Factors for SICH per SITS-MOST

We have identified 9 clinical and anamnestic parameters that have been included in the risk score. They are presented in this section by order of decreasing multivariate ORs for SICH, as shown in Table 2. The strongest predictor of SICH in our material is current dual antiplatelet therapy with aspirin and clopidogrel. This has been previously suggested by Diedler et al26 as well as in a pooled analysis of the Stroke-Acute Ischemic NXY Treatment (SAINT) I and II trials.27 Single antiplatelet treatment with aspirin is also an independent risk factor, which, however, is not the case for monotherapy with clopidogrel.

Stroke severity has been shown in several studies to be associ-

### Table 2: Final Multivariate Scoring Model Using Risk Factors for SICH per SITS-MOST After Stratification of Continuous Variables

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin + clopidogrel</td>
<td>3.2 (1.9–5.2)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td>1.8 (1.5–2.1)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS ≥13</td>
<td>2.2 (1.7–3.0)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS 7–12</td>
<td>1.6 (1.1–2.1)</td>
<td>0.006</td>
<td>1</td>
</tr>
<tr>
<td>B–Glucose ≥180 mg/dL</td>
<td>2.1 (1.7–2.6)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥72 y</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP ≥146 mm Hg</td>
<td>1.6 (1.3–2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Weight ≥95 kg</td>
<td>1.6 (1.2–2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Onset-to-treatment time ≥180 min</td>
<td>1.5 (1.2–2.0)</td>
<td>0.002</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.4 (1.1–1.7)</td>
<td>0.004</td>
<td>1</td>
</tr>
</tbody>
</table>

Overall Risk Level | Total Score | SICH Rate (95% CI) |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–2 points</td>
<td>0.4% (0.2%–0.6%)</td>
</tr>
<tr>
<td>Average</td>
<td>3–5 points</td>
<td>1.5% (1.3%–1.7%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6–8 points</td>
<td>3.6% (3.1%–4.1%)</td>
</tr>
<tr>
<td>High</td>
<td>≥9 points</td>
<td>9.2% (5.9%–12.5%)</td>
</tr>
</tbody>
</table>

Multivariate ORs with CIs. For clinical practicality, the total score is tiered into 4 levels according to risk severity. Points are attributed strictly either for “aspirin combined with clopidogrel” or “aspirin as antplatelet monotherapy.” Absence of aspirin treatment and history of hypertension, NIHSS 0–6, and values of continuous parameters below the stated cut points are scored as zero points. SICH indicates symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure.
ated with various definitions of SICH after thrombolysis. Multivariate analysis of outcomes in the SITS-MOST study has previously shown NIHSS score ≥8 to be associated with increased risk for SICH per SITS-MOST. In our study, explorative stratification of the NIHSS, aiming to maximize the difference in OR for SICH between groups, resulted in 3 levels: NIHSS 0 to 6, 7 to 12, and ≥13. Further stratification did not improve model performance. An elevated baseline serum glucose level ≥10 mmol/L is also independently associated with SICH, a finding consistent with previously published results. It is noteworthy that this association was not seen in patients with known diabetes mellitus and baseline glucose levels <10 mmol/L. Current guidelines recommend treatment with insulin titration in patients with stroke and serum glucose >10 mmol/L, although it is unclear whether reducing blood glucose reduces the risk of hemorrhage. Age is another well-known predictor of SICH. In our population, the sharpest increase in risk for SICH occurs in the beginning of the eighth decade of life with 72 years being the optimal cutoff level between lower and higher risk groups. A detailed analysis of age-related SICH risk in the SITS material was recently published by Ford et al. Elevated baseline blood pressure is another independent risk factor for SICH in our register, previously reported by Ahmed et al. Meanwhile, it remains an open question whether acute antihypertensive therapy attenuates SICH risk. Dichotomizing baseline systolic blood pressure, we aimed for a maximum risk difference between groups above and below the cut point. Here, a level of 146 mm Hg was found optimal. Adding more strata did not improve overall score performance. Stratifying the next risk factor, body weight, we found the level of ≥95 kg to have the strongest association with an increased risk for SICH. It is intriguing that neither the net dose of alteplase nor the dose in mg/kg of body weight elevated the risk for SICH. A recent analysis by Diedler et al has demonstrated a higher incidence of symptomatic intracerebral hemorrhage in patients >100 kg despite the lower per-kilogram dose of alteplase. Furthermore, in agreement with findings in the ECASS III trial as well as previous results from the SITS-ISTR, we found a small but significant increase in the risk for SICH in patients treated between 3 and 4.5 hours after symptom onset. Lastly, the independent risk factor with the lowest but statistically significant impact is a known history of hypertension. This is, to our knowledge, previously unreported; however, results from the SITS-ISTR have shown that patients with a history of untreated hypertension have increased rates of SICH per SITS-MOST.

Comparison With Previous SICH Scores
Major differences exist between the present study and the 2 previously published risk scores for intracerebral hemorrhage.
after stroke thrombolysis. The SITS SICH score predicts large parenchymal hemorrhages associated with severe clinical deterioration. It is designed using data from >30,000 patients using weighted risk factors. The Hemorrhage After Thrombolysis (HAT) score was designed through a literature review and tested on 400 patients. The Multicenter Recombinant Tissue-Type Plasminogen Activator Stroke Survey Group score was constructed with unweighted parameters using data from 1205 patients; however, of these, only 481 had complete data for relevant variables. Importantly, both scores were designed to assess the risk for any amount of blood extravasation on CT related to any clinical deterioration, that is, the NINDS definition of SICH. This definition is confounded by clinical deterioration due to infarct edema, new infarction, and intra- and interrater variability in assessment of NIHSS deterioration of 1 point, required for labeling as “symptomatic” in the NINDS studies. These confounders may be present concomitantly with small amounts of blood in the infarct core on follow-up imaging. Thus, it can be argued that the 2 previous scores predict any clinical deterioration, which only in part may depend on cerebral hemorrhage.

In the HAT score study, the C statistic was 0.74, whereas the score by Cucchiara et al had a C statistic of 0.68 in the original population. Both scores have recently been subjected to external validation using the pooled SAINT I and II cohorts. This resulted in lower predictive capability with C statistic values of 0.59 for both algorithms.

The SITS-SICH risk score does not require waiting for a measurement of a blood platelet count (required by the Stroke Survey Group score) nor a volumetric measurement of the manifest infarct size on initial imaging (used in the HAT score). It can thus readily be calculated immediately on presentation or even in the prehospital setting en route to the hospital. Under these circumstances, the stroke center’s average door-to-needle time could be used to calculate a probable onset-to-treatment time required by our score.

**Study Limitations**

Despite our belief that the patient data in the SITS-ISTR are representative for clinical practice across a variety of demographics and stroke center types, for the risk score to be suitable for routine clinical practice, an external validation is warranted. Like with other register-based studies, the presented results are based on retrospective, explorative analysis of observational material. Data for the relevant variables and outcomes were missing in 12.1% of our patients, which may have had an influence on the outcome. Furthermore, stratification of continuous variables as well as conversion of risk factor ORs to score point values, although necessary for clinical practicality, can be assumed to have resulted in a loss of information and decreased

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**Figure 2.** The Safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage (SICH) risk score, SICH per the European Cooperative Acute Stroke Study (ECASS) II definition. Bars show the rate of SICH for each score category. Percentages indicate rates per score category in the all patient cohort. At risk: proportion of all thrombolized patients with the respective risk score.
model accuracy. We cannot exclude that some patients in the intravenous thrombolysis register were given additional intra-arterial therapy, although this is likely to be marginal. The present study is based on patients treated between the end of 2002 and beginning of 2010. During this period, intra-arterial therapy was not widely available across Europe, where 93.3% of our patients were treated.

Conclusions

The SITS SICH risk score shows good predictive ability for the risk of SICH in patients with ischemic stroke treated with intravenous thrombolysis. Our score may aid clinicians to identify patients with the highest as well as the lowest risk of SICH. However, we cannot propose withholding treatment with alteplase in patients otherwise eligible according to current guidelines. An external validation of our score is warranted. Furthermore, a study of the clinical effect of recombinant tissue-type plasminogen activator across risk score categories is needed to assess whether some patients at high risk of SICH may still have a favorable risk-to-benefit ratio with treatment.

Appendix

Scientific Committee of SITS International

Figure 3. The Safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage (SICH) risk score, SICH per the National Institute of Neurological Disorders and Stroke (NINDS) definition. Bars show the rate of SICH for each score category. Percentages indicate rates per score category in the all patient cohort. At risk: proportion of all thrombolysed patients with the respective risk score.

Scientific Committee of Fighting Stroke (Uppdrag Besegra Stroke)

Acknowledgments
We thank all SITS-ISTR investigators and their centers for their participation. We also pass on our thanks to all patients who participated in SITS-ISTR. Uppsala Clinical Research (UCR) center, Uppsala, Sweden, developed, maintained, and upgraded the software for the SITS register in close collaboration with SITS until September 2010. The current SITS registry is developed, maintained, and upgraded by Zitelab, Copenhagen, Denmark, in close collaboration with SITS.

Sources of Funding
SITS-ISTR is funded by an unrestricted grant from Boehringer Ingelheim, Ferrer, and by a grant from European Union Public Health Executive Authority (PHEA). Financial support was also provided through the regional agreement on medical training and research (ALF) between Stockholm County Council and the Karolinska Institute. This study is a part of the Fighting Stroke Project (Uppdrag Besegra Stroke), supported by the Swedish Heart and Lung Foundation and Karolinska Institutet, Friends of Karolinska Institutet, USA, and Johanniterorden.

Disclosures
J.A.E. has received fees from Boehringer Ingelheim as a member of an Advisors’ Committee and for educational activities. He has also received fees for the ECASS II and ECASS III trials. He has also received fees from Novo Nordisk as an investigator for the Factor
Seven for Acute Hemorrhagic Stroke (FAST) trials. G.A.F. has received fees and expenses from Boehringer Ingelheim for educational activities. He has also received fees and expenses from Lundbeck for educational activities. His institution has received grant assistance from Boehringer Ingelheim toward administrative expenses for coordination of SITS in the United Kingdom, fees for consultancy work, and study payments. K.R.L. has received fees and expenses from Boehringer Ingelheim for his role as chairman of the independent data safety monitoring board of the ECASS III trial with alteplase and related lectures. He has also received fees from Paion, Forest and Lundbeck for the Desmoteplase in Acute Ischemic Stroke Trial (DIAS) trials with desmoteplase. His institution has received grant assistance toward administrative expenses for coordination of SITS in the United Kingdom. R.M. has received research support from European Regional Development Fund Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123). D.T. has served as a consultant for Boehringer Ingelheim and has been paid lecture fees for attending and speaking at workshops held by Boehringer Ingelheim, Sanofi-Aventis and Novo Nordisk. N.W. has received expenses from Boehringer Ingelheim for his role as member of the Steering Committee in relation to the ECASS III trial with alteplase and served as a consultant to Thrombogenics as chairman of the Data Safety Monitoring Board. SITS International (chaired by N. Wahlgren) received a grant from Boehringer Ingelheim and Ferrer for the SITS-MOST/SITS-ISTR. His institution has also received grant support toward administrative expenses for coordination of the ECASS III trial. N.W. has also received lecture fees from Boehringer Ingelheim and Ferrer. N.A. is a senior researcher in SITS International, which receives a grant from Boehringer Ingelheim and Ferrer for the SITS-MOST/SITS-ISTR.

References

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Stroke, published online March 22, 2012;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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アルテプラーゼ静注で治療した虚血性脳卒中における症候性脳内出血のリスクの予測
—Safe Implementation of Treatments in Stroke (SITS)症候性脳内出血のリスクスコア

Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated With Intravenous Alteplase
—Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score

Michael Mazya, MD1; José A. Egido, MD, PhD2; Gary A. Ford, MD, FRCP3; Kennedy R. Lees, MD, FRCP4; Robert Mikulik, MD, PhD5; Danilo Toni, MD, PhD6; Nils Wahlgren, MD, PhD1; Niaz Ahmed, MD, PhD1; PhD; for the SITS Investigators

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背景および目的: 症候性脳内出血 (SICH) は静脈内血栓溶解療法で治療した急性期虚血性脳卒中患者の重篤な合併症である。本研究は、SICH のリスクを予測するために容易に適用することができる臨床的スコアの作成を目的とした。

方法: Safe Implementation of Treatments in Stroke (SITS) International Stroke Thrombolysis Register に登録されている、アルテプラーゼ静注による治療を受けた患者 31,627例のデータを解析した。転帰の尺度は Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) の定義による SICH である (NIHSS スコアの 4 ポイント以上の悪化を伴う 2 型実質性出血または死亡)。連続変数で層別化後、転帰に関与する単変量危険因子をロジスティック回帰モデルにあてはめた。独立危険因子に関する補正 OR をポイントに変換し、それらを合計してリスクスコアとした。

結果: 9 つの SICH の独立危険因子が同定された: ベースラインの NIHSS スコア、血清グルコース値、収縮期血圧、年齢、体重、脳卒中発症から治療までの時間、アスピリンまたはアスピリンとクロピドグレルの併用、および高血圧の既往。SICH の全体の発生率は 1.8%であった。リスクスコアは 0 ~ 12 ポイントの範囲であり、スコア 10 ポイント以上の患者 (14.3%) はスコア 0 ポイントの患者 (0.2%) と比べて、SICH の発現率が 70 倍超に段階的に上昇した。C 統計量で示した予後識別能は、0.70 であった。

結論: STS SICH リスクスコアは、重度の臨床的悪化を伴う脳実質の大量出血を予測する。このスコアは、臨床医がアルテプラーゼ静注後に SICH をきたすリスクが高い患者や低い患者を同定するために役立つと考えられる。

表 2 連続変数について層別化後の SITS-MOST による SICH の危険因子の最終的な多変量スコア化モデル

<table>
<thead>
<tr>
<th>危険因子</th>
<th>OR (95% CI)</th>
<th>p 値</th>
<th>ポイント</th>
</tr>
</thead>
<tbody>
<tr>
<td>アスピリン＋クロピドグレル</td>
<td>3.2 (1.9 ～ 5.2)</td>
<td>&lt; 0.001</td>
<td>3</td>
</tr>
<tr>
<td>アスピリン単独療法</td>
<td>1.8 (1.5 ～ 2.1)</td>
<td>&lt; 0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS ≧ 13</td>
<td>2.2 (1.7 ～ 3.0)</td>
<td>&lt; 0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS 7 ～ 12</td>
<td>1.6 (1.1 ～ 2.1)</td>
<td>0.006</td>
<td>1</td>
</tr>
<tr>
<td>血清グルコース ≧ 180 mg/dL</td>
<td>2.1 (1.7 ～ 2.6)</td>
<td>&lt; 0.001</td>
<td>2</td>
</tr>
<tr>
<td>年齢 ≧ 72 歳</td>
<td>1.7 (1.4 ～ 2.0)</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>収縮期 BP ≧ 146 mmHg</td>
<td>1.6 (1.3 ～ 2.0)</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>体験 ≧ 95 kg</td>
<td>1.6 (1.2 ～ 2.0)</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>発症から治療開始までの時間 ≧ 180 分</td>
<td>1.5 (1.2 ～ 2.0)</td>
<td>0.002</td>
<td>1</td>
</tr>
<tr>
<td>高血圧の既往</td>
<td>1.4 (1.1 ～ 1.7)</td>
<td>0.004</td>
<td>1</td>
</tr>
</tbody>
</table>

全体のリスクレベル | 総スコア | SICH 発生率 (95% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>低度</td>
<td>0 ～ 2 ポイント</td>
<td>0.4% (0.2 ～ 0.6%)</td>
</tr>
<tr>
<td>平均的</td>
<td>3 ～ 5 ポイント</td>
<td>1.5% (1.3 ～ 1.7%)</td>
</tr>
<tr>
<td>中等度</td>
<td>6 ～ 8 ポイント</td>
<td>1.5% (3.1 ～ 4.1%)</td>
</tr>
<tr>
<td>高度</td>
<td>≧ 9 ポイント</td>
<td>9.2% (5.9 ～ 12.5%)</td>
</tr>
</tbody>
</table>

多変量 OR と CI。臨床での実用性を考慮し、総スコアをリスクの程度に従って 4 つのレベルに分類した。ポイントには「アスピリンとクロピドグレルの併用」か「アスピリン単独による抗血小板療法」のいずれかのポイントが必ず含まれる。アスピリン療法なし、高血圧の既往なし、NIHSS 0 ～ 6 および連続パラメーターを満たすカットオフ値未満である場合は、0 ポイントとして評価した。

Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated With Intravenous Alteplase

Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score

Michael Mazya, MD; José A. Egido, MD, PhD; Gary A. Ford, MD, FRCP; Kenneth R. Lees, MD, FRCP; Robert Mikulik, MD, PhD; Danilo Toni, MD, PhD; Nils Wahlgren, MD, PhD; Niaz Ahmed, MD, PhD; for the SITS Investigators

(Stroke. 2012;43:1524-1531.)

Key Words: cerebral infarct ■ database ■ intracerebral hemorrhage ■ prognosis ■ stroke management ■ thrombolysis

Table 2. Final Multivariate Scoring Model Using Risk Factors for SICH per SITS-MOST After Stratification of Continuous Variables

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin + clopidogrel</td>
<td>3.2 (1.9–5.2)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td>1.8 (1.5–2.1)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS ≥13</td>
<td>2.2 (1.7–3.0)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>NIHSS 7–12</td>
<td>1.6 (1.1–2.1)</td>
<td>0.006</td>
<td>1</td>
</tr>
<tr>
<td>B–Glucose ≥180 mg/dL</td>
<td>2.1 (1.7–2.6)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥72 y</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP ≥146 mm Hg</td>
<td>1.6 (1.3–2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Weight ≥95 kg</td>
<td>1.6 (1.2–2.0)</td>
<td>0.001</td>
<td>1</td>
</tr>
<tr>
<td>Onset-to-treatment time ≥180 min</td>
<td>1.5 (1.2–2.0)</td>
<td>0.002</td>
<td>2</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.4 (1.1–1.7)</td>
<td>0.004</td>
<td>1</td>
</tr>
</tbody>
</table>

Overall Risk Level | Total Score | SICH Rate (95% CI)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–2 points</td>
<td>0.4% (0.2%–0.6%)</td>
</tr>
<tr>
<td>Average</td>
<td>3–5 points</td>
<td>1.5% (1.3%–1.7%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6–8 points</td>
<td>3.6% (3.1%–4.1%)</td>
</tr>
<tr>
<td>High</td>
<td>≥9 points</td>
<td>9.2% (5.9%–12.5%)</td>
</tr>
</tbody>
</table>

Multivariate ORs with CIs. For clinical practicality, the total score is tiered into 4 levels according to risk severity. Points are attributed strictly either for “aspirin combined with clopidogrel” or “aspirin as antiplatelet monotherapy.” Absence of aspirin treatment and history of hypertension, NIHSS 0–4, and values of continuous parameters below the stated cut points are scored as zero points.

SICH indicates symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke–Monitoring Study; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure.

배경과 목적
중상성 뇌출혈은 정맥혈 혈전응해제 치료를 받은 급성기 휘혈뇌출혈 환자에서 발생할 수 있는 심각한 합병증의 하나이다. 저자들은 중상성 뇌내출혈의 위험도를 예측하기 위해 쉽게 적용될 수 있는 임상적 점수를 개발하는 연구를 진행하였다.

방법

결과
저자들은 중상성 뇌내출혈에 대한 9개의 위험인자로 초기 NIHSS 점수, 혈당, 수축기 혈압, 혈청, 향증, 뇌출혈 발생에서 치료까지의 시간, 아스피린 혹은 아스피린/클로피도그램 병용 및 고혈압의 병력을 확인하였다. 뇌내출혈의 전체발생율은 1.8% 였다. 위험도 점수는 0점에서 12점으로 조사되었는데, 0점의 위험도 점수를 가진 환자들의 뇌내출혈 발생율은 0.2%였고, 10점 이상의 점수를 가진 환자들의 경우 뇌내출혈의 발생률이 14.3%로 70배 이상 위험도가 증가하는 것으로 나타났다. C statistic에 의한 예측분화능력은 0.70으로 나타났다.