Improved Prediction of Poor Outcome After Thrombolysis Using Conservative Definitions of Symptomatic Hemorrhage

Christoph Gumbinger, MD*; Philipp Gruschka, MD*; Markus Böttinger, MD; Kristin Heerlein, MD; Robin Barrows, MD; Werner Hacke, MD; Peter Ringleb, MD

Background and Purpose—Direct comparison of symptomatic intracerebral hemorrhage (sICH) rates among different thrombolysis studies is complicated by the variability of definitions of sICH. The prediction of outcome still remains unclear.

Methods—Baseline data and clinical courses of patients treated with thrombolytic therapy were collected in a prospective database. The 3-month outcome was evaluated using the modified Rankin Scale. Results of 24-hour follow-up imaging were reevaluated by at least 2 independent raters. Four common definitions of sICH (National Institute of Neurological Disorders and Stroke [NINDS], European Cooperative Acute Stroke Study [ECASS] 2, Safe Implementation of Thrombolysis in Stroke [SITS], ECASS 3) were applied. Kappa interrater statistics were calculated. Our objective was to find the sICH definition with the highest predictive value for mortality, poor (modified Rankin Scale 5 or 6) and unfavorable (modified Rankin Scale ≥3) clinical outcome after 90 days.

Results—The data of 314 patients were analyzed. The NINDS definition revealed the highest sICH rate (7.7%); the lowest rate was found for the ECASS 3 definition (3.2%) of sICH. The highest interrater agreement was found for the ECASS 2 definition (κ 0.85) and the lowest for the NINDS definition (κ 0.57). Patients with sICH according to the SITS definition had the highest risk for death (OR, 14.4) and poor outcome (OR, 26.6).

Conclusions—None of the different definitions contains an optimal combination of prediction of mortality and outcome and a high interrater agreement rate. For the clinical evaluation of mortality, we recommend using the SITS definition; for studies needing a high interrater agreement rate, we recommend using the ECASS 2 definition. Due to the lack of 1 single optimal definition, future thrombolytic trials should preferably use different definitions.

Key Words: acute stroke | cerebral infarct | intracerebral hemorrhage | stroke management | therapy | thrombolysis | stroke

Differences between definitions of symptomatic intracerebral hemorrhage (sICH) complicate the comparability and interpretation of thrombolytic therapy trials and lead to different rates of sICH.1 Thrombolysis trials (National Institute of Neurological Disorders and Stroke [NINDS], European Cooperative Acute Stroke Study [ECASS] 2, ECASS 3, Safe Implementation of Thrombolysis in Stroke [SITS]) present sICH rates according to several definitions.2–5 In their analysis of the ECASS 2 patients, Berger et al have shown only parenchymal hematomas (PH) Type 2 were correlated with a poor clinical outcome at 3 months.6

We applied different definitions of sICH to all patients with an anterior circulation stroke treated with thrombolytic therapy over a period of 32 months at the Department of Neurology at the University Clinic of Heidelberg, Germany. We analyzed the data to find out which definition of sICH had the highest interrater agreement and the highest predictive value for mortality and unfavorable and poor outcome.

At our institution, thrombolysis is performed according to the European Stroke Organization guidelines.7 Furthermore, we perform this treatment on an individual basis in patients >80 years or within an extended time window, usually on the basis of multimodal imaging.

To detect post-therapeutical complications, all of our patients included in this study underwent CT or MRI within 24 to 36 hours after thrombolysis or immediately in case of clinical deterioration. The modified Rankin Scale8 was used to assess the outcome 90 days after the initial stroke.

Imaging as well as the clinical data of the patients were evaluated applying the NINDS, ECASS 2, ECASS 3, and SITS definitions by 2 independent experienced stroke neurologists. Definitions of sICH were extracted from the original publications (Table 1). In addition, the size of PH was estimated following the ECASS classification by the same investigators. Discrepancies were resolved by discussion. To compare the classification of the different raters, χ2 statistics were calculated. Rates and their 95 CIs were calculated assuming a Poisson distribution. To identify the clinically most relevant definition of intracerebral hemorrhage, ORs were calculated comparing
Table 1. Definitions of Symptomatic Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Definition</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>ECASS 3</td>
<td>Any hemorrhage with neurologic deterioration as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 d or any hemorrhage leading to death; in addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.</td>
</tr>
<tr>
<td>ECASS 2</td>
<td>Blood at any site in the brain on the CT scan, documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening or causing a decrease in the NIHSS score of ≥4 points than the value at baseline or the lowest value in the first 7 d or any hemorrhage leading to death.</td>
</tr>
<tr>
<td>SITS-MOST</td>
<td>Local or remote parenchymal hema to ma Type 2 on the imaging scan obtained 22 to 36 hours after treatment plus neurologic deterioration as indicated by a score on the NIHSS that was higher by ≥4 points than the baseline value.</td>
</tr>
<tr>
<td>NINDS</td>
<td>If a hemorrhage had not been seen on a previous CT scan but there was subsequently either a suspicion of hemorrhage or any decline in neurologic status.</td>
</tr>
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NIHSS indicates National Institutes of Health Stroke Scale; ECASS, European Cooperative Acute Stroke Study; SITS-MOST, Safe Implementation of Thrombolysis in Stroke—Monitoring Study; NINDS, National Institute of Neurological Disorders and Stroke.

Data of 314 patients with an anterior circulation stroke were analyzed, 137 (44%) of which were male. Follow-up CT or MRI was obtained from 313 patients. Clinical follow-up information after 90 days was available from 311 patients (1 patient died due to myocardial infarction before follow-up information after 90 days was available from 311 patients (1 patient died due to myocardial infarction before follow-up imaging; 2 patients without 90-day follow-up imaging had no bleeding on a 24-hours follow-up CT).

The patients’ median age was 75 years (interquartile range, 65–81), 90 patients were >80 years, and the median National Institution of Health Stroke Scale score on admission was 12 (interquartile range, 7–17). Two hundred sixty-five (85%) patients were treated within the 3-hour time window, whereas 28 patients received thrombolysis >4.5 hours after stroke onset using multimodal imaging.

Altogether, 34 PHs were able to be detected; 22 of those were classified as PH1 (7.0%; 95% CI, 4.4%–10.6%) and 12 as PH2 (3.8%; 95% CI, 1.9%–6.7%). The interrater variability measured with the κ value for hematoma size (PH1 versus PH2) was 0.61. The interrater variability of PH (PH1 and PH2) assessment was 0.74 (95% CI, 0.63–0.85).

Due to different definitions, between 10 and 24 sICH could be identified (rates are given in Table 2). The use of the NINDS definition led to the highest sICH rate (7.7%; 95% CI, 4.9%–11.4%), whereas the lowest rate was found for the ECASS 3 definition (3.2%; 95% CI, 1.5%–5.8%). The highest interrater agreement was found for the ECASS 2 definition (κ 0.85) and the lowest for the NINDS definition (κ 0.57).

Patients with sICH according to the SITS definition had the highest risk for death (OR, 4.4; 95% CI, 3.3–8.5). The best prediction of unfavorable outcome was achieved with the NINDS definition and the second best with the SITS definition (OR, 8.9; 95% CI, 1.2–387.5). The definition with the lowest predictive value was the ECASS 2 definition (mortality OR, 4.7; 95% CI, 1.5–14.3; unfavorable outcome 6.8; 95% CI, 1.5–62.21). Other rates for unfavorable clinical outcome are given in Table 2.

**Discussion**

We found the application of different definitions of sICH to our cohort not only to lead to different rates of sICH, but also to differences in the prediction of outcome after thrombolytic therapy. Also, all definitions of sICH had different limitations either in prediction of outcome or in the applicability due to a low interrater agreement rate.

We found interrater agreements with κ values between 0.57 and 0.85. The highest interrater agreement was found for the ECASS 2 definition. This might be due to the fact that this definition contains a simple imaging paradigm (“any blood on CT”) and a precise definition of clinical deterioration (“at least 4 points on the National Institute of Health Stroke Scale”).On the contrary, determining hematoma as the predominant cause for neurological deterioration (according

Table 2. OR and 95% CI for End points ‘Mortality,’ ‘Favorable Outcome’ (mRS 0–2), and ‘Unfavorable Outcome’ (mRS 3–6), After 3 Months for Different Definitions of sICH and Parenchymal Hemorrhages as Compared With Patients Without Hemorrhage

<table>
<thead>
<tr>
<th>Definition</th>
<th>Kappa</th>
<th>OR for Mortality (mRS 0 – 5 Versus mRS 6; 95% CI)</th>
<th>OR for Unfavorable Outcome (mRS 0 – 2 Versus mRS 3 – 6; 95% CI)</th>
<th>Rate of ICH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.57</td>
<td>5.67 (2.16–14.72)</td>
<td>10.42 (2.49–93.06)</td>
<td>7.7% (4.9%–11.4%)</td>
</tr>
<tr>
<td>ECASS 2</td>
<td>0.85</td>
<td>6.67 (1.48–14.33)</td>
<td>6.02 (1.54–62.21)</td>
<td>5.4% (3.2%–8.7%)</td>
</tr>
<tr>
<td>SITS</td>
<td>0.85</td>
<td>14.35 (3.25–85.86)</td>
<td>8.87 (1.23–387.52)</td>
<td>3.5% (1.7%–6.3%)</td>
</tr>
<tr>
<td>ECASS 3</td>
<td>0.62</td>
<td>12.30 (2.66–75.31)</td>
<td>7.93 (1.07–350.05)</td>
<td>3.2% (1.5%–5.8%)</td>
</tr>
<tr>
<td>PH2</td>
<td>0.61</td>
<td>3.56 (0.85–13.55)</td>
<td>4.40 (0.91–18.83)</td>
<td>3.8% (2.0%–6.7%)</td>
</tr>
<tr>
<td>PH</td>
<td>0.61</td>
<td>2.96 (1.24–6.80)</td>
<td>3.67 (1.49–10.28)</td>
<td>10.0% (7.5%–15.2%)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage; NINDS, National Institute of Neurological Disorders and Stroke; ECASS, European Cooperative Acute Stroke Study; SITS, Safe Implementation of Thrombolysis in Stroke; PH, parenchymal hematoma; OR, odds ratio; CI, confidence interval.
to the ECASS 3 definition) or distinguishing between PH1 and PH2 (like in the SITS definition) seemed to be difficult and therefore led to a higher interrater disagreement. Subdividing PH into PH1 and PH2 according to the SITS definition had a $k$ score of only 0.61. The reason for this might the subjectivity of visual analysis resulting in different results, even among stroke-experienced physicians. Thus, the approach used in the literature using the more objective definition of any PH could prove to be more reliable.

However, based on our data, the outcome prediction of the easy to use ECASS 2 definition leads to a relatively low predictive value for unfavorable outcome as well as mortality. The NINDS definition had the lowest predictive value for mortality. This might be due to the relatively broad definition, including intracranial hemorrhages only leading to a slight clinical deterioration, leading to the highest rate of sICH. The more conservative SITS definition, only counting large PH Type 2 as sICH, had a relatively good predictive value for poor outcome and mortality.

Our study has different limitations and deviations to other studies. Our study population is slightly different from the (heterogeneous) study population of the thrombolytic therapy trials. An important risk factor of sICH is an age of at least 80 years. In our study, we included 90 patients >80 years. Also, our study included patients treated later than the 3-hour time window (28 patients were treated after the 4.5-hour time window using multimodal imaging), which might have increased the rates of sICH. Like in clinical settings, thrombolytic therapy—still being an off-label therapy in Europe—was used in patients >80 years and patients within the 3- to 4.5-hour time window. In our opinion, future studies should also include this study population, because thrombolytic therapy has a proven effect on the outcome in patients >80 years as well as within the 3- to 4.5-hour time window.

Another limitation of our study is the lack of follow-up CTs between 22 and 24 hours post-treatment like in the SITS-MOST study. Theoretically, there is a small risk for new hemorrhage between 22 and 24 hours after thrombolytic therapy so that it is possible to overlook new sICH within this time frame using the SITS definition performing follow-up cranial CT between 22 and 36 hours after therapy. We do not think that this has a major effect on our recommendation to use the SITS definition for clinical investigation, because in any case of a clinical deterioration, an additional cranial CT has been performed.

The optimal definition of sICH would have a high interrater agreement and a very good prediction of poor outcome. None of the different definitions has an optimal combination of prediction of mortality, unfavorable outcome, and a high interrater agreement rate. For clinical investigation of mortality, we recommend using the SITS definition because this definition has a good prediction for mortality and outcome. In addition, this definition is easy to use for multicenter registries. It should be investigated if training for differentiation between types of PHs could lead to a better interrater agreement rate. A study that needs to have a high interrater agreement rather should use the ECASS 2 definition. We hope that future thrombolytic therapy trials specify sICH with regard to different definitions to further investigate which definition has the best predictive value for each question.

**Disclosures**

None.

**References**

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*Stroke*. 2012;43:240-242; originally published online October 13, 2011; doi: 10.1161/STROKEAHA.111.623033

*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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