Hemorrhage After Thrombolytic Therapy for Stroke
The Clinically Relevant Number Needed to Harm

Jeffrey L. Saver, MD

Background and Purpose—A clinically relevant number needed to harm for tissue plasminogen activator (tPA)-related symptomatic intracerebral hemorrhage (SICH) would greatly assist therapeutic decision-making.

Methods—A 15-variable prognostic model was derived from a placebo group enrolled in National Institute of Neurological Disorders and Stroke tPA Trials 1 and 2 and used to predict final global disability outcome for patients with tPA-related SICH had they been treated with placebo, rather than tPA, and not experienced SICH.

Results—Among 312 tPA-treated patients, 20 experienced SICH. Compared with placebo patients, patients treated with tPA who experienced SICH were older, had more severe stroke deficits, had higher serum glucose levels, and more often displayed mass effect on pretreatment imaging. Observed 3-month modified Rankin Scale outcomes among the patients experiencing SICH after tPA were: 0–5%, 1–5%, 4–10%, 5–5%, and 6–75%. Predicted outcomes had they been treated with placebo were: 0–2%, 1–5%, 2–7%, 3–14%, 4–28%, 5–12%, and 6–32%. The number needed to harm for one more patient to have a final disabled or dead outcome (modified Rankin Scale ≥3) attributable to tPA-related SICH was 707. Number needed to harm for severely disabled or dead outcome (modified Rankin Scale ≥4) was 126; for fatal outcome 36.5, and for worsened outcome by any degree (≥1 modified Rankin Scale grade) between 29.7 and 40.1.

Conclusions—Most patients who experience SICH have severe baseline infarcts and already are destined for poor outcomes. For every 100 patients treated with tPA, approximately 1 will experience a severely disabled or fatal final outcome as a result of tPA-related SICH. (Stroke. 2007;38:2279-2283.)

Key Words: intracerebral hemorrhage ■ ischemic stroke ■ number needed to treat ■ stroke ■ thrombolysis

The number needed to harm (NNTH) quantifies the risk associated with a medical intervention in a manner that is intuitively meaningful to physicians and patients.1,2 Symptomatic intracerebral hemorrhage (SICH) is the most feared risk of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke. The number needed to treat (NNT) to cause protocol-defined symptomatic intracerebral hemorrhage (PDSICH) in National Institute of Neurological Disorders and Stroke (NINDS) Trials 1 and 2 has been derived (17.2) but does not represent the clinically most relevant NNTH, because it reflects early and sometimes inconsequential events in the patient’s course.3–5

Patients and physician decision-makers would benefit from a NNTH value that indicates the impact of SICH on the most important outcome of stroke, final global function.6 This study was undertaken to derive NNTH values for the impact of SICH on final 3-month score on the most widely used stroke trial measure of global disability, the modified Rankin Scale (mRS; Table 1).

Methods
Although the rates of adverse outcomes in patients who experienced SICH after intravenous lytic therapy are easily identified, they overestimate the net harm. Some of these patients would have experienced severe disability or death even without intravenous tPA and resulting SICH. We used the placebo group to estimate the outcomes that would have occurred in these patients had they not been treated with intravenous tPA.

In NINDS Trials 1 and 2 combined, 20 patients experienced SICH among 312 tPA-treated subjects. Pretreatment characteristics and final actual 3-month global functional outcomes (mRS) in these 20 patients were extracted from the publicly available study data set. Predictive models were derived from the 312 patients in the placebo group of NINDS Trials 1 and 2 that projected 3-month mRS outcomes among patients not treated with intravenous tPA. The ordinal logistic regression model used the following 15 baseline variables identified in previous studies of the NINDS and other acute ischemic stroke trials as important prognostic determinants7–11: age, sex, pretreatment National Institutes of Health Stroke Scale (NIHSS), age–NIHSS interaction, history of hypertension, diabetes, smoking, time from onset to treatment, mean arterial pressure, pretreatment serum glucose, hyperdense artery sign on CT, hypodensity on CT, mass effect on CT, preexisting disability, and stroke subtype. Different models were derived for each dichotomized cut point of the mRS and for the full 7-level distribution of the mRS. Performance of the models was evaluated with the c statistic. The proportional odds test was used to determine whether the proportional odds assumption was valid.

From these models, the predicted 3-month Rankin values without tPA treatment were calculated for the 20 tPA-treated patients who experienced SICH by entering into the model the mean covariate values at baseline for the 20 patients. The models yielded the distribu-

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outcomes across all 7 levels of the mRS similarly showed good performance (c statistic = 0.75) and satisfied the proportional odds assumption.

Three-month outcomes among tPA-treated patients with SICH, actual and predicted had they not received tPA, in the 7-level mRS model are shown in Figure 1. Mean actual 3-month (SD) mRS score in the tPA-treated patients with SICH was 5.20 (1.69) and projected 3-month (SD) mean mRS score in these patients had they not been exposed to tPA was 4.26 (1.59). The mean (SEM) difference in the mRS score was 0.94 (0.52).

Table 3 shows NNTHs for all dichotomized break points of the mRS and for the minimum and maximum possible NNTHs for worsening by one or more steps over the entire range of the 7-level mRS.

### Discussion
This study demonstrates that, for different dichotomized global functional end points, the number needed to harm as a result of tPA-related SICH ranges widely, from 36.5 to 707. Which is the most relevant dichotomized end point is ultimately a matter of patient preference; the most important health state transition for an individual patient is the one that matters most to that individual patient. One reasonable key dichotomization for NNTH estimation, used by prior investigators, is the number needed to treat for one additional patient to end up severely disabled or dead (mRS 0 to 3 versus 4 to 6). For this end point, the NNTH is 126.

However, because most patients value as important health state transitions across the entire range of disability outcomes, the NNTH across all levels of the mRS is also of great clinical relevance. The NNTH across all levels of mRS for tPA must fall within a range from 29.7 to 40.1, indicating that for every

### Table 1. The Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NINDS Placebo, n=312</th>
<th>NINDS tPA SICH, n=20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.9</td>
<td>72.8</td>
<td>0.022</td>
</tr>
<tr>
<td>Sex, female</td>
<td>41%</td>
<td>50%</td>
<td>0.49</td>
</tr>
<tr>
<td>NIHSS, median</td>
<td>15</td>
<td>21</td>
<td>0.015</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>66%</td>
<td>65%</td>
<td>0.99</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>20%</td>
<td>20%</td>
<td>0.99</td>
</tr>
<tr>
<td>Current smoking</td>
<td>36%</td>
<td>16%</td>
<td>0.086</td>
</tr>
<tr>
<td>Time onset to treatment, minutes</td>
<td>120</td>
<td>118</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>112</td>
<td>116</td>
<td>0.26</td>
</tr>
<tr>
<td>Glucose</td>
<td>151</td>
<td>174</td>
<td>0.023</td>
</tr>
<tr>
<td>CT hypodensity</td>
<td>14%</td>
<td>20%</td>
<td>0.51</td>
</tr>
<tr>
<td>CT mass effect</td>
<td>9%</td>
<td>15%</td>
<td>0.42</td>
</tr>
<tr>
<td>Preexisting disability</td>
<td>8%</td>
<td>0%</td>
<td>0.38</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>39%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Large-vessel atherothrombosis</td>
<td>21%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Small-vessel atherothrombosis</td>
<td>10%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>30%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>
100 patients treated with intravenous tPA, between 2.5 and 3.4 are harmed.

These NNTH values reflecting final global outcome contrast with the lower value for the number needed to treat to be associated with protocol-defined SICH (NNT PDSICH), which has a value of 17.2. The NNT PDSICH has sometimes previously been stated to be the NNTH for tPA. However, the NNT PDSICH is not the NNTH for several reasons.

First, the two NINDS Trials (1 and 2) used an extremely conservative protocol definition of clinical worsening, any deterioration in the patient’s neurologic condition, now generally recognized as inaccurate. Under this definition, minor fluctuations in the patient’s course that caused a decrease in the NIHSS of 1 point or even no points were counted as symptomatic. However, it has come to be widely recognized that the NIHSS may vary by several points from one examination to the next in a patient who is fundamentally clinically stable attributable to inter- and intrarater variability, circadian wakefulness variation, patient fatigue, effects of concomitant medications, and other factors. Only increase in examination score by a substantial degree can be taken as evidence of symptomatic decline. As a result, the most common definition of symptomatic hemorrhage in stroke treatment trials is hemorrhage associated with worsening by 4 or more points on the NIHSS, a far more stringent threshold than was used in the NINDS trials.

Second, many patients have hemorrhage temporally associated with, but not causally related to, early worsening. Although some hemorrhages in the NINDS trials were indeed major hematomas, with mass effect and strong likelihood of causing worsening, others were minor petechial leakages without mass effect and unlikely to contribute to worsening (Figure 2). For example, a patient with a persistent arterial occlusion despite tPA may experience petechial hemorrhage around the same time he or she worsens from infarct expansion. The NINDS definition of SICH will count this actually asymptomatic petechial hemorrhage as “symptomatic.” The problem of disentangling worsening attributable to cerebral edema, infarct expansion, and other causes of ischemic stroke progression from worsening attributable to hemorrhage is difficult because the variables that independently identify patients destined for NINDS protocol-defined SICH, severe baseline NIHSS and mass effect on pretreatment CT, are also variables that predict symptomatic worsening and poor final outcome even if patients are not treated with tPA.

Third, even among the subset of patients in whom hemorrhage causes early worsening, many do not have their final outcome altered as a result. On the one hand, many patients who have truly symptomatic early hemorrhages were destined for later worsening from cytotoxic edema, infarct expansion, pneumonia, or other medical complications of stroke anyway, and the occurrence of hemorrhage did not alter their final outcome. Conversely, in other patients, hemorrhage may accompany ultimately beneficial reperfusion that saves threatened brain tissue. The 7-level mRS predictive model generated in this study indicates that 32% of patients who experienced SICH were destined for a fatal outcome even had they not been treated with tPA. This scenario is likely uncommon. However, one of the 20 patients labeled as SICH in the NINDS Trials had a final day 90 mRS outcome of 0, indicating no residual stroke symptoms whatsoever. This patient’s final outcome was not harmed in any way by the hemorrhage.

For these and additional reasons, the most important NNTH value for the patient and bedside physician to consider when making tPA treatment decisions is not the number needed to treat to cause a hemorrhage temporally associated with early worsening of any degree, but rather the number needed to treat to cause worsened final functional outcome.

The findings of this study accord well with a prior study deriving the NNTH for tPA for final global outcome using a different methodology, expert specification of a joint out-
In the earlier study, the mean value derived from the 10 expert panels for NNTH across all levels of the mRS was 30.1, falling within the fully data-specified range derived in this study of 29.7 to 40.1. The current study derives NNTH values related to SICH directly from trial data with no expert judgment mediation.

This study has several limitations. Because the number of patients experiencing SICH after tPA in NINDS Trials 1 and 2 was small, the precision of the estimates of the baseline covariate means for this population is modest. Also, the analyses in this study apply only to patients who match the NINDS Trials populations and not to patients treated later than 3 hours or otherwise ineligible for NINDS Trials 1 and 2. If the pooled data set of all 6 major intravenous tPA trials were made public, the methods used in this analysis could be extended to a larger data set to increase the precision and applicability beyond 3 hours of the NNTH values derived here.

Several authors have emphasized the need to understand better the true clinical impact of SICH after intravenous tPA driven by the widespread incorrect emphasis in the literature on the number needed to treat to cause protocol-defined SICH (NNT PDSICH) as the most clinically relevant NNTH value for intravenous tPA therapy. Although stroke experts widely recognize that this value is not especially clinically relevant, some nonexperts continue to emphasize this value as a reason to avoid tPA therapy. The incorrect interpretation of NNT PDSICH has had major adverse public policy effects on acute stroke care in the United States and internationally. This study’s derivation of a value for NNTH attributable to SICH for the more clinically relevant end point of final global functional end point will permit patients, physicians, payors, and policymakers to frame the benefits and harm conferred by intravenous tPA therapy more accurately.

In conclusion, most patients who experience SICH after tPA therapy have severe baseline insults and are already destined for a poor outcome. Many do not have their final outcome altered as a result of the hemorrhage. For every 100 patients treated with tPA who match the NINDS Trials populations, across all levels of final global disability, approximately 32 will benefit and approximately 3 will be harmed. This highly favorable benefit–risk ratio should inform treatment decision-making.

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References
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