In Acute Ischemic Stroke, Are Asymptomatic Intracranial Hemorrhages Clinically Innocuous?

David M. Kent, MD, MS; Judith Hinchey, MD; Lori Lyn Price, MS; Steven R. Levine, MD; Harry P. Selker, MD, MSPH

Background—In patients with acute ischemic stroke, intracranial hemorrhages are categorized as symptomatic or asymptomatic based on the presence or absence of a clinically detectable neurological deterioration. Asymptomatic intracranial hemorrhages are believed by many to be clinically innocuous. We examined whether the occurrence of an asymptomatic intracranial hemorrhage affects functional outcome in patients with acute ischemic stroke (AIS) treated or not treated with recombinant tissue plasminogen activator (rt-PA).

Methods—We combined data from the NINDS rt-PA Stroke Trial and the ATLANTIS Trials, excluding patients with symptomatic intracranial hemorrhage (n=1193). We used generalized estimating equations to test whether asymptomatic intracranial hemorrhage altered the likelihood of a normal or near-normal outcome at 90 days, as measured across 4 commonly used functional outcome scales, controlling for other variables that affect outcome. To look at additional outcomes, including the likelihood of disability and death, we used logistic regression equations. Additionally, we systematically reviewed previous studies that assessed the effect of intracranial hemorrhage in AIS.

Results—In the combined database, the rate of asymptomatic intracranial hemorrhage was higher in rt-PA treated than in nontreated patients (9.9% versus 4.2%, P<0.0001). Controlling for other prognostic factors, the odds of a normal or near-normal outcome was lower when a patient had an asymptomatic intracranial hemorrhage, but this effect did not reach statistical significance (OR=0.69, 95% CI: 0.43 to 1.12, P=0.13). Similarly, the odds of not being moderately to severely disabled (modified Rankin Score ≤2) was also lower for patients with asymptomatic intracranial hemorrhage (OR=0.60, 95% CI: 0.33 to 1.08, P=0.09). Despite using a larger sample than any previously published study, the power in our study to detect a 30% decrease in the odds of a good outcome was inadequate (~32%).

Conclusion—We could not confirm or exclude a clinically significant effect for asymptomatic intracranial hemorrhages based either on our analysis or on any previously published trial. Analysis of substantially larger databases are needed to assess the import of this common clinical event. (Stroke. 2004;35:1141-1146.)

Key Words: stroke, acute ■ stroke, ischemic ■ thrombolytic therapy ■ hemorrhage ■ intracranial hemorrhages ■ cerebrovascular accident ■ cerebral hemorrhage

In acute ischemic stroke, intracranial hemorrhages are classified as symptomatic or asymptomatic based on whether they are accompanied by clinically detectable neurological deterioration. Symptomatic intracranial hemorrhages are typically clinically catastrophic and occur more frequently in the context of thrombolytic therapy.1,2 In contrast, whether asymptomatic intracranial hemorrhages have any prognostic importance is not completely clear. Many believe that so-called hemorrhagic transformations are part of the natural history of acute ischemic stroke and are clinically innocuous, a “CT scan event” without any adverse sequelae.3,4 Indeed, several studies have been unable to detect any effect on overall prognosis once other factors associated with a poor prognosis are accounted for.1–6 However, previous studies have had several important limitations, including relatively small samples and the absence of any power calculations.4–6 We performed an analysis on a larger combined database that should have more power to discern clinically important effects. We also performed a systematic review of previous studies that assessed the functional significance of hemorrhagic transformation in acute ischemic stroke.

Methods

We combined several randomized clinical trials that tested thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) against placebo: The National Institutes for Neurological Disorders and Stroke (NINDS) rt-PA Study (n=624) (Parts 1 and
Trials and Subjects
The NINDS and ATLANTIS studies were randomized controlled studies testing rt-PA therapy against placebo. The methods of these trials, including inclusion and exclusion criteria, have been reported in detail in the original articles. In all 4 trials, inclusion was based on a clinical diagnosis of ischemic stroke determined by a focal neurologic deficit measurable on the National Institutes of Health Stroke Scale with a clearly defined time of onset and a baseline head CT scan that excluded hemorrhage. These trials had similar exclusion criteria, excluding patients at high risk for bleeding and patients with possible stroke mimics. All studies used the same recombinant tissue plasminogen activator (rt-PA) dosage (0.9 mg/kg, to a maximum dose of 90 mg, with the initial 10% given as a bolus) and precluded the use of oral or intravenous anticoagulants or antiplatelet agents for the first 24 hours after treatment. The studies also measured similar outcomes at 3 months, although they did not use the same primary outcome in their initial analysis.

An important difference in inclusion criteria between the studies was the allowed time from stroke onset to treatment. In the NINDS Trials, all patients were required to be randomized within 3 hours of symptom onset. ATLANTIS A enrolled consecutive patients arriving for therapy between 0 and 360 minutes without any stratification. ATLANTIS B initially enrolled patients from 0 to 300 minutes. However, soon after enrollment began, the results of the NINDS Trial became known, and the therapeutic time window was narrowed to 180 to 300 minutes from symptom onset.

Unlike the NINDS Trial, which had no upper or lower limits for stroke severity and included patients regardless of CT scan findings (provided hemorrhage was excluded), the ATLANTIS A Trial excluded patients with minor stroke (NIHSS <4), the ATLANTIS B Trial excluded patients with extended early infarct signs on the baseline CT scan (ie, diffuse swelling, parenchymal hypodensity, and/or effacement of cerebral sulci in >33% of the middle cerebral artery territory). The ATLANTIS studies also excluded patients younger than 18 and older than 80 years, whereas there was no age cut-off in the NINDS Study.

Both the NINDS and ATLANTIS studies differentiated between symptomatic and asymptomatic intracranial hemorrhage. Any patient with a deterioration of 2 points on the NIHSS who also had any blood present on a CT scan, mandated by the protocol at 24 hours or at the time of any deterioration, was considered to have had a symptomatic intracranial hemorrhage. Neither study differentiated between parenchymal hemorrhages nor hemorrhagic infarcts (HI) on CT imaging.

Model Development
To assess the impact of asymptomatic intracranial hemorrhage on patient outcome, we developed statistical models predicting 90-day outcomes in patients receiving and not receiving thrombolytic therapy in the combined database. There were 1197 patients in the combined database after excluding patients with symptomatic intracranial hemorrhage (n=56) and any patients missing variables necessary for modeling (n=131). These models could then be used to test the effect of asymptomatic intracranial hemorrhage on outcome after the effect of all other variables had been accounted for.

To select variables for inclusion in the model, we reviewed the literature for published prognostic models. In our model, we used clinical variables that have previously been shown to be important prognostic determinants of 90-day outcomes and also tested additional clinical variables available in our database, based on clinical reasoning. Likewise, interactions between variables were explored based on the existing literature and clinical reasoning. Because of differences in the coding of CT scan variables between the databases, we were unable to include radiologic variables in our model.

Our primary outcome was the global outcome, as described in the original NINDS article. For this outcome, generalized estimating equations are used to estimate the odds of a normal or near-normal outcome across 4 different stroke scales simultaneously (the modified Rankin Score [mRS], the Barthel Index, the Glasgow Outcome Score, and the NIHSS). This outcome was chosen because we reasoned that using all 4 scales should maximize the power available for model development, provided the required assumptions were met (ie, a common dose effect across all scales). We performed similar analyses using logistic regression equations and the 3 secondary outcomes: mRS ≤1 (normal or near-normal outcome), mRS ≤2 (nondisabled), and death.

For all our models, we included all variables and interaction terms that were independent predictors of the global outcome at the P=0.05 level. Once the best models were determined, we tested whether asymptomatic intracranial hemorrhage at the time of the first posttreatment CT scan added significant prognostic information.

Power Calculations
In the event that we found an estimated effect size that was clinically important but not statistically significant, we planned a post hoc power analysis to calculate the size of the database that would be needed to reliably detect an effect of the magnitude observed. To do this, we performed analyses on samples of patients drawn with replacement (ie, bootstrapped samples) from our 1197-patient database. To estimate the power of our overall database to detect an effect of the magnitude observed, we drew 1000 bootstrapped samples, with each sample containing 1197 observations. For each sample, generalized estimating equations were used to determine if the effect of asymptomatic intracranial hemorrhage on patient outcome was significant, controlling for the same variables included in our final model. We then calculated the proportion of the bootstrapped samples in which a statistically significant effect for asymptomatic hemorrhage was observed. We drew incrementally larger samples until statistically significant effects were found in at least 80% of these samples to estimate the sample size required for adequate power to reliably detect an effect.

Systematic Review
To identify relevant articles comparing outcomes in patients with hemorrhagic transformations to those in patients without, we searched MEDLINE from the years 1966 to present using the following strategies: (1) [cerebrovascular disease (exploded)] + [intracranial hemorrhage or parenchymal hematoma] + [prognosis]; (2) [cerebrovascular disease (exploded)] + [intracranial hemorrhage] + [thrombolytic therapy]; and (3) [cerebrovascular disease (exploded)] + [hemorrhagic transformation]. We also hand-searched references in the identified articles for relevant studies. The research team reviewed titles, abstracts, and articles from the literature identified. Studies were excluded if they reported only on symptomatic intracranial hemorrhages, if they did not measure functional outcomes, and if they did not include a control group without intracranial hemorrhage. Only English-language studies were included.

Results
In the combined database, asymptomatic intracranial hemorrhage was more frequent in rt-PA–treated compared with untreated patients (9.9% versus 4.2%, P<0.0001).

The best predictive model for the global outcome (predicting a normal or near-normal outcome) is shown in Table 1, with inclusion of asymptomatic intracranial hemorrhage. As can be seen, although there was a trend for patients with asymptomatic intracranial hemorrhage to fare worse after accounting for the other prognostic variables (odds ratio [OR]=0.69), this trend did not reach statistical significance (P=0.13). The variables used in this model were similarly predictive in logistic regression models using mRS ≤1 and mRS ≤2 as the outcome. The ORs for the effect of asymptomatic intracranial hemorrhage on outcome for each of the models are shown in Table 2.
When the interaction term between treatment with rt-PA and asymptomatic intracranial hemorrhage was tested, there was no apparent effect (P=0.73, in primary model), indicating that we could not detect any difference in the effects of hemorrhage on outcome in patients with versus without rt-PA treatment. There was also no evidence that there was any interaction between asymptomatic intracranial hemorrhage and study, indicating that any differences in the study protocols or in case ascertainment between studies did not have an appreciable effect on this analysis.

Ninety-day mortality was best predicted by baseline stroke severity (NIHSS), age, serum glucose (log-transformed), and systolic blood pressure. Asymptomatic intracranial hemorrhage did not add any substantial prognostic information to this model (P=0.69).

**Power Calculations**

Our bootstrap simulations indicated that a sample of 1197 has ≈32% power to detect a statistically significant effect if the true population effect is of the observed magnitude (OR=0.69) and if the true effect of the other included variables are also the same as observed in our sample. Simulations with larger bootstrapped samples indicated that to reliably detect (ie, with >80% power) the observed 30% decrease in the odds of a favorable outcome with asymptomatic hemorrhage would require >4000 patients (Table 3).

**Systematic Review**

Our review of the literature revealed 9 previous studies4–6,19–24 that evaluated outcomes in patients with acute ischemic stroke compared with those with and without intracranial hemmorhages (Table 4). Studies varied in size from 32 to 790. There were no previous studies that specifically examined the impact of asymptomatic intracranial hemorrhages. Seven studies5,6,19–23 differentiated between parenchymal hemorrhages and HI (based on the CT scan appearance), but only 3 studies5,19,20 reported results separately for HI. Although 7 had results that were not statistically significant,4–6,20,21,23,24 none of these studies assessed whether, given a true effect of hemorrhage on functional outcome, they had adequate statistical power to detect it. Uniformly, these studies interpreted their results as indicating that the hemorrhagic event did not effect prognosis (except for 1 study that inappropriately concluded that HI worsened outcome24). One study found that HI was associated with a more favorable outcome,19 whereas 1 study22 found that hemorrhage was associated with a less favorable outcome.

**Discussion**

We did not detect a statistically significant effect for asymptomatic intracranial hemorrhage on our primary outcome (ie, the global outcome). Despite this, these data offer no reassurance that asymptomatic intracranial hemorrhages are clin-
A common error in research design of studies that examine the clinical impact of hemorrhagic transformation of acute ischemic stroke. Our study was the only study that looked specifically at asymptomatic intracranial hemorrhages. ECASS 1 and 2, however, classified hemorrhages radiographically, but not clinically. These differences make combined analyses difficult. Additionally, although NINDS and ATLANTIS had similar rates of hemorrhage and of asymptomatic hemorrhagic transformation, the ECASS studies showed substantially higher hemorrhage rates overall; in ECASS 1, 9.9% of placebo-treated patients had hemorrhagic transformations (of all types combined), compared with 30.0% of patients who received rt-PA. In ECASS 2, the corresponding proportions were 18.5% and 29.5%, respectively. The substantially higher rate of hemorrhage in the ECASS studies compared with that found in NINDS and ATLANTIS suggests important differences in case definition and/or ascertainment that is not apparent from the published reports.

Not surprisingly, there was some heterogeneity in the results of the reviewed studies. Although most studies did not find statistically significant effects, one study found statistically significant worse outcomes in patients with hemorrhages. Another study claimed worse outcomes in patients with hemorrhages, but their data did not fully support this conclusion. More recently, a small but intriguing study (n=32) found an enormous increase (OR=10.6, 95% CI: 1.7 to 69.9) in the likelihood of a good outcome among patients receiving thrombolysis who manifest HI, which they found to be associated with reperfusion as measured by transcranial Doppler. It is unclear how the results of this small study may be reconciled with the results of the other much larger studies, including our own.

Whether asymptomatic hemorrhages, or a portion of such hemorrhages, affect outcome (for good or ill) is particularly important because they are so common in acute ischemic stroke and their frequency is increased with the use of antithrombotic therapy. Because their clinical impact is unknown, putative benefits of antithrombotic agents need to be rigorously proven before routine adoption of such therapies, even in patient subgroups.

In addition to the insufficient power to detect clinically meaningful effects, there are additional limitations to our study. A fundamental limitation of this study is that in developing our multivariable model, the estimation of effect size is somewhat dependent on which additional variables are controlled in the model. Only when the model was refined by adding interaction terms did the effect of hemorrhage cease to be statistically significant. Similarly, the effect of asymptomatic intracranial hemorrhage seen in our analysis might be overestimated in our model if there are other variables associated with the likelihood of asymptomatic intracranial hemorrhage and with outcome, which are not included in the model. Perhaps most important among these variables is a decrease statistical power. To reliably detect the effect we observed (a 30% reduction in the odds of a good outcome), a sample size of between 4000 and 5000 patients would be needed. The number of patients required to “prove” equivalence would be substantially greater and may not be feasible.

- TABLE 3. Power Calculations

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Estimated Power to Detect an Odds Ratio of 0.69*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1197</td>
<td>0.32</td>
</tr>
<tr>
<td>3000</td>
<td>0.66</td>
</tr>
<tr>
<td>4000</td>
<td>0.78</td>
</tr>
<tr>
<td>5000</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*Proportion of bootstrapped samples demonstrating a significant effect for asymptomatic intracranial hemorrhage, when each bootstrapped sample is of a given size.

Clinically innocuous. Our model shows a point estimate for the effect size of asymptomatic intracranial hemorrhage that, if true, would be clinically significant, and this analysis does not rule-out effect sizes considerably larger. For example, according to the primary model, in the absence of a hemorrhage on follow-up CT scan, a representative patient (calculated for a “median” patient: a 68-year-old man without diabetes with a systolic blood pressure of 154 mm Hg, a baseline NIHSS score of 11, and receiving rt-PA at 3 hours) has a 40% probability of a normal or near-normal outcome (on the mRS), whereas this probability decreases to 32% in the presence of an asymptomatic hemorrhage. The magnitude of the estimated effect on outcome of an asymptomatic intracranial hemorrhage is of a similar order to that of thrombolytic therapy. Further, this model, which used the global outcome, gave a slightly more conservative estimate of the effect than did the models using mRS alone, for either cut-off used.

Our study is intended to caution other investigators who might too hastily conclude that asymptomatic intracranial hemorrhages are clinically innocuous. A common error in clinical epidemiology is to mistake the lack of a statistically significant effect as evidence for the absence of an effect. Our review of the literature for asymptomatic intracranial hemorrhage shows that this is common. Although our study found that even a sample size of almost 1200 would be expected to have negative results (70% of the time even if hemorrhages in fact reduce the odds of a good outcome by 30%, other researchers have confidently asserted the lack of an effect with far fewer subjects (as little as 36 or 121 subjects), and even when their studies found clinically substantial but statistically nonsignificant effects. For example, in the ECASS 1 study, among patients treated with rt-PA, the likelihood of 3-month disability was 43% among those without any bleeding and 79% among those with HI; yet, based on the absence of sufficient power to detect a statistically significant effect, the authors conclude that 3-month outcomes are not influenced by hemorrhagic infarcts. In these studies, the lack of statistical significance is essentially predetermined by an inadequate sample size.

Because the main predictors of an intracranial hemorrhage are also determinants of a poor outcome (notably baseline stroke severity), estimating the prognostic significance of an asymptomatic intracranial hemorrhage is difficult. The high degree of collinearity between determinants of the hemorrhage and the outcome increases the imprecision of the estimated effect of hemorrhage on the outcome and thus...
TABLE 4. Results of Systematic Review

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Population</th>
<th>Method and Outcome</th>
<th>Differentiate Between Symptomatic and Asymptomatic ICH</th>
<th>Differentiate Between HI &amp; PH</th>
<th>Estimated Effect Size* (OR of Poor Outcome) (CI)</th>
<th>If Negative, Consider Statistical Power</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayramoglu,4 2003</td>
<td>N=121 Retrospective study of patients admitted to rehabilitation facility</td>
<td>t test and χ²  Outcomes: FIM &amp; APECS scores</td>
<td>No</td>
<td>No</td>
<td>Not available</td>
<td>No</td>
<td>HT of an ischemic lesion does not affect rehabilitation outcome in stroke survivors</td>
</tr>
<tr>
<td>Molina,19 2002</td>
<td>N=32 MCA strokes treated with rt-PA: excluded those with early CT signs in:&gt;33% MCA territory at baseline</td>
<td>Multivariate LR  Outcome: 90-day mRS &gt;2</td>
<td>Not in analysis of outcomes</td>
<td>Yes</td>
<td>OR in HI patients=0.09 (0.01 to 0.59)†</td>
<td>Not applicable</td>
<td>HI (HI1-HI2) represents a surrogate marker of early successful reperfusion and good clinical outcome in patients receiving rt-PA</td>
</tr>
<tr>
<td>Berger,20 2001</td>
<td>N=790 ECASS II trial, testing t-PA against placebo.</td>
<td>Multivariate LR  Outcome: MRS &gt;2 at 3 mo</td>
<td>No</td>
<td>Yes</td>
<td>For HI1: OR=0.7 (0.4–1.2)  For HI2: OR=0.9 (0.4–1.9)</td>
<td>No</td>
<td>Heterogenous, petechial HI [HI1 and HI2] are not associated with worse early or late outcome</td>
</tr>
<tr>
<td>Mayer,21 2000</td>
<td>N=36 MAST trial, testing SK against placebo</td>
<td>Methods: χ² without multivariable adjustment  Outcome: change in neurological deficit on the Mathew scale</td>
<td>No</td>
<td>Yes</td>
<td>Not available</td>
<td>No</td>
<td>HT had no influence on patient’s neurological status</td>
</tr>
<tr>
<td>Motto,5 1999</td>
<td>N=554 MCA strokes treated with rt-PA: excluded those with early CT signs in:&gt;33% MCA territory at baseline</td>
<td>Multivariate LR  Outcome: MRS ≥3 (ie, unfavorable outcome)</td>
<td>No</td>
<td>Yes, (categories similar, but not identical, to HI &amp; PH)</td>
<td>HT Overall: OR=1.2 (0.7–2.2)  SK tx subgroup: OR=1.4 (0.7–3.0)</td>
<td>No</td>
<td>Fears concerning an undefined intraparenchymal hemorrhagic transformation could be dispelled</td>
</tr>
<tr>
<td>Fiorelli,5 1999</td>
<td>N=609 ECASS 1 trial, testing t-PA against placebo</td>
<td>Multivariate LR  Outcome: disability mRS ≥1)</td>
<td>No</td>
<td>Yes</td>
<td>HI rt-PA: OR=1.05 (0.47–2.08)  Placebo: OR=2.34 (0.62–8.81)</td>
<td>No</td>
<td>PH2 is the only type of hemorrhagic transformation that may alter the clinical course of ischemic stroke</td>
</tr>
<tr>
<td>Davalos,22 1999</td>
<td>N=615 ECASS 1 trial, testing t-PA against placebo</td>
<td>Multivariate LR  Outcome: late progressing stroke</td>
<td>No</td>
<td>Yes, but analyzed together</td>
<td>HT: OR=1.8 (1.1–3.0)</td>
<td>Not applicable</td>
<td>Mass effect of the underlying infarct rather than HI contributes to deterioration</td>
</tr>
<tr>
<td>Toni,23 1996</td>
<td>N=150 Stroke registry of patients admitted within 5 h of onset</td>
<td>Multivariate LR  Outcome: Barthel Index, poor &lt;60</td>
<td>No</td>
<td>Yes, but analyzed together</td>
<td>HT: OR=0.76 (0.25–2.37)</td>
<td>No</td>
<td>Apart form the infrequent case of massive hematoma, HT does not influence prognosis</td>
</tr>
<tr>
<td>Beghi,24 1989</td>
<td>N=123 Case-control study (age- and sex-matched) Mantel Haenszel Student t test No multivariate adjustment  Outcome: clinical worsening or death</td>
<td>No</td>
<td>No</td>
<td>RR=2.36 (0.81–6.89)</td>
<td>No</td>
<td>Clinical worsening or death at discharge were more common in HI patients</td>
<td></td>
</tr>
</tbody>
</table>

LR indicates logistic regression; OR, odds ratio; MCA, middle cerebral artery; HT, hemorrhagic transformation (includes PH and HI); PH, parenchymal hemorrhage; homogeneous region of high attenuation with or without associated mass effect; HI, hemorrhagic infarct: patchy areas of high attenuation within an infarct, no mass effect; mRS, modified Rankin Score; FIM, functional independence measure; APECS, adapted patient evaluation conference system; CT, head CAT scan; SK, streptokinase.

*Expressed as likelihood of a bad outcome (ie, OR or RR >1 indicates worsening of outcomes with hemorrhage).
†Original article reports results in terms of likelihood of a good outcome (ie, the reciprocal of the outcome report here).
measurement of infarct size on baseline CT scan. However, these measures were not available for all trials in our database.

Conclusion

Our study did not find a statistically significant effect of intracranial hemorrhage on 90-day functional outcome, although a consistent trend for poorer outcomes was seen across several measures. Previous studies that conclude that hemorrhagic transformation does not have an important clinical effect have not been sufficiently powered to uncover effects that would be clinically important. Careful analysis of substantially larger databases, including detailed information on other prognostic variables, is necessary to assess whether asymptomatic intracranial hemorrhages are clinically innocuous.

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References

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