Intracranial Hemorrhage Associated With Revascularization Therapies

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Background and Purpose—This review discusses the state of our current knowledge on hemorrhagic transformation (HT) and summarizes key factors to be considered when comparing risk associated with various approaches to revascularization.

Summary of Review—HT is a common and natural consequence of infarction, likely related to matrix metalloproteinases and free radical pathways disrupting permeability barriers between blood and brain during ischemia and reperfusion. Symptomatic HT rates within 24 to 36 hours of stroke are increased in the setting of revascularization therapy regardless of modality. HT incidence rates must be considered in the context of the timing of imaging, the period of the study, the definition of clinically significant HT, and other key predictors of HT. The most consistently identified predictors of clinically significant HT in acute revascularization trials have been thrombolytic therapy, dose of lytic agents, edema or mass effect on head CT, stroke severity, and age. Other risk factors may be hyperglycemia, concurrent heparin use, timing of therapy, and timing of successful recanalization. Future predictors may also include imaging parameters, serological markers, variables related to intra-arterial technique, and arterial lesion location.

Conclusions—Understanding how baseline and treatment variables impact HT rates after acute stroke is critical for those designing and interpreting acute stroke trials. Future trials should consider the use of PH-2 as a standardized safety end point, putting hemorrhagic changes in the context of overall clinical outcome, and developing strategies to reduce the rates of clinically significant intracranial hemorrhage. (Stroke. 2007;38:431-440.)

Key Words: stroke ■ ischemia ■ reperfusion ■ thrombolysis ■ endovascular treatment ■ intracranial hemorrhage

Ever since fibrinolysis was first administered to stroke patients in the 1950s, intracranial hemorrhage (ICH) associated with cerebral revascularization therapy has deterred its use. CT imaging in the 1970s ensured that revascularization therapies, such as thrombolytic agents, were rarely administered to patients with hemorrhagic stroke. However, a significant hemorrhage risk associated with revascularization therapy remains.

Clinical trials of thrombolysis for acute ischemic stroke in the 1980s taught us that hemorrhagic transformation (HT) frequently accompanies moderate-to-large ischemic strokes without any specific therapy. We now have a greater understanding of the factors underlying HT in the setting of revascularization therapy, as well as new questions about its clinical significance. This review discusses the state of our current knowledge and summarizes key factors to be considered when comparing risk associated with various approaches to revascularization.

Subtypes of HT and their Clinical Significance
HT can be categorized based on its association with acute clinical symptoms or its radiological appearance. In either case, the most clinically relevant question is the long-term significance of each subtype. Clearly, if certain HT subtypes are not deleterious, prevention of those subtypes is less important.

Clinically Classified HT
Symptomatic ICH
Symptomatic ICH refers to the presence of HT associated with neurological decline. Recent trials have used a variety of definitions of “decline” (Tables 1 to 5). ICH is usually attributed to thrombolytics if within 24 to 36 hours of treatment.

Regardless of the definition, data suggest that symptomatic ICH is often devastating, with mortality rates of 45% in National Institute of Neurological Disorders and Stroke (NINDS)2 and 83% in PROACT-II.3 Notably, even subgroups at the highest risk for ICH show a net benefit of treatment with intravenous recombinant tissue plasminogen activator (rt-PA) within 3 hours.4

Asymptomatic ICH
Recent thrombolytic trials have reported significantly higher asymptomatic ICH rates than the NINDS rt-PA trial placebo and treatment groups (Tables 1 to 5). Variability in detection
TABLE 1. Rates of HT Among Placebo Groups in Acute Stroke Trials of Intravenous Therapies

<table>
<thead>
<tr>
<th>Trial Cohorts</th>
<th>DIAS (Low+High Dose)</th>
<th>AbESTT-II²⁴</th>
<th>CLOTBUST-II²³</th>
<th>NINDS²</th>
<th>ECASS-II²⁵</th>
<th>ECASS-I²⁶</th>
<th>Atlantis-B²⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>27</td>
<td>199</td>
<td>63</td>
<td>312</td>
<td>386</td>
<td>305</td>
<td>275</td>
</tr>
<tr>
<td>Baseline, median NIHSS</td>
<td>12</td>
<td>9</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>0</td>
<td>1.0%</td>
<td>4.8%</td>
<td>0.6%</td>
<td>3.4%</td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Criteria for symptomatic ICH</td>
<td>NIHSSS*</td>
<td>P†</td>
<td>NIHSSS‡</td>
<td>P§</td>
<td>P or NIHSSS¶</td>
<td>N/A</td>
<td>P</td>
</tr>
<tr>
<td>Timing of CT</td>
<td>72 hours</td>
<td>36–48 hours</td>
<td>N/A</td>
<td>24 hours</td>
<td>7 days</td>
<td>7 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>18.5%</td>
<td>14.1%</td>
<td>N/A</td>
<td>2.9%</td>
<td>36.8%</td>
<td>29.9%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

*Any ICH associated with a worsening of 4 points or more on the NIHSS and confirmed by CT.
†If neurological deterioration was found and if hemorrhage was detected on brain imaging Causal link required.
‡Hemorrhage with clinical worsening (indicated by an NIHSS score of ≥4) within 72 hours of the onset of stroke.
¶Not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status.
| Documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase in hemiparesis) or causing a decreased in the NIHSS score of 4 or more points.
| Determined by the local investigator.

and definitions of asymptomatic ICH may provide some explanation. CT technique and interpretation have changed over time. For example, during the NINDS rt-PA trial era, head CT scan slice thickness was typically 10 mm, in contrast to the current 5-mm standard. Modern CT scanners have increased sensitivity. More frequent use of MR, rather than CT, imaging leads to higher rates of detection of small asymptomatic ICHs. MRI has taught us that some subtle hyperdensities on CT do indeed represent hemorrhage. Finally, in the context of intra-arterial (IA) therapy, contrast deposition may be incorrectly classified as ICH. Alternatively, increased asymptomatic ICH rates may partly represent more successful reperfusion strategies. Evidence discussed further below suggests that early and successful reperfusion may lead to higher rates of asymptomatic ICH and accelerate the timing of HT seen in natural history studies.

Radiographically Classified HT

The ECASS trialists classified HT based on radiological distinctions first proposed by Pessin et al. They defined 4 categories of HT: (1) hemorrhagic infarction type 1 (HI-1), small petechiae along the margins of the infarct; (2) hemorrhagic infarction type 2 (HI-2), more confluent petechiae within the infarcted area, but without space-occupying effect; (3) parenchymal hematoma type 1 (PH-1), a hematoma in ≤30% of infarcted area with some slight space-occupying effect; and (4) parenchymal hematoma type 2 (PH-2), a dense hematoma >30% of the infarcted area with substantial space-occupying effect, or as any hemorrhagic lesion outside the infarcted area.

Compared with placebo groups, only PH-2 rates were higher with rt-PA treatment in both the ECASS-I and ECASS-II trials. In fact, the incidence of HI was lower in the rt-PA groups than placebo in both trials.

In addition, in both ECASS trials, only PH-2s impacted long-term outcome, which was defined as death or severe disability at 3 months after stroke. Interestingly, PH-1s were associated with only early deterioration, but not long-term clinical outcome. This raises the possibility that not all “symptomatic” hemorrhages adversely impact long-term clinical outcome.

In contrast to PHs, HI-1s may be a marker of good outcome. In ECASS-II, HI-1 was inversely associated with early neurological deterioration (adjusted OR, 0.2; 95% CI, 0.1 to 0.6; P=0.003) and death at 3 months (adjusted OR, 0.2; 95% CI, 0.07 to 0.6; P=0.004). In a prospective cohort (n=32) of stroke patients with proximal MCA occlusions treated with rt-PA within 3 hours, those with HI-1 or HI-2 ICHs had smaller infarcts and better clinical outcomes, compared with those without HI (mRS 1.9 versus 3.5; P=0.009) and those with PH-1s and PH-2s (mRS 1.9 versus 4.6; P<0.001).

Given the varying definitions of “symptomatic” ICH in the stroke literature, comparing PH-2s, or PH-1s and PH-2s combined, between trials may be a more useful strategy, as performed in the pooled analysis of rt-PA trials. Secondary analyses of the ECASS-II trial demonstrated that 73.5% of symptomatic ICHs were PH-1s and PH-2s. In NINDS, symptomatic ICHs consisted of 70% (14/20) PHs by NINDS definitions (ie, not taking into account mass effect as in the ECASS definitions).

Incidence of HT: Natural History and Placebo Trial Cohorts

In the absence of revascularization therapy, HT (including all types) is a common and natural consequence of infarction.

Among natural history cohorts, total HT rates range widely, from 6.2% to 43% in small CT-based cohorts. This wide range is probably best explained by timing of imaging. For example, among natural history cohorts given no anticoagulation or antithrombotics (except low-dose subcutaneous heparin and/or aspirin), the HT rate was 6% within 3 days, 17% to 26% within 5 to 7 days, and 43% within...
4 weeks. Rates of specific ICH subtypes are difficult to determine from natural history cohorts because of limited data and the heterogeneity of definitions.

Among placebo cases from randomized, acute stroke trials, despite the potential for selection or referral bias, ICH rates are generally in keeping with these cohort study rates (Table 1).2,22–26 Key considerations when interpreting ICH rates, in addition to the timing of imaging relative to stroke onset, include definitions of ICH subtypes, the era of the study, and baseline clinical stroke severity among the population in a given trial.

Pathophysiology: HT With and Without Revascularization Therapy

Structurally, evidence suggests that the fundamental mechanism leading to fluid and blood extravasation (ie, vasogenic edema and HT) is disruption of the permeability barriers between the blood and brain, which consist of the endothelial cell tight junctions, referred to as the blood–brain barrier, and the basal lamina consisting of extracellular matrix proteins. This blood extravasation then leads to parenchymal injury through mechanical compression, ischemia, and toxicity of blood components.27 Whether subtypes of HT that are clinically significant represent a continuum of hemorrhages that simply reach a threshold based on size, or whether subtypes are phenomenologically distinct, is debatable.

Our understanding of the biochemical pathways leading to HT is evolving. Some evidence suggests that free radicals produced during ischemia and reperfusion may lead to overlapping molecular changes that activate inflammatory cytokines, which directly and indirectly undermine the integrity of both basal lamina and endothelial tight junctions. More recently, the concurrent activation of proteolytic enzymes that can degrade basal lamina, matrix metalloproteinases (MMPs), have been demonstrated during ischemia and reperfusion.28 In addition, high MMP-9 levels independently predict HT in patients with (OR, 1.31; 95% CI, 1.31 to 70.26; \(P=0.025\)) and without thrombolysis (OR, 12; 95% CI, 3 to 51; \(P<0.001\)) treatment.29,30 Furthermore, free radical production and MMP induction increase the activity of each other.27,31

In the setting of revascularization, the fundamental question is how much the increased rates of HT are caused by reperfusion and the biochemical pathways discussed, or are specific consequences of the lytic state itself. For example, rt-PA may impact HT rates directly by amplifying MMP-9, increasing NMDA excitotoxicity, and impacting vasoactivity.32,33

Pharmacological strategies to reduce revascularization-induced HT under preclinical investigation include hypothermia, free radical–spin trap compounds, platelet inhibitors, and MMP inhibitors.34 Clinical evidence of possible hemorrhage protection by a free radical-trapping agent was suggested by the Phase 1 SAI NT trial of NXY-059. Among rt-PA–treated cases (n=489), those who received NXY-059 (n=240) had significantly less symptomatic ICH than those receiving placebo (N=249; 6.4% versus 2.5%; \(P=0.036\)).35 Whether this is a true neuroprotective effect or related to diminished effectiveness of rt-PA remains to be determined.

Risk Factors for Clinically Significant HT

The most consistently identified predictors of symptomatic ICH and/or PH-2s in acute revascularization trials have been thrombolytic therapy, dose of thrombolytic agent, edema or mass effect on head CT, stroke severity, and age (Table 6).

Use of Revascularization Therapy

It is well-established that revascularization therapies increase the rate of clinically significant HT. In a pooled analysis of 6 major intravenous rt-PA stroke trials, consisting of 2775 patients, 5.9% of rt-PA and 1.1% of placebo cases had PH-2 hemorrhages (\(P<0.0001\)).36

Symptomatic HT rates within 24 to 36 hours of treatment are increased in the setting of revascularization therapy regardless of the modality: intravenous lytics (Table 2), intra-arterial lytics (Table 3), antithrombotics (Table 4), and mechanical devices (Table 5). As with untreated cohorts, these symptomatic ICH rates must be considered in the context of key variables including clinical stroke severity (ie, median baseline National Institutes of Health Stroke Scale [NIHSS]), how “symptomatic” is defined in each trial, the timing of the CT, and the study periods of each specific trial (Tables 2 to 5). Experienced community centers report comparable symptomatic ICH rates after intravenous lytic therapy when the NINDS tPA Stroke Study protocol is strictly followed.24

Symptomatic ICHs tend to occur within the vascular territory of the ischemic insult and they tend to occur relatively early. Only 20% of symptomatic ICHs in the NINDS trial occurred in a clinically silent territory, and no hemorrhages in PROACT-II occurred outside the infarct zone.2,37 In the NINDS trial, all fatal hemorrhages occurred within 24 hours of rt-PA administration, including 80% within 12 hours.4

Rates of symptomatic ICH are generally higher in intra-arterial lytic trials (10% in PROACT-II) compared with intravenous lytic trials (6.4% in NINDS). Likely explanations include the higher baseline median NIHSS scores among intra-arterial subjects (17 in PROACT-II versus 14 in NINDS), longer door-to-needle times, less lacunar subtypes seen in PROACT-II, and differing definitions of “symptomatic.”25

Antithrombotic trials using heparins and heparinoids have shown lower HT rates compared with rt-PA. However, their relatively low HT rates remain in excess of their minimal benefit in the acute setting and often included less severely affected subjects.38–40 Newer classes of antithrombotics, such as GP IIb/IIIa inhibitors and direct thrombin inhibitors, are currently under investigation.

In contrast to therapeutic strategies for acute myocardial infarction, symptomatic ICH after revascularization therapy limits the use of aggressive multimodal strategies for reperfusion and prevention of reocclusion in acute ischemic stroke. As discussed below, this was seen in the PROACT trial when high-dose heparin was administered concurrently with intra-arterial thrombolysis.41

Lytic Dose

Several lines of evidence suggest that higher doses of lytics lead to higher hemorrhage rates. In the early pilot trials of rt-PA, 18% (4/22) of patients administered >0.9 mg/kg had...
symptomatic ICH, compared with 1% (1/72) administered /H11349 0.9 mg/kg. (//P/H11021 0.01)42 In addition, a retrospective analysis of the Multicenter rt-PA Acute Stroke Survey recalculated rt-PA doses using actual weights (rather than weights esti-

mated at the time of rt-PA administration) and showed a trend toward higher rates of ICH at the highest quintile of rt-PA dosing, compared with the lower tiers.43 Finally, the higher rates of symptomatic ICH seen in the streptokinase trials of acute stroke are likely caused in part by the use of the full cardiac dose of streptokinase in these trials.44 By comparison, the rt-PA trials used two-thirds of the cardiac dose of rt-PA, based on dose-escalation pilot trials of rt-PA. Dose-escalation studies of newer generation thrombolytic agents, desmote-

plase and tenecteplase, also show increased HT rates with higher lytic doses.22,45 Upcoming phase II studies of desmote-

plase and tenecteplase may offer the opportunity to determine whether lower thrombolytic dosing provides the same revas-

cularization efficacy with lower hemorrhage rates.

Clinical Stroke Severity

Clinical stroke severity, as measured by the NIHSS score, was significantly associated with symptomatic ICH in the NINDS trial. (Table 6) It was not associated with PH-2 risk in the ECASS trials, but was associated with HI risk in ECASS-I.8,13

The TOAST trial experience shows how the severity of stroke in a study population can impact an acute stroke trial. In its original inception, the trial tested a 7-day course of the low-molecular-weight heparinoid, danaparoid, among ische-

mic stroke patients with any significant stroke symptoms. An initial “serious” ICH rate of 12.5% (10/80) was seen in the treated subgroup of enrolled patients with NIHSS scores greater than 15 (versus 1/80 in placebos with NIHSS scores <15; /H11022 P<0.01). Concerns about this high HT rate led to amending the study protocol to exclude patients with NIHSS scores >15, and the final HT rate was 2.4% among the total 638 patients in the treatment arm.40

TABLE 2. Rates of HT among Subjects Treated with Lytic Agents in Intravenous Acute Stroke Trials

<table>
<thead>
<tr>
<th></th>
<th>SAINT25</th>
<th>TNK46</th>
<th>DIAS (Low-Dose)22</th>
<th>DIAS (High Dose)22</th>
<th>NINDS rt-PA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>249</td>
<td>25/25/25/13</td>
<td>45/30/30/312</td>
<td>45/30/30/312</td>
<td>45/30/30/312</td>
</tr>
<tr>
<td>Baseline, median NIHSS</td>
<td>14.5 (mean)</td>
<td>12/14/10/8</td>
<td>12/14/10/8</td>
<td>12/14/10/8</td>
<td>12/14/10/8</td>
</tr>
<tr>
<td>Time to rx</td>
<td>3 hours</td>
<td>3 hours</td>
<td>9 hours</td>
<td>9 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Lytic dose</td>
<td>0.9 mg/kg rt-PA</td>
<td>0.1/0.2/0.4/0.5 mg/kg</td>
<td>62.5, 90, and 125 mcg/kg</td>
<td>25, 37.5, and 50 mg</td>
<td>0.9 mg/kg rt-PA</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3.6%</td>
<td>0/0/0/15%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Criteria for Symptomatic ICH</td>
<td>NIHSSS*</td>
<td>Pt†</td>
<td>NIHSSS‡</td>
<td>NIHSS§</td>
<td>Pt6</td>
</tr>
<tr>
<td>Timing of CT</td>
<td>72 hours</td>
<td>36 hours</td>
<td>72 hours</td>
<td>72 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>20.9%</td>
<td>8/32/28/23%</td>
<td>31.1%</td>
<td>16.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Mortality at 3 months</td>
<td>N/A</td>
<td>12/24/16/15</td>
<td>9.3%</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*An increase in the NIHSS score of at least 4 points within 36 hours.
†Associated with neurological worsening judged to be caused by the hemorrhage.
‡Any ICH associated with a worsening of 4 points or more on the NIHSS and confirmed by CT.
§Not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status.
¶Documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (e.g., drowsiness, increase in hemiparesis) or causing a decreased in the NIHSS score of 4 or more points.
∥Determined by the local investigator.
**Considered by local investigator to be causally related to clinical deterioration.

TABLE 3. Rates of HT Among Subjects Treated With Antithrombotics in Acute Stroke Trials

<table>
<thead>
<tr>
<th></th>
<th>AbESTT-II24</th>
<th>ARGIS-I77</th>
<th>TAIST29</th>
<th>HAEST78</th>
<th>TOAST40</th>
<th>IST38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group, n</td>
<td>195</td>
<td>171</td>
<td>486</td>
<td>224</td>
<td>638</td>
<td>4856</td>
</tr>
<tr>
<td>Baseline, median NIHSS</td>
<td>8/9</td>
<td>N/A</td>
<td>N/A</td>
<td>8.8 (mean)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Time to rx</td>
<td>6 hours</td>
<td>12 hours</td>
<td>48 hours</td>
<td>30 hours</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3.6%</td>
<td>4.3%</td>
<td>1.0%</td>
<td>2.7%</td>
<td>2.3% Serious</td>
<td>1.2% at 14 days</td>
</tr>
<tr>
<td>Criteria for symptomatic ICH</td>
<td>Pt*</td>
<td>NIHSS change†</td>
<td>Pt†</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Timing of CT</td>
<td>5 days</td>
<td>5–5.5 days</td>
<td>10±2 days</td>
<td>7 days</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>9.7%</td>
<td>4.3%</td>
<td>N/A</td>
<td>8.9%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mortality at 3 months</td>
<td>9.2%</td>
<td>6.0%</td>
<td>12.1%</td>
<td>17.9%</td>
<td>6.6%</td>
<td>22.9% within 6 months</td>
</tr>
</tbody>
</table>

*If neurological deterioration was found and if hemorrhage was detected on brain imaging causal link required.
†Parenchymal hemorrhage, hemorrhagic infarction, or hemorrhagic transformation detected by CT and associated with neurologic deterioration, defined as an increase of 4 points in total NIHSS score, 2 points in NIHSS motor component, or 1 point in NIHSS level of consciousness component) within 30 days.
‡Clinical deterioration associated with intracranial bleeding on computed tomography or necropsy.
Early CT Changes

Another risk factor for symptomatic ICH is the presence of clear CT edema or mass effect. In the NINDS trial, edema was defined as a focal or diffuse area of hypodensity that was less dense (darker) than white matter and denser (whiter) than cerebrospinal fluid. Mass effect was defined as effacement of the cerebral sulci, sylvian fissures, or basal cisterns, or compression of the ventricles. Patients with these CT findings had a 31% (5/16) symptomatic ICH rate, compared with 6% (17/290) without these findings. Edema and/or mass effect on head CT independently predicted symptomatic ICH in multivariate analysis (OR, 7.8; 99% CI, 2.2 to 27.1).

The ECASS-I trial introduced the concept of excluding patients from revascularization therapy based on CT findings of clear or subtle ischemia in an extended area, such as more than one-third of the MCA territory, based on the concern that these patients would have a higher risk of ICH than benefit from rt-PA. Subsequently, NINDS trial CT scans were retrospectively reevaluated for both clear and subtle early ischemic changes (EICs), defined as the presence of one or more of the following: (1) loss of gray–white matter distinction; (2) hypodensity or hypoattenuation (ie, darker than white matter and whiter than CSF); and (3) compression of CSF spaces. The 31% (194/624) of cases with EICs showed no significantly increased risk of symptomatic ICH after adjusting for baseline NIHSS score. The subset with EICs in more than one-third of MCA territory (N=84) also did not have higher symptomatic ICH rates. Another NINDS reanalysis, using the semiquantitive approach of the Alberta Stroke Programme Early CT Scale (ASPECTS), also found that patients with subtle and clear EICs (ASPECTS ≤7) in more than one-third of MCA territory did not have higher rates of symptomatic ICH. Both studies concluded that patients with subtle EICs should not be excluded from rt-PA treatment within 3 hours of symptom onset based on current evidence.

The impact of EICs on CT at the 3- to 6-hour time window may be different. ECASS-II showed a significant association between EICs and both PHs and symptomatic ICH. In PROACT II (N=154), nonsignificantly more cases with ASPECTS ≤7 had symptomatic ICH (OR, 1.9; 95% CI, 0.4 to 9.8).

Age

Age was the only independent risk factor for PH-2s (P=0.0002), other than thrombolytic administration, in the pooled analysis of major intravenous rt-PA trials. Age was also an independent risk factor for both PH and symptomatic ICH in ECASS-II alone. Of note, both studies treated predominantly within 3 to 6 hours, and all but one of the

### TABLE 2. Continued

<table>
<thead>
<tr>
<th>ECASS II²</th>
<th>ECASS-I²⁶</th>
<th>Atlantis B²³</th>
<th>Atlantis A²⁴</th>
<th>MAST-E²⁵</th>
<th>ANCOROD²⁶</th>
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<tbody>
<tr>
<td>407</td>
<td>308</td>
<td>272</td>
<td>71</td>
<td>156</td>
<td>248</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>6 hours</td>
<td>6 hours</td>
<td>3–5 hours</td>
<td>6 hours</td>
<td>6 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>0.9 mg/kg rt-PA</td>
<td>1.1 mg/kg rt-PA</td>
<td>0.9 mg/kg rt-PA</td>
<td>0.9 mg/kg rt-PA</td>
<td>1.5 million units SK</td>
<td>N/A</td>
</tr>
<tr>
<td>8.8%</td>
<td>N/A (19.8% PH)</td>
<td>7%</td>
<td>11.3%</td>
<td>21.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
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<td></td>
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</table>

### TABLE 4. Rates of HT Among Subjects Treated With Lytic Agents in Intra-arterial Acute Stroke Trials

<table>
<thead>
<tr>
<th>IMS²⁹</th>
<th>EMS³⁰</th>
<th>PROACT II³</th>
<th>NINDS Subset: rt-PA Group, NIHSS³¹⁰, ages 18–80²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>80</td>
<td>35</td>
<td>180</td>
</tr>
<tr>
<td>Baseline median NIHSSs</td>
<td>18</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Time to rx</td>
<td>3 hours</td>
<td>3 hours</td>
<td>6 hours</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>6.3%</td>
<td>5.7%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Criteria for Symptomatic ICH</td>
<td>PI*</td>
<td>PI†</td>
<td>NIHSSs‡</td>
</tr>
<tr>
<td>Timing of CT</td>
<td>24±6 hours</td>
<td>72±6 hours</td>
<td>24 hours/10 days</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>42.5%</td>
<td>17%</td>
<td>26% at 24 hours/58% at 10 days</td>
</tr>
<tr>
<td>Mortality at 3 months</td>
<td>16%</td>
<td>17%</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Any hemorrhage within 36 hours associated with clinical deterioration was considered symptomatic.
†CT-documented hemorrhage that was temporally related to deterioration in the patient’s clinical condition as judged by the clinical investigator.
‡Guidelines for neurological deterioration were a 4-point or greater increase in the NIHSS score or a 1-point deterioration in level of consciousness.
§If not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status.
pooled trials (ie, NINDS) excluded patients older than 80 years old. In the only major acute stroke trial without an age exclusion, the NINDS rt-PA trial, posthoc analysis showed that age was not a significant independent predictor of symptomatic ICH. In addition, a benefit of rt-PA treatment was shown among older age subgroups. Furthermore, the 2 largest cohorts of patients older than 80 years treated with rt-PA demonstrated these findings as well. Thus, limited data suggest that, although increased age may increase symptomatic ICH risk, rt-PA is likely to benefit older patients.

Other Risk Factors

Hyperglycemia
Baseline glucose ≥200 was the only risk factor for symptomatic ICH identified in exploratory analysis of the PROACT II trial (36% versus 9% for glucose ≤200; P = 0.022). Two large registries have also found hyperglycemia to be a significant risk factor for symptomatic ICH as well.

Glucose may accelerate blood–brain barrier disruption by increasing MMP-9 expression.

Heparin Dose During IA Therapy
The PROACT trials indicate that the degree of concurrent anticoagulation with thrombolyis also impacts HT rates. In the PROACT-I trial, the first 16 patients received =10 000 U of heparin (100 IU/kg bolus plus 1000 IU/h×4 hours) and symptomatic ICH rates were 20.0% for placebos and 27.3% for IA thrombolysis patients. In conjunction with these unacceptable high symptomatic ICH rates, partial or complete recanalization rates among the thrombolysis group were 81.8%, which is higher than any other major trial to date. The subsequent 24 patients in the trial were administered 4000 U of heparin (2000 IU bolus plus 500 IU/h×4 hours) and symptomatic ICH rates decreased to 0% in placebos and 6.7% in IA lysis cases, whereas recanalization rates decreased to 40.0% in the IA group. Lower dosing regimens of heparin, comparable to the latter regimen, are now used for most intra-arterial procedures.

Timing of Revascularization Therapy
Longer stroke onset-to-treatment times may be associated with higher rates of symptomatic ICH. Pre-NINDS pilot data with Duteplase showed that those treated at <6 hours had a 25% (15/61) total ICH rate including 8% (5/61) PH-2s. Those treated at 6 to 8 hours had a 53% (17/32) total ICH rate (versus 25%; P = 0.012), including 19% (6/32) PH-2s. The pooled analysis of major rt-PA trials showed nonsignificantly higher rates of parenchymal hematoma at later stroke onset-to-treatment times (P = 0.71). However, in the DIAS
Timing and Success of Recanalization
The timing of actual recanalization may predict symptomatic ICH rates better than the timing of the administration of revascularization therapy.

The hypothesis that recanalization predisposes to HT was first proposed in 1951 by Fisher and Adams, who found persistent arterial occlusions more commonly associated with ischemic infarcts than hemorrhagic infarcts in autopsy cases. Subsequent autopsy studies have shown HT in the presence of persistent arterial occlusions. However, these studies cannot exclude the possibility of distal migration of the clot before the HT event or retrograde collateral blood flow leading to reperfusion of an ischemic leaky vascular bed.

Molina et al showed that PHs may be determined by the timing of recanalization in the setting of rt-PA. By performing serial TCD assessments of recanalization at 6, 12, 24, and 48 hours after stroke, they observed proportionally more total PHs by 36 to 48 hours in late (>6 hours) versus early (<6 hours) recanalizers (50% versus 6%; \( P=0.025 \)). All PH-2s \( (n=2) \) were in the late recanalizing group. In addition, there was a trend toward overall increased HT rate among late recanalizers (35% versus 17%; \( P=0.12 \)).

The increased rate of clinically significant ICH seen after revascularization therapies may be related to proportionally later recanalization. Future, large studies confirming this hypothesis are needed. In addition, the timing of recanalization in the context of “physiological time,” such as depth and potential reversibility of ischemia, may also be relevant and requires further study.

Additional Considerations

Imaging Parameters
Imaging parameters may also predict HT. Blood–brain barrier permeability is one potential marker based on MRI assessments including hyperintense acute reperfusion marker (HARM), a delayed gadolinium enhancement of the CSF space on fluid-attenuated inversion recovery (FLAIR) MRI imaging, early GAD enhancement on T1 images, and permeability imaging. Persistence and severity of ischemia may also predict HT. This has been suggested by MRI studies assessing diffusion-restriction volume and very low or absent apparent cerebral blood volume or flow, as well as SPECT studies measuring cerebral blood flow semiquantitatively and Xe-CT studies measuring cerebral blood flow quantitatively. These parameters all need prospective validation in larger studies with particular attention to their effects on clinically meaningful HT subgroups.

Limited data from cohort studies suggest that previous microbleeds do not significantly increase symptomatic ICH rates after thrombolysis. Further study of this issue, including the role of multiple previous microbleeds, is needed.

Serological Predictors
Pretreatment serological predictors of hemorrhage are currently undergoing investigation. A combination of 2 pretreatment endogenous fibrinolysis inhibitors, plasminogen activator inhibitor-1 and thrombin-activated fibrinolysis inhibitor, has been shown to independently predict symptomatic ICH after thrombolysis in a prospective cohort of 77 patients (positive predictive value, 75%; negative predictive value, 97.6%). High plasma cellular-fibronectin (c-Fn), a possible marker of vascular endothelial damage, was significantly associated with total ICH after controlling for other relevant risk factors (OR, 2.1; 95% CI, 1.3 to 3.4; \( P=0.002 \)) in a prospective cohort of 87 patients. High MMP-9 levels may be an additional serological marker, as previously discussed. A prospective series of 157 patients showed that PHs after thrombolysis may be related to an “explosive” increase in fibrinogen degradation products, suggesting a possible coagulopathy caused by rt-PA in patients in whom HT develops. All of these potential markers need further validation in larger studies.

Antiplatelet Use During Thrombolysis
It is currently standard practice to avoid antiplatelet use during or after thrombolysis. Specifically, the NINDS tPA protocol does not allow for administration of antiplatelet agents during thrombolysis, or up to 24 hours after thrombolysis, because of this concern. Limited data suggest that concurrent aspirin use should be avoided. For example, in the MAST-I, patients who received aspirin with streptokinase had higher rates of symptomatic ICH than those who were administered the thrombolytic agent alone (10% versus 6%). However, subsequent trials have not found baseline antiplatelet use (within 24 hours before thrombolysis) to be a risk factor for symptomatic ICH (Table 6). Definitive data on this issue is lacking.

IA Technique
Specific predictors of ICH in the intra-arterial revascularization setting have also been suggested. Contrast extravasation seen on a noncontrast CT after intra-arterial thrombolysis, another possible marker of blood–brain barrier permeability and possibly directly toxic, may be an HT risk factor based on several small studies. In a retrospective analysis of the Interventional Management of Stroke (IMS) Phase I and II trials of combined intravenous/IA thrombolysis, an increased number of microcatheter contrast injections during the intra-arterial lysis procedure was found to be an independent risk factor of total ICH. Postulated mechanisms for this risk include increased contrast extravasation and pressure transmission. These issues also require further study with larger populations, including clinically meaningful HT subgroups.

Lesion Location
Limited data suggest that lesion location may be associated with hemorrhagic complications. Specifically, internal carotid artery occlusions (versus middle cerebral artery; OR, 4.196; 95% CI, 1.229 to 14.325) and atrial fibrillation (OR, 7.294; 95% CI, 1.567 to 33.956) were the only independent predictors of total hemorrhage in the IMS I trial after controlling for baseline NIHSS score.

Cardioembolic Stroke Subtype
Atrial fibrillation was associated with symptomatic ICH in NINDS and total PHs in ECASS I in univariate analyses.
only. In addition, after adjustment for significant covariates, atrial fibrillation was independently associated with symptomatic ICH in a combined analysis of the IMS I and II trials (The IMS I and II Investigators, unpublished results). This analysis may have had increased power to identify atrial fibrillation as a significant risk factor attributable to greater stroke severity and higher rates of atrial fibrillation in the IMS I and II trials compared with the NINDS tPA Stroke Study. The contribution of stroke subtype on ICH risk after revascularization therapy needs further exploration.

Summary: Considerations Regarding HT for Future Acute Stroke Trials
Understanding how baseline and treatment variables impact HT rates after acute stroke is critical for those designing and interpreting acute stroke trials. With this knowledge, key considerations emerge.

First, stroke severity is likely to be a major predictor of symptomatic ICH because it is associated with volume of ischemic brain at risk for hemorrhagic transformation. One needs to consider the median NIHSS score of the study population when interpreting or anticipating symptomatic ICH rates in a given trial or comparing with other trials.

Second, older patients may be at greater risk of symptomatic ICH. Whereas these high-risk patients are likely to benefit from revascularization, their inclusion may prematurely end a trial. Especially in smaller Phase I trials, upper age limits may be needed to allow a promising therapy to be identified. However, this given therapy will need eventual evaluation in older patient subgroups.

Third, higher lytic doses are associated with higher symptomatic ICH risk, but whether lower doses can achieve adequate benefit with less risk is not known. Therefore, new agents must always be evaluated using dose-escalation studies in human stroke patients. Also, because the relationship between increasing efficacy and increasing risk is not well understood, consideration should be given to testing lower doses, not maximizing the dose to a tolerable safety profile.

Fourth, delayed revascularization minimizes benefit and likely increases risk. The goal of acute revascularization should not be to open occluded vessels, but to open them quickly. Patient selection based on physiological parameters is likely important to reduce late hemorrhage attributable to revascularization as well.

Fifth, future trials should consider using PH-2s as a standardized safety end point. The widely varying definitions of “symptomatic” make clinically relevant comparisons difficult.

Sixth, hemorrhagic changes must always be put in the context of overall clinical outcome. Blood on a scan may not necessarily imply a poor clinical outcome. Whereas symptomatic ICHs and PH-2s can clearly have devastating consequences, asymptomatic ICH and early HI-1 may actually be markers of better clinical outcome.

Finally, in addition to increasing efficacy and good outcomes, future trials of acute stroke therapies should aim to reduce rates of symptomatic ICH or PH-2s.

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References


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