Predictors of Hemorrhagic Transformation in Patients Receiving Intra-Arterial Thrombolysis

Chelsea S. Kidwell, MD; Jeffrey L. Saver, MD; Joaquin Carneado, MD; James Sayre, PhD; Sidney Starkman, MD; Gary Duckwiler, MD; Y. Pierre Gobin, MD; Reza Jahan, MD; Paul Vespa, MD; J. Pablo Villablanca, MD; David S. Liebeskind, MD; Fernando Vinuela, MD

Background and Purpose—Hemorrhagic transformation (HT) is a major complication of intra-arterial (IA) thrombolytic therapy. Identifying significant predictors of hemorrhage after thrombolysis would be useful in guiding patient selection for IA treatment.

Methods—Data were collected retrospectively on consecutive patients with acute focal cerebral ischemia within the anterior or posterior circulation who were treated with combined intravenous (IV)-IA or pure IA thrombolysis over an 8-year period at the UCLA Medical Center.

Results—Eighty-nine patients were treated. Median baseline National Institutes of Health Stroke Scale (NIHSS) score was 16, and mean age was 69 years. Twenty-six patients received IA tissue plasminogen activator (tPA) only, 22 received IV-IA tPA, and 41 received IA urokinase only. Asymptomatic HT occurred in 29 patients (33%), minor symptomatic HT (1- to 3-point worsening in NIHSS score) occurred in 10 patients (11%), and major symptomatic HT (≥4-point worsening in NIHSS score) occurred in 6 patients (7%). The rate of any HT was similar in patients treated with pure IA thrombolysis (39%) versus combined IV-IA thrombolysis (41%). In pure IA cases, the rate of any HT was 50% with tPA versus 32% with urokinase (P=0.2). Eighty-six percent of the patients with HT versus 39% of the patients without HT were dead or disabled (modified Rankin score >2) at day 7 (P<0.0001). On multivariate analysis, independent predictors of any HT were higher NIHSS score, longer time to recanalization, lower platelet count, and higher glucose level. A model using these variables correctly predicted HT with positive predictive value 70% and overall accuracy 78%.

Conclusions—In this large series of IA thrombolysis, rates of HT were similar to those demonstrated in prior series and clinical trials. Higher NIHSS score, longer time to recanalization, lower platelet count, and higher glucose level were independent predictors of any HT. (Stroke. 2002;33:717-724.)

Key Words: hemorrhage ■ stroke, ischemic ■ thrombolysis ■ tissue plasminogen activator ■ urokinase

Intravenous (IV) tissue plasminogen activator (tPA), the only Food and Drug Administration (FDA)-approved treatment for acute ischemic stroke, must be administered within 3 hours of symptom onset.1 Recently, a large phase III clinical trial demonstrated that intra-arterial (IA) thrombolytics may improve clinical outcome when they are administered to select patients up to 6 hours from symptom onset.2 An alternative approach to pure IV or pure IA thrombolysis that is currently under investigation in clinical trials is the use of combined IV-IA thrombolytics.3 However, the main complication and limiting factor for all these routes of agent administration is the development of hemorrhagic transformation (HT).2,4 Identification of factors that lead to HT after thrombolysis could provide a means to select optimal patients for therapy, thus limiting overall complications and potentially allowing the time window for thrombolysis to be extended beyond currently accepted standards in select patients.

Rates of HT in trials of thrombolysis for acute ischemic stroke have varied widely depending on the thrombolytic agent, route of administration, and time window allowed for the initiation of therapy. In trials of IV thrombolysis, the rates of symptomatic and total hemorrhage in treated patients have ranged from 6% and 10%, respectively, in the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial to 21% and 68% in the Multicenter Acute Stroke
(MAST)-E trial of streptokinase.\textsuperscript{4,5} In the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial, the only large randomized clinical efficacy trial of intra-arterial thrombolysis, symptomatic hemorrhage occurred in 10% of treated patients, and any hemorrhage occurred by day 10 in 68%.\textsuperscript{2} In a multivariate analysis, the PROACT II investigators found that elevated glucose was the only independent variable associated with an increased risk of HT.\textsuperscript{6}

The objectives of the present study were as follows: (1) to characterize the frequency of HT in patients treated with IA thrombolysis at an academic stroke center, (2) to characterize variables predictive of HT in our cohort, and (3) to develop a preliminary multivariate model to predict HT in patients receiving IA thrombolytics.

**Subjects and Methods**

**Patient Demographics and Inclusion/Exclusion Criteria**

Data were retrospectively collected and analyzed for all patients receiving IA thrombolytic therapy through May 2000 at our institution, including 26 patients described in a previous report.\textsuperscript{7} IA thrombolysis was considered whenever a patient presented with acute cerebral ischemia and the attending stroke neurologist and interventional neuroradiologist felt that the patient could potentially benefit from the procedure. Our institutional policy is to consider IA thrombolysis for anterior circulation occlusions if the IA infusion can be started within 6 hours of symptom onset and for posterior circulation occlusions if the IA infusion can be started within 24 hours of symptom onset. Ever since FDA approval of IV tPA, pure IA thrombolysis has been considered for patients with contraindications to standard IV tPA within 3 hours of symptom onset, and combined IV-IA thrombolysis has been considered for patients who meet all criteria for standard IV tPA.\textsuperscript{3}

Patients experiencing thromboembolic ischemic complications during a surgical or interventional radiological procedure were included in the series. There were no upper or lower age limitations for treatment. Active treatment with warfarin with or without an elevated prothrombin time or international normalized ratio was not an exclusion criterion for treatment. CT scan evidence of an acute or subacute intracerebral hemorrhage on pretreatment CT scan of the head was the only absolute exclusion criteria for treatment. Evidence of hypodensity or other early infarct signs on head CT in more than one third of the middle cerebral artery (MCA) territory was variably considered or not considered to be a relative contraindication for therapy on the basis of the attending physician’s preference, with final treatment decisions made on a case-by-case basis. Written informed consent was obtained for all patients before the thrombolytic procedure. IA thrombolytic therapy was administered as part of a clinical trial, the Emergency Management of Stroke Bridging Protocol,\textsuperscript{7} in 1 patient and on a compassionate-care basis in the remainder.

**Angiographic/Thrombolytic Procedure**

Cerebral angiography was performed via a femoral approach. A diagnostic angiogram was obtained to document an arterial occlusion corresponding to the patient’s symptoms before the start of IA treatment. Patients received (1) combined IV-IA tPA, with the IV portion administered at a dose of 0.6 mg/kg (10% to 15% bolus, remainder over 30 minutes) started within 3 hours of the last known well time, followed by IA tPA up to a maximum dose of 22 mg, (2) only IA urokinase up to a total dose of 1 250 000 IU, or (3) only IA tPA, generally up to a total dose of 22 mg but occasionally higher. IV heparin was generally administered at the start of the procedure at doses determined by the interventional radiologist’s preference.

The thrombolytic agent was delivered through a microcatheter. Generally, a small dose of lytic agent was delivered distal to the thrombus, the catheter was repositioned, a small dose of lytic agent was then infused directly into the thrombus, the catheter was again repositioned, and the bulk of the dose was infused proximal to the occlusion. Mechanical thrombus disruption was performed by passing the catheter through the thrombus several times when deemed appropriate by the treating interventional neuroradiologist. In select

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**Table 1. List of Demographic, Clinical, and Laboratory Patient Variables Recorded and Analyzed**

<table>
<thead>
<tr>
<th>Order of treatment</th>
<th>Thrombolytic agent (tPA vs urokinase)</th>
<th>Current use of antiplaletes</th>
<th>Current use of warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Thrombolytic dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Heparin bolus dose</td>
<td>International normalized ratio*</td>
<td>Use of heparin after procedure</td>
</tr>
<tr>
<td>Weight</td>
<td>Total heparin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature*</td>
<td>Mechanical thrombus disruption</td>
<td>Head CT early infarction signs</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure*</td>
<td>Total number of risk factors</td>
<td>MCA hypodensity§</td>
<td>Hyperdense MCA sign</td>
</tr>
<tr>
<td>Diastolic blood pressure*</td>
<td>Number of risk factors stratified‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest systolic blood pressure*</td>
<td>Cigarette smoking</td>
<td>Anterior or posterior circulation</td>
<td></td>
</tr>
<tr>
<td>Lowest systolic blood pressure*</td>
<td>Hypertension</td>
<td>Vessel involved</td>
<td></td>
</tr>
<tr>
<td>Highest diastolic blood pressure*</td>
<td>Diabetes mellitus</td>
<td>Caliber of vessel involved</td>
<td></td>
</tr>
<tr>
<td>Lowest diastolic blood pressure*</td>
<td>Hyperlipidemia</td>
<td>Etiology of stroke</td>
<td></td>
</tr>
<tr>
<td>Glucose*</td>
<td>Alcohol abuse</td>
<td>Presence of tandem occlusion</td>
<td></td>
</tr>
<tr>
<td>White blood cell count*</td>
<td>Coronary artery disease</td>
<td>TIMI grade</td>
<td></td>
</tr>
<tr>
<td>Platelet count*</td>
<td>Cardioembolic source</td>
<td>Mori grade</td>
<td></td>
</tr>
<tr>
<td>Hematocrit*</td>
<td>High-risk cardioembolic source</td>
<td>Presence of multiple occlusions</td>
<td>Use of general anesthesia</td>
</tr>
<tr>
<td>Time to emergency department‡</td>
<td>History of prior cerebrovascular disease</td>
<td>Attending neuroradiologist</td>
<td></td>
</tr>
<tr>
<td>Time to angiography</td>
<td>Presence of proximal stenosis</td>
<td>Pretreatment NIHSS score</td>
<td>Pretreatment modified Rankin score</td>
</tr>
<tr>
<td>Time to procedure completion</td>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technique (IV-IA vs IA)</td>
<td>Presence of systemic illness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pretreatment.  
‡From symptom onset.  
§Categorized as none, ≤1/3 MCA territory, or ≥1/3 MCA territory.
cases, angioplasty was also performed to treat residual stenosis or to achieve recanalization in unresponsive cases. Diagnostic angiograms were completed at regular intervals to assess recanalization. The thrombolytic infusion was discontinued when full recanalization was achieved, when partial or no recanalization occurred but the treating physicians felt that a maximal safe dose of thrombolytic drug had been administered, or when there was suspicion that HT may have occurred (contrast extravasation visualized on angiography, acute severe elevation in blood pressure, or acute clinical deterioration). The angiographic result was graded by the treating interventional neuroradiologist according to the Thrombolysis and Myocardial Infarction (TIMI) and Mori scales.8,9

Clinical Variables and Outcome Measures
Demographic, clinical, and laboratory data for 57 variables (Table 1) were recorded for each patient. The National Institutes of Health Stroke Scale (NIHSS) score was calculated before treatment, 24 hours after treatment, and at day 7.10 Modified Rankin scores were assessed for the day-7 and -90 time points.11 For some patients, the clinical scales were assessed retrospectively by a stroke neurologist certified in use of the NIHSS. For the 89 patients as a whole, 153 of the 5073 data items were missing. For the predictive models, missing data were imputed from the remaining data.

Imaging Techniques
Patients underwent head CT scanning before angiography (5 patients experiencing a thromboembolic complication during a surgical or angiographic procedure did not undergo pretreatment CT scanning).

<table>
<thead>
<tr>
<th>TABLE 2. Patient Characteristics (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
</tr>
<tr>
<td>NIHSS score, median (range)</td>
</tr>
<tr>
<td>Stroke subtype, n (%)</td>
</tr>
<tr>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Atherosclerotic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Target vessel localization, n (%)</td>
</tr>
<tr>
<td>Cerebral internal carotid artery bifurcation</td>
</tr>
<tr>
<td>Intracranial internal carotid artery</td>
</tr>
<tr>
<td>MCA</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
</tr>
<tr>
<td>Vertebral artery</td>
</tr>
<tr>
<td>Basilar artery</td>
</tr>
<tr>
<td>Time from onset to start of IA infusion as median (interquartile range), h</td>
</tr>
<tr>
<td>Time from onset to procedure completion as median (interquartile range), h</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
</tr>
<tr>
<td>IA urokinase</td>
</tr>
<tr>
<td>IA IPA</td>
</tr>
<tr>
<td>IV-IA IPA</td>
</tr>
</tbody>
</table>

Statistical Analysis
The Student t test and the Mann-Whitney U test were used to identify univariate predictors of HT for continuous variables. The \( \chi^2 \) test was used to identify univariate predictors of HT for variables with binary outcomes. Multivariate logistic regression and classification and regression tree (CART)13 analyses were performed to identify independent predictors of any HT. Missing values were imputed from available data. A multivariate predictive model was developed incorporating these variables. For the model, sensitivity, specificity, negative predictive value, positive predictive value, overall accuracy, and the c statistic were determined. SAS and SPSS programs were used to perform the statistical analyses.

Results
Between July 1992 and May 2000, a total of 89 patients received IA thrombolytic therapy for acute cerebral ischemia at our institution. Baseline patient characteristics are presented in Table 2. Mean age was 69 years, and median baseline NIHSS score was 16. Table 2 shows the major vessels involved, with occlusions located in the anterior circulation in 77 patients and in the posterior circulation in 12 patients. The median time from

![Figure 1](http://stroke.ahajournals.org/)

Figure 1. Day-90 modified Rankin score in the reported cohort as a whole (UCLA all cases) and in the subset of patients with MCA occlusions meeting PROACT II entry criteria (UCLA M1/M2 MCA) compared with treated and control patients from the PROACT II trial.
symptom onset (defined as time the patient was last known to be well) to the start of IA drug infusion was 4.2 hours, and the median time from onset to the completion of the angiographic procedure was 5.7 hours. Forty-one patients received IA urokinase, 26 received pure IA tPA, and 22 received combined IV-IA tPA. Twelve patients underwent angioplasty in addition to thrombolysis. Recanalization (TIMI 2 or 3) by the end of the IA procedure was achieved in 61 patients (68%).

HT occurred in a total of 35 patients (39%) (Table 3). HT was categorized as petechial in 26 patients (74%), major symptomatic HT occurred in 10 patients (26%), and asymptomatic HT occurred in 19 patients (21%). The baseline NIHSS score was ≥8 in all 6 patients with major symptomatic hemorrhage.

HT occurred within the first 24 hours in 32 (91%) of the 35 patients and beyond 24 hours in the remaining 3 patients. HT occurred in the basal ganglia or thalamus in 13 patients (37%), in the lobar regions in 13 patients (37%), in both the subcortical and lobar regions in 5 patients (14%), and in the brain stem in 3 patients (9%; all 3 underwent thrombolysis for a basilar occlusion), and an isolated subarachnoid hemorrhage occurred in 1 patient (3%). Hemorrhage within the infarct field was found in 34 patients and was remote (contralateral hemisphere) from the infarct in 1 patient. There was a trend toward increased rates of any HT in patients without recanalization versus patients with partial or complete recanalization (54% versus 33%, respectively; \(P=0.1\)), although no difference in rates of major symptomatic hemorrhage was noted in patients with and without recanalization (7% versus 7%, respectively).

Of the 45 patients with M1 or M2 segment MCA occlusions treated with pure IA thrombolysis, 4 (9%) had major symptomatic HT. Of the 30 patients with M1 or M2 MCA occlusions meeting full PROACT II criteria, 3 (10%) had major symptomatic HT. Eight patients with M1 or M2 MCA occlusions with early infarct signs in more than one third of the MCA territory were treated with pure IA thrombolytics. Of these, 5 developed HT, but major symptomatic neurologic deterioration occurred in only 1. Among all patients with any MCA occlusion (including M3 thrombi), HT occurred in 6 (67%) of 9 patients with an occlusion proximal to the origin of the lenticulostriates and in 17 (33%) of 42 patients with occlusions distal to the lenticulostriates (\(P=0.128\)).

No difference was noted in the rate of any HT with pure IA thrombolysis (39%) versus combined IV-IA thrombolysis (41%) (\(P=0.35\)). In analyses of thrombolytic agents used among pure IA cases, differences in the rates of any HT between tPA (50%) and urokinase (32%) did not reach statistical significance (\(P=0.2\)).

As measured by the day-90 modified Rankin score, our patients as a whole, as well as the subgroup meeting PROACT II criteria, fared as well as or better than the treated group of patients in the PROACT II trial (Figure 1). At day 90, 47% of the patients had a modified Rankin score of \(\leq 2\). However, patients with HT had worse outcomes than did patients without HT. At day 7, for patients with versus patients without major symptomatic HT, the median NIHSS score was 36 versus 7, respectively.

### Table 4. Univariate Predictors of HT

<table>
<thead>
<tr>
<th></th>
<th>Any HT</th>
<th>SHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HT (n=35)</td>
<td>No HT (n=54)</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Median TR, min</td>
<td>355</td>
<td>328</td>
</tr>
<tr>
<td>Mean glucose, mg/dL</td>
<td>158</td>
<td>129</td>
</tr>
<tr>
<td>Mean platelet count, (\times 10^3/\mu L)</td>
<td>224</td>
<td>256</td>
</tr>
<tr>
<td>Mean hematocrit, %</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Warfarin</td>
<td>35%</td>
<td>8%</td>
</tr>
<tr>
<td>Recanalization*</td>
<td>37%</td>
<td>65%</td>
</tr>
<tr>
<td>High-risk CE source</td>
<td>66%</td>
<td>48%</td>
</tr>
</tbody>
</table>

**TR** indicates time to recanalization; SHT, symptomatic HT; OR, odds ratio; and CE, cardioembolic.

*Dichotomized by Mori scale 0–2 (<50%) vs 3–4 (>50%).

### Table 5. Relationship Between Patient Outcome (HT and mRS) and Baseline NIHSS Scores

<table>
<thead>
<tr>
<th>Baseline NIHSS Score</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any HT</td>
</tr>
<tr>
<td></td>
<td>mRS 0</td>
</tr>
<tr>
<td>0–5</td>
<td>5</td>
</tr>
<tr>
<td>6–10</td>
<td>15</td>
</tr>
<tr>
<td>11–15</td>
<td>24</td>
</tr>
<tr>
<td>16–20</td>
<td>20</td>
</tr>
<tr>
<td>21–25</td>
<td>19</td>
</tr>
<tr>
<td>≥26</td>
<td>6</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin scale.
(P<0.01), and the median modified Rankin score was 5.5 versus 3, respectively (P=0.001). At day 90, the median modified Rankin score for patients with versus patients without major symptomatic HT was 6 versus 2, respectively (P=0.004). Compared with 46% of those patients without major symptomatic HT, no patient with major symptomatic HT had a modified Rankin score ≤2 at day 7 (P=0.048). Three (50%) of 6 patients with major symptomatic HT were dead at day 7 compared with 7 (8%) of 83 patients without symptomatic HT (P=0.01).

On univariate analysis (Table 4), variables associated with any HT were as follows: higher NIHSS score, longer time to recanalization, higher serum glucose level, lower platelet count, higher hematocrit, pretreatment with warfarin, and lesser degree of vessel recanalization (all P<0.1). Variables associated with any symptomatic hemorrhage were as follows: higher NIHSS score, longer time to recanalization, higher serum glucose level, higher hematocrit, pretreatment with warfarin, lesser degree of vessel recanalization, and presence of a high-risk cardioembolic source (all P<0.1). Relationships between entry NIHSS and occurrence of HT and final Rankin score are delineated in Table 5 and Figure 2.

In multivariate analysis, leading predictors of any hemorrhage were NIHSS score, platelet count, time to recanalization, and glucose level (Table 6). A final multiple logistic regression model incorporating these variables showed a good fit to the data with a C statistic of 0.79. The model demonstrated sensitivity 74%, specificity 80%, negative predictive value 83%, positive predictive value PPV 70%, and overall accuracy 78%.

Two case examples are shown in Figures 3 and 4.

Discussion

In this large series of IA thrombolysis for acute ischemic stroke performed at an academic stroke center, rates of HT were similar to those demonstrated in prior series and clinical trials. The rate of major symptomatic HT was 7% for the group as a whole and 10% for M1 or M2 MCA occlusions, comparable to the 10% rate observed in the PROACT II trial.2 These results suggest that experienced academic stroke centers can achieve results in routine clinical practice similar to those obtained in clinical trials of IA thrombolytics.

Our unique data set allowed analyses of HT rates by thrombolytic agent (tPA versus urokinase) and by route (combined IV-IA versus pure IA). In neither case was there a significant difference in HT rates, although there was a trend toward higher bleeding rates with tPA.

In addition, our data set allowed analysis of the influence of heparin and warfarin on the development of HT. Although there was no association between HT and the use of heparin or heparin dose during the procedure, in univariate analysis, there was a significant association between warfarin use and any HT (P=0.005) and a trend toward an association between warfarin use and symptomatic HT (P=0.09). However, neither heparin use nor warfarin use entered into the multivariate predictive model. It is possible that warfarin use was simply a marker of patients likely to have large embolic strokes due to atrial fibrillation. Of note, no treated patient, including all patients taking warfarin, had an international normalized ratio level >1.7. We are unaware of prior studies examining the role of warfarin use in the setting of thrombolysis, inasmuch as warfarin

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**Table 6. Multivariate Model of Any HT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td>1.148 (0.933–1.211)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.994 (0.986–1.010)</td>
<td>0.089</td>
</tr>
<tr>
<td>Time to recanalization</td>
<td>1.004 (0.996–1.006)</td>
<td>0.117</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.007 (0.995–1.012)</td>
<td>0.216</td>
</tr>
</tbody>
</table>

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Figure 2. Day-90 dichotomized modified Rankin scale (mRS) and any HT outcomes relative to entry NIHSS.

Figure 3. Example of HT in a 64-year-old man with a left M1 occlusion (a) visualized on cerebral angiography. Vessel recanalization was not achieved, and post-treatment head CT (b) demonstrates HT within the basal ganglia and a large MCA territory ischemic infarct.
use has been a contraindication to treatment in most prior thrombolytic trials. Although the PROACT I investigators found an increased rate of HT with higher doses of heparin during the procedure, this association was not apparent in our data, likely because of the significantly higher doses of heparin used in PROACT I.14

As expected, we found increased hemorrhage rates in patients without recanalization and a trend toward increased hemorrhage rates in patients with more proximal occlusions. These findings suggest that the duration and severity of ischemia are both important factors in the development of hemorrhage. Patients with proximal M1 occlusions not only have a larger cerebral territory at risk but also have more profound ischemia within the lenticulostrate territory. This finding is in accord with the finding of Maiza et al.,15 who found an increased rate of HT in 100 patients treated with IA thrombolysis for MCA occlusions if the occlusion involved the lenticulostrate arteries.

In our series, patients with HT fared significantly worse than did patients without HT. However, it is not clear to what extent the hemorrhage contributed to poor outcome independent of the severity of the initial ischemic event. In the European Cooperative Acute Stroke Study (ECASS) I trial, only symptomatic parenchymal hematomas, not petechial hemorrhages or small asymptomatic hematomas, were found to have a deleterious effect on clinical outcome.16 In the ECASS II trial, only parenchymal hematoma type 2 was found to independently cause clinical deterioration and contribute to worse prognosis.17

Identification of predictors of HT is critical in patients receiving thrombolytic therapy. Predictive models could be used in the future to select patients at low risk for complications independent of the time window from symptom onset. In the NINDS trial of intravenous tPA, stroke severity (as measured by the NIHSS score) and major early infarct changes (by head CT) were identified as important predictors of HT.18 In the ECASS I trial, stroke severity and early CT changes predicted hemorrhagic infarction, and increased age was associated with parenchymal hematoma.16 In a series of patients treated with IV tPA outside a clinical trial setting, Demchuk et al19 found elevated serum glucose and NIHSS scores to be independent predictors of HT.

In contrast to the multiple studies of predictors of HT in IV thrombolytic series, few reports have analyzed predictors of HT after IA thrombolysis. In PROACT II, on the basis of a multivariate analysis of 32 variables, only elevated glucose was an independent predictor of HT. There was a trend toward an
increased risk of symptomatic hemorrhage in patients with larger infarct volume on baseline CT (P=0.12). In a series of 54 patients treated with IA urokinase, Suarez et al. found in univariate analysis that patients who developed HT had significantly higher baseline NIHSS scores and serum glucose levels.

Our analysis identified several similar important predictors of HT on multivariate analysis. For any HT, these variables included NIHSS score, lower platelet count, increased time to recanalization, and elevated serum glucose level. The goodness of fit analysis (C statistic) suggested good model accuracy. Model sensitivity and specificity were presented because of their clinical salience but are likely overestimated in this derivation study and require confirmation in an independent data set.

In our analyses, the NIHSS score emerged as a powerful predictor of HT in both univariate and multivariate analyses. It is likely that the NIHSS score is acting as a marker of larger infarcts. Time to recanalization likely enters into our model as a marker of irreversible tissue ischemia and injury. Several prior reports have suggested an association between HT and elevated glucose levels in patients receiving IA thrombolytics (PROACT II) and in patients receiving IV tPA. Elevated glucose levels may act as a marker of patients with prior vessel injury due to poorly controlled diabetes mellitus or may act as a marker of direct toxic tissue effects of hyperglycemia that are present at the time of the stroke. Decreased platelet count may contribute to HT simply by the decreased overall number of platelets available for activation and aggregation. Finally, we found a strong association between symptomatic HT and a high-risk cardioembolic source on univariate analysis. Several prior studies have found increased rates of HT in patients with cardioembolic events. The increased HT rates in patients with strokes due to cardioembolism may be due to larger infarcts occurring with more sudden and profound ischemia.

Of note, agent route (combined IV-IA versus pure IA), agent type (tPA versus urokinase), thrombolytic dose, heparin dose, active treatment with warfarin, and elevated blood pressure did not enter into our models as independent predictors of HT.

The present study has several limitations. Our analysis was retrospective in nature, and a prospective series will be required to confirm and validate our findings. The present study population was somewhat heterogeneous and included patients with both anterior and posterior circulation occlusions, patients treated with different thrombolytic agents and routes, and patients with a wide range of severity of neurological deficit at entry. Although these differences introduced variability into the cohort, they allowed us to perform analyses comparing hemorrhage rates within these various subsets as well as within the cohort as a whole. This patient heterogeneity may weaken the validity of our multivariate prediction model. However, supporting the validity of our model is the fact that the predictive variables that we identified are consistent with those previously published. Our series also spanned an 8-year period. Over this time, techniques and expertise of interventional neuroradiologists likely evolved. However, we did not find a significant change in HT rates over time. Because of limited numbers, we were not able to develop a predictive model for the subgroup of patients categorized as major symptomatic hemorrhage. Because of our limited sample size, we probed only single variables and not interactions among variables in the multiple regression model. Finally, our predictive model did not incorporate measures of collateral flow or novel imaging measures of diffusion and perfusion abnormality. These are possibly important independent determinants of the likelihood of HT with thrombolytic therapy, and combining clinical and novel imaging predictive variables would be of interest. Future analyses will need to be performed to include this measure.

In conclusion, in this open series of IA thrombolysis, the rates of HT were comparable to those demonstrated in similar case series and in the PROACT II clinical trial. In multivariate analysis, a higher NIHSS score, lower platelet count, longer time to recanalization, and elevated glucose level were important predictors of HT. A model incorporating these variables identified with 78% accuracy the patients who would develop HT. This model needs to be validated in an independent larger series of patients and, in the future, may be used to identify patients at high and low risk of HT if treated with IA thrombolytic therapy.

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References

Thrombolysis and Hemorrhagic Transformation

An important issue in thrombolysis for acute stroke is to select patients who are likely to benefit. Even if patients with severe stroke, extensive ischemic changes on CT scan, advanced age, and high blood pressure are excluded from thrombolytic therapy, there is still a substantial risk of symptomatic hemorrhagic transformation (HT). This risk is offset by a net reduction in the proportion of patients dead or dependent in activities of daily living, it remains a dreadful complication of both intravenous and intra-arterial thrombolysis.

Kidwell et al studied 89 patients undergoing intra-arterial thrombolysis with either tissue plasminogen activator or urokinase. Among 57 variables, they identified a higher National Institutes of Health Stroke Scale score, longer time to recanalization, lower platelet count, and higher glucose level as independent predictors of HT. A multivariate analysis of 24 variables in the PROlyse in Acute Cerebral Thromboembolism II trial, in which investigators studied the effect of intra-arterial thrombolysis with pro-urokinase, also identified high blood glucose concentrations as an independent predictor of HT. A correlation between hyperglycemia and HT was found in other studies of thrombolytics in acute stroke. The risk of symptomatic HT may be increased in patients who have a blood glucose >200 mg/dL at stroke onset. Currently, most centers have incorporated the National Institute of Neurological Disorders and Stroke criteria in their thrombolysis protocol, excluding patients who have blood glucose levels >400 mg/dL. With all data taken together, it may now be prudent to lower this upper limit of blood glucose to a level of 200 mg/dL.

What is the underlying mechanism of HT? In experimental focal cerebral ischemia, a significant loss of basal lamina components of the cerebral microvessels has been demonstrated, and this loss in vessel wall integrity appears to be associated with the development of HT. Fibronectin, as well as tissue plasminogen activator and urokinase, are matrix metalloproteinases that can damage the basal lamina, and this effect may be potentiated in the presence of hyperglycemia. Hyperglycemia in ischemic brain not only aggravaes neuronal and glial cell damage, but it also damages the endothelial cells of the microvasculature. It may be worthwhile to investigate pharmacological strategies that protect the basal lamina before the administration of thrombolytics.

The 57 variables analyzed by Kidwell and coworkers are not the end of the story. A recent observation suggests that the presence of old, silent microbleeds, visualized with T2-weighted magnetic resonance imaging, may also be a marker of increased risk of HT in patients receiving thrombolytic therapy for acute ischemic stroke. The predictive value of pretreatment screening of thrombolytic candidates with these magnetic resonance imaging sequences should be further explored.

Jacques De Keyser, MD, PhD, Guest Editor
Department of Neurology
University Hospital Groningen
The Netherlands

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Predictors of Hemorrhagic Transformation in Patients Receiving Intra-Arterial Thrombolysis

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