Hemorrhagic Transformation of Ischemic Brain Tissue
Asymptomatic or Symptomatic?

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Background and Purpose—The term symptomatic hemorrhage secondary to ischemic stroke implies a clear causal relationship between clinical deterioration and hemorrhagic transformation (HT) regardless of the type of HT. The aim of this study was to assess which type of HT independently affects clinical outcome.

Methods—We used the data set of the European Cooperative Acute Stroke Study (ECASS) II for a post hoc analysis. All patients had a control CT scan after 24 to 96 hours or earlier in case of rapid and severe clinical deterioration. HT was categorized according to radiological criteria: hemorrhagic infarction type 1 and type 2 and parenchymal hematoma type 1 and type 2. The clinical course was prospectively documented with the National Institutes of Health Stroke Scale and the modified Rankin Scale. The independent risk of each type of HT was calculated for clinical deterioration at 24 hours and disability and death at 3 months after stroke onset and adjusted for possible confounding factors such as age, severity of stroke syndrome at baseline, and extent of the ischemic lesion on the initial CT.

Results—Compared with absence of HT, only parenchymal hematoma type 2 was associated with an increased risk for deterioration at 24 hours after stroke onset (adjusted odds ratio, 18; 95% CI, 6 to 56) and for death at 3 months (adjusted odds ratio, 11; 95% CI, 3.7 to 36). All other types of HT did not independently increase the risk of late deterioration.

Conclusions—Only parenchymal hematoma type 2 independently causes clinical deterioration and impairs prognosis. It has a distinct radiological feature: it is a dense homogeneous hematoma >30% of the ischemic lesion volume with significant space-occupying effect. (Stroke. 2001;32:1330-1335.)

Key Words: hematoma ■ hemorrhagic stroke ■ stroke outcome ■ thrombolysis

Several large, randomized, placebo-controlled trials of thrombolytic therapy in acute ischemic stroke have been conducted during the past years. Secondary hemorrhagic transformations (HT) after different types of thrombolytic therapy are frequently reported as important safety parameters in these studies, but they also occur as natural events in the evolution of a cerebral infarct.1–4 The increase of HT in the actively treated arm is often used as evidence against the treatment tested, as reported in the early streptokinase trials,5–7 although the large European and American tissue plasminogen activator (tPA) trials provided evidence of a benefit in ischemic stroke patients, the fear of hemorrhagic events frequently precludes the use of thrombolysis in clinical practice. Unfortunately, previous trials addressing safety and efficacy of thrombolytic therapy in acute stroke applied different definitions for the term symptomatic hemorrhage or symptomatic hemorrhagic transformation. In the tPA trial sponsored by the National Institutes of Neurological Disorders and Stroke (NINDS),8,9 symptomatic intracranial hemorrhage was defined as “any CT-documented hemorrhage that was temporally related to deterioration in the patient’s clinical condition in the judgment of the clinical investigator,” no matter how trivial the hemorrhage on the CT scan might have been. In addition, symptomatic intracranial hemorrhage attributable to study medication was defined as “symptomatic hemorrhage that occurred within 36 hours from treatment onset.” In the Multicenter Acute Stroke Trial of Italy and Europe,6,7 symptomatic HT was defined as “clinical deterioration temporally related to HT documented by CT-scan or autopsy.” A CT scan was regularly obtained at 5 days after stroke onset or earlier in the event of clinical deterioration. Further studies continued to apply the term symptomatic hemorrhage according to the NINDS protocol8–11 or without a definition.12,13

The European Cooperative Acute Stroke Study (ECASS) I and II14,15 went in the opposite direction and used a pure radiological, prospective definition: HT were categorized into 4 different subtypes without taking into consideration whether or not any hemorrhage was associated with clinical
deterioration. In addition to the pure radiological definition, the category of symptomatic hemorrhage was used for patients with clinical deterioration by ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) and with no CT findings that might have been responsible for this deterioration other than a hemorrhage.

Fiorelli et al recently demonstrated on the basis of the ECASS I data that, in both the placebo and the rtPA groups, only parenchymal hematomas (PH) >30% of the infarcted area with significant space-occupying effect increased the risk of early neurological deterioration and of 3-month death. Hemorrhagic infarctions (HI) or PH with only mild space-occupying effect did not modify the risk of early neurological deterioration, death, and disability. The different clinical outcome after different subtypes of HT illustrates the difficulty in defining symptomatic hemorrhage precisely and clearly. In fact, the spectrum of HTs differs widely and may include some trivial hemorrhagic petechiae as well as PH with space-occupying effect. To determine whether any neurological deterioration is due to HT itself or due to massive infarct and ischemic edema with a coincidental HT remains crucial in thrombolysis or other stroke trials. The aim of this study on the ECASS II data set was to define specific HT that are independently associated with an increased risk of clinical deterioration or worse outcome according to the hypothesis of Fiorelli et al. We sought to further assess the impact of possible confounding factors on clinical deterioration in patients with HT.

Subjects and Methods

The study design and primary results of ECASS II have been described in detail elsewhere. ECASS II was a double-blind, placebo-controlled trial evaluating safety and efficacy of 0.9 mg/kg IV recombinant tPA (rtPA) in patients presenting within 6 hours from the onset of an acute hemispheric ischemic stroke. Intravenous heparin or oral anticoagulants within the first 24 hours were not allowed.

All patients were examined with CT scan before randomization and after 24 to 96 hours (median, 1 day; range, 0 to 4 days). Nine patients had their follow-up scan within 24 hours of stroke onset, 643 patients between 24 and 48 hours, 128 between 48 and 72 hours, and 3 between 72 and 96 hours. An additional CT was performed after 1 week. We used this CT for analysis in 6 patients in whom the first follow-up CT was not available. Following the prospective ECASS protocol, all CT scans were evaluated twice, first by the local investigators and then independently by 3 members of the CT reading panel. The members of the CT reading panel were blinded to treatment allocation, any clinical events occurring after randomization, and the reading of the local investigators and then independently by 3 members of the CT reading panel. The CT scans to the members of the CT reading panel. Any clinical events occurring after randomization, and the reading of the local investigators and did not see follow-up scans before evaluating the baseline CT. After the exclusion of 10 patients (3 rtPA, 7 placebo) with CT scans of two poor quality to allow unequivocal assessment of HT, 790 of 800 randomized patients remained for the analysis. HT occurring on the first follow-up CT scan after randomization were prospectively categorized according to definitions previously described. HI and PH, HI type 1 (HI-1) was defined as small petechiae along the margins of the infarct, and HI type 2 (HI-2) was defined as more confluent petechiae within the infarcted area but without space-occupying effect. PH type 1 (PH-1) was defined as hematoma in ≤30% of the infarcted area with some slight space-occupying effect; PH type 2 (PH-2) was defined as dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (examples are shown in Figure 1). In cases of >1 hemorrhagic lesion on CT scan, the worst possible HT category was assumed.

Baseline and follow-up CT scans were obtained nonenhanced and on the same scanner if possible. Windows and center levels were set to optimally distinguish gray and white matter. The study protocol recommended a window width of 80 to 100 Hounsfield units and a center level of 30 to 40 Hounsfield units. The chairman of the CT reading panel gathered the categorized findings from the panel members, checked them for disagreements, disclosed disagreements to the other panel members, and discussed each discrepant CT to achieve consensus. The final judgments were sent to the data management center, which then was allowed to send the follow-up scans to the members of the CT reading panel. We defined hypodensity as a visible decrease in x-ray attenuation of brain tissue compared with other portions of the same anatomic structure or its contralateral counterpart. We categorized the extent of hypodensity of the middle cerebral artery (MCA) territory as none, ≤33% (small), and >33% (large). The total MCA territory was considered the brain volume between 2 lines being drawn from the anterior horn of the ventricle and from the trigonum perpendicular to the skull involving most parts of the frontal, temporal, and parietal lobe with the exception of the parasagittal structures. On follow-up CT scans, we measured the volume of acute ischemic lesions by multiplying the maximum diameter of hypoattenuation, maximum diameter perpendicular to it in the same slice, number of slices affected, slice distance, and a conversion factor of 0.5 using the formula for irregular volumes. In patients with HT, the entire ischemic and hemorrhagic lesion was measured.

From the ECASS II database, we retrieved the following variables: age, sex, allocation to placebo/rtPA treatment, severity of neurological deficit on admission as quantified with the NIHSS and the Scandinavian Stroke Scale, NIHSS score 24±2 hours after stroke onset, extent of initial ischemic lesion on baseline CT scan (none, ≤33% of MCA territory, and >33% of MCA territory), body temperature, blood glucose, and blood pressure at the inclusion time.

Figure 1. Examples of different subtypes of HT: HI-1 with scattered, heterogeneous petechiae along the margins of the infarct (A); HI-2 with more confluent but still heterogeneous petechiae within the infarcted area (B); PH-1 with a homogeneous hematoma covering <30% of the infarcted area and only mild space-occupying effect (C), and PH-2 with a dense hematoma >30% of the lesion volume with significant space-occupying effect (D).
We calculated the frequencies of the different subtypes of HT for placebo and rtPA groups. Statistical difference was tested with the χ² test.

To examine which of the collected variables accounted for clinical deterioration 24 hours after stroke onset (increase in NIHSS score by ≥4 between baseline and after 24±2 hours according to the prospective definition used in ECASS II), for disability and death at 3 months (modified Rankin Scale score >2), and for death up to 3 months after stroke onset, we performed a logistic regression analysis on each of these variables. Variables with a P > 0.05 in the Wald test and the logistic likelihood ratio test were assumed to be irrelevant for the outcome tested and were excluded from further analysis. We calculated the odds ratios (ORs) and 95% CIs for each HT subtype, comparing the ORs of each level of HT with no HT. Subsequently, we performed a multiple regression analysis including all variables considered relevant factors from the univariate analysis and calculated ORs for clinical deterioration at 24 hours, disability and death at 3 months, and death at 3 months alone. PH-1 accounted for an increased risk of early deterioration but not of disability or death at 3 months. Thus, outcome at 3 months was modified only by presence of PH-2 on the first follow-up CT scan. In our search for factors contributing significantly to outcome, we found a confounding effect of severity of stroke syndrome at onset and of presence of hypodensity >33% on baseline CT scan. Both were associated with an increased risk rate for disability and death. Presence of a large hypodensity was associated with early deterioration. Other contributing factors for outcome were age and glucose level. Increase of age or glucose was associated with an increased risk of HT subtype, comparing the ORs of each level of HT with no HT.

**Results**

Of a total of 790 intent-to-treat patients in ECASS II, 406 patients received rtPA (0.9 mg/kg), and 384 patients were treated with placebo. In the first follow-up CT scan, significantly more HT occurred in the rtPA group: 29.5% versus 18.5% in the placebo group (Table 1). This was mainly due to a higher incidence of PH-2 in the rtPA group (7.6% versus 0.5%; P < 0.0001). The incidences of HI-1, HI-2, and PH-1 were statistically not different between the placebo and the actively treated group, although there was a clear trend for HI-2 and PH-1 to more likely occur after thrombolysis.

Table 2 presents the unadjusted and adjusted risk ratios for the 4 different types of HT and for other factors found to contribute significantly to outcome. Sex, body temperature, and blood pressure at the inclusion time were irrelevant for outcome and thus were excluded from analysis. PH-2 significantly increased the risk of early deterioration, of disability and death at 3 months, and of death at 3 months alone. PH-1 accounted for an increased risk of early deterioration but not of disability or death at 3 months. Thus, outcome at 3 months was modified only by presence of PH-2 on the first follow-up CT scan. In our search for factors contributing significantly to outcome, we found a confounding effect of severity of stroke syndrome at onset and of presence of hypodensity >33% on baseline CT scan. Both were associated with an increased risk rate for disability and death. Presence of a large hypodensity was associated with early deterioration. Other contributing factors for outcome were age and glucose level. Increase of age or glucose was associated with an increased risk of disability and death at 3 months. Treatment with rtPA led to a significantly decreased risk of disability or death after 3 months.

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**TABLE 1.** Frequencies of Different Types of Hemorrhage in the Placebo and rtPA Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=384)</th>
<th></th>
<th>rtPA (n=406)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>HI-1</td>
<td>53</td>
<td>13.8</td>
<td>50</td>
<td>12.3</td>
</tr>
<tr>
<td>HI-2</td>
<td>11</td>
<td>2.9</td>
<td>28</td>
<td>6.9</td>
</tr>
<tr>
<td>PH-1</td>
<td>5</td>
<td>1.3</td>
<td>11</td>
<td>2.7</td>
</tr>
<tr>
<td>PH-2*</td>
<td>2</td>
<td>0.5</td>
<td>31</td>
<td>7.6</td>
</tr>
<tr>
<td>Total*</td>
<td>71</td>
<td>18.5</td>
<td>120</td>
<td>29.5</td>
</tr>
</tbody>
</table>

*Significant difference in frequency between placebo and rtPA group according to χ² test (P < 0.05).

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**TABLE 2.** Comparison of Adjusted and Unadjusted ORs

<table>
<thead>
<tr>
<th></th>
<th>Deterioration After 24 h</th>
<th>Disability/Death up to 3 mo</th>
<th>Death up to 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI) P</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonadjusted HT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-1</td>
<td>0.6 (0.2–1.3) 0.2</td>
<td>1.4 (0.9–2.2) 0.09</td>
<td>0.9 (0.4–2.1) 0.9</td>
</tr>
<tr>
<td>HI-2</td>
<td>0.8 (0.2–2.6) 0.7</td>
<td>1.3 (0.7–2.6) 0.4</td>
<td>0.9 (0.3–3.2) 0.9</td>
</tr>
<tr>
<td>PH-1</td>
<td>4.2 (1.4–12.4) 0.01</td>
<td>1.2 (0.4–3.1) 0.8</td>
<td>2.6 (0.7–9.6) 0.1</td>
</tr>
<tr>
<td>PH-2</td>
<td>41 (16–104) &lt;0.0001</td>
<td>6.5 (2.5–17.0) 0.0002</td>
<td>20 (9–43) &lt;0.0001</td>
</tr>
<tr>
<td>Adjusted HT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-1</td>
<td>0.2 (0.1–0.6) 0.003</td>
<td>0.7 (0.4–1.2) 0.2</td>
<td>0.2 (0.07–0.6) 0.004</td>
</tr>
<tr>
<td>HI-2</td>
<td>0.5 (0.2–1.9) 0.3</td>
<td>0.9 (0.4–1.9) 0.8</td>
<td>0.6 (0.2–2.5) 0.5</td>
</tr>
<tr>
<td>PH-1</td>
<td>3.5 (1.1–11.6) 0.04</td>
<td>0.6 (0.2–1.9) 0.4</td>
<td>1.0 (0.2–4.8) 0.9</td>
</tr>
<tr>
<td>PH-2</td>
<td>18 (6–56) &lt;0.0001</td>
<td>1.9 (0.7–5.7) 0.2</td>
<td>11.4 (3.7–36) &lt;0.0001</td>
</tr>
<tr>
<td>Treatment with rtPA</td>
<td>0.8 (0.5–1.3) 0.4</td>
<td>0.7 (0.4–0.9) 0.02</td>
<td>0.6 (0.3–1.2) 0.2</td>
</tr>
<tr>
<td>Hypodensity &gt;33% on initial CT</td>
<td>2.6 (1.0–6.5) 0.047</td>
<td>2.8 (1.2–6.4) 0.01</td>
<td>8 (3.3–19.5) &lt;0.0001</td>
</tr>
<tr>
<td>Severe stroke syndrome at onset</td>
<td>1.1 (0.6–2.1) 0.7</td>
<td>4.1 (2.5–6.5) &lt;0.0001</td>
<td>4.3 (2.4–7.7) &lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (0.9–1.0) 0.8</td>
<td>1.04 (1.02–1.05) &lt;0.0001</td>
<td>1.09 (1.05–1.13) &lt;0.0001</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.0 (0.9–1.1) 0.6</td>
<td>1.1 (1.04–1.13) 0.0006</td>
<td>1.1 (1.02–1.2) 0.02</td>
</tr>
</tbody>
</table>

The adjusted ORs are given for all variables finally kept in the model. Variables leading to a clear change of the ORs for HT were considered confounding factors.

Finally, we evaluated the relationship between the frequency of PH-2 and the extent of hypopattenuation on baseline CT scan and calculated ORs for the development of PH-2. The Newman-Keuls test was applied to assess the relationship between incidence of different types of HT and the lesion volume at 24 hours. In all tests, a statistical significance was assumed for P < 0.05. Analyses were performed with StatView statistical software (edition 5.0.1).
months; however, its influence for early deterioration or death alone at 3 months was insignificant.

Figure 2 demonstrates the positive correlation between large lesion volumes and large PH in both the actively treated and the placebo-treated groups. In both treatment groups, the total lesion volumes in patients with PH-2 were significantly larger than those of all other groups, including the group without any HT. In the rtPA group, lesion volume in patients without HT was also significantly lower than in patients with HI-1 and HI-2 (Newman-Keuls test). See Table 1 for frequencies of different HT subtypes.

Discussion

HT of a brain infarct is a major concern when thrombolysis is used in acute stroke. Frequently, HT of any type and extent found on routine follow-up CT scans is considered a serious adverse event and is often termed symptomatic hemorrhage regardless of whether a certain type of HT was really causing symptoms. In the larger thrombolysis studies, various definitions for symptomatic hemorrhage consisting of radiological and clinical criteria were applied. The NINDS tPA trial defined symptomatic hemorrhage as “any CT-documented hemorrhage that was temporally related to deterioration in the patient’s clinical condition in the judgment of the clinical investigator.”8 Symptomatic hemorrhage was considered to be due to study medication if it occurred within 36 hours of treatment. It appears inconceivable that a clinical deterioration under this definition could not be merely coincidental with any HT appearing on CT scan. In fact, the deterioration could well have been the natural course of a stroke independent of the coinciding HT, especially if the HT was only a minor part of a large infarct. In a post hoc analysis by the NINDS Stroke Study Group,9 it was nevertheless stated that presence of a severe neurological deficit and clear signs of brain edema or mass effect on pretreatment CT increased the risk of symptomatic hemorrhage. Again, pure radiological criteria of different types of HT were not considered, and other factors causing clinical deterioration were ignored. Similar definitions for symptomatic hemorrhage were applied in the Multicenter Acute Stroke Trial of Italy and Europe6,7 and in recent thrombolysis surveys.10,11

In ECASS I and II, prospective radiological definitions of the 4 different subtypes of HT were applied regardless of clinical events, and CT scans with or without HT were analyzed regardless of clinical data. CT was performed at 24 hours and 7 days after symptom onset and treatment and in case of clinical deterioration. Almost all major hemorrhages were detected by the first follow-up CT. However, local investigators collecting data on neurological status might have created some unavoidable bias in that they knew the result of the CT scan and might have implemented a preconceived notion of any relationship between HT and neurological deterioration. We believe that a prospective protocol for CT scanning at predetermined dates is necessary to study the question of whether certain types of hemorrhage are associated with clinical deterioration. In our view, an early follow-up CT within 48 hours of treatment is necessary to detect hemorrhages caused by rtPA.

In this post hoc analysis of the ECASS II data set, we confirm previous results by Fiorelli et al16 that only PH >30% of the infarcted area with considerable space-occupying effect (PH-2) significantly increased the risk of early clinical deterioration and of a worse long-term outcome, including death. Other types of HT, particularly HI-1 and HI-2, were not associated with clinical deterioration. This was also true for PH-1, which at least did not increase the risk of disability or death up to 3 months after stroke onset. Thus, while these latter types of HT would have been termed symptomatic hemorrhages according to the definition of many ongoing trials, their presence might not have been responsible for deterioration. Instead, other factors such as age, initial glucose level, extent of initial hypodensity on baseline CT scan, and severity of stroke syndrome at baseline were thought to be responsible for this.
additionally contributed to clinical outcome, as described in a previous study.\textsuperscript{23} Treatment with rtPA, although associated with a higher incidence of PH-2, decreased the overall risk of disability and death at 3 months.

In particular, stroke severity and the presence of large hypodensity on the initial CT scan were associated with a significantly increased risk for disability and death up to 3 months after stroke onset. Thus, they appear as confounding factors for the influence of HT on outcome. After adjustment for these confounding factors, the risk for disability or death at 3 months was increased insignificantly after PH-2, but with respect to a long-term outcome, PH-2 independently and significantly increased only the risk of death at 3 months. HI-1 was even associated with some clinical improvement and may, at least in this early stage, indicate the effect of successful early reperfusion. Since PH-2 is of major clinical relevance or may in fact be considered hemorrhage that is most likely to be symptomatic, emphasis must be placed on the recognition of stroke patients who are more likely to develop large PH and subsequently should be excluded from thrombolysis. PH-2 occurred more frequently in patients with hypodensity >33% on early CT. These early ischemic changes identified on the pretreatment CT represent early cytotoxic edema and possibly the development of irreversible injury.\textsuperscript{24} In a study by Hamann et al,\textsuperscript{25} the presence of microscopic hemorrhages in the ischemic area has been related to a loss of cerebrovascular basal lamina integrity. Since these microscopic hemorrhages always occur within the infarcted area, particularly in the subcortical core, a large infarct volume a priori offers a larger area of lost basal lamina integrity, thus possibly leading more frequently to parenchymal hemorrhages. We were able to confirm this relationship by demonstrating a positive correlation between large lesion volume and presence of PH-2. Thus, to detect signs of early infarction on CT remains crucial, although it is questioned whether these signs can be detected reliably.\textsuperscript{26} In a previous study the interobserver agreement in assessing subtle CT signs of cerebral infarction was moderate to substantial.\textsuperscript{20} Similar results for assessment of the hypodensity in thirds of the MCA territory were obtained by the Alberta Stroke Programme Early CT Score (ASPECTS) study group.\textsuperscript{27} Whether general reading of CT scans can be improved by quantification and division of the MCA territory into many regions of interest remains to be confirmed in clinical practice. To date, presence of hypodenuation larger than one third of the MCA territory on baseline CT seems to be the most simple and readily available predictor of the development of large PH.

In summary, only large PH >30% of the infarcted area with space-occupying effect (PH-2) independently modify the risk of a worse clinical outcome both early and late after stroke onset. Smaller but still homogeneous PH (PH-1) increase the risk of early deterioration but not of a worse long-term outcome. Heterogeneous, petechial HI are not associated with worse early or late outcome. Thus, the term symptomatic hemorrhage should be applied with caution because it implies a causal relationship between signs of HT found on CT and clinical deterioration. Additional factors, such as extent of the lesion, edema formation, and severity of the stroke syndrome, however, offer an explanation for a patient’s deterioration or bad outcome. In future reports dealing with safety aspects of thrombolysis, a clearer distinction between nonrelevant forms of HT and PH with risk of clinical deterioration should be made.

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References

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