Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) improves the outcome for ischemic stroke patients who can be treated within 3 hours of symptom onset. The efficacy of thrombolysis has been demonstrated despite an increased risk of severe hemorrhagic transformation (HT) in patients treated with rtPA. In the European Cooperative Acute Stroke Study (ECASS), HTs were classified according to their appearance on CT into hemorrhagic infarction (HI) or parenchymal hemorrhage (PH). Interpretation of their results is difficult because different classifications of HTs were used. In the European Cooperative Acute Stroke Study (ECASS), HTs were classified according to their appearance on CT into hemorrhagic infarction (HI) or parenchymal hemorrhage (PH). In the National Institute of Neurological Disorders and Stroke (NINDS) rtPA stroke trial, HTs were classified into symptomatic or asymptomatic intracerebral hemorrhage whatever their appearance on CT. Both classifications have limitations. The CT-based classification provides no direct information on the clinical consequences of HT, whereas the clinical classification does not acknowledge the contribution of ischemic edema to clinical deterioration. In ECASS, risk factors for HI were the severity of neurological deficit at baseline, the presence of early ischemic changes on pretreatment CT scan, and treatment with rtPA. Risk factors for PH were increasing age and treatment with rtPA. The interaction of age with rtPA was not tested. Risk factors for symptomatic intracerebral hemorrhage in the NINDS rtPA stroke trial were the severity of neurological deficit at baseline, the presence of ischemic changes on pretreatment CT scan, and treatment with rtPA. No treatment-by-variable interaction could be detected, but the incidence of HT was very low in the placebo group.

In the present study, we analyzed risk factors for severe HT in ECASS II, the largest trial of rtPA in acute ischemic stroke.
To allow comparison of our findings with those of previous analyses, we used both the clinical and radiological classifications of HTs.

Subjects and Methods
The methods and primary results of ECASS II have been reported in detail elsewhere. Briefly, ECASS II was a nonangiographic, randomized, placebo-controlled, double-blind trial of intravenous rtPA (0.9 mg/kg body wt, maximum dose 90 mg) in acute ischemic stroke. Eligible patients were men or women aged 18 to 80 years who had a clinical diagnosis of moderate to severe ischemic hemispheric stroke and who could be treated within 6 hours of symptom onset. Patients with signs of intracerebral hemorrhage or parenchymal hypoattenuation or brain swelling >33% of the middle cerebral artery territory on the pretreatment CT scan were excluded. The trial enrolled 800 patients in 108 centers in Europe, Australia, and New Zealand. The present analysis was performed on 793 patients because 7 patients were randomized but not treated.

Classification of HTs
All patients had a CT scan before treatment to determine eligibility for the trial. A second CT scan was performed 22 to 36 hours after the infusion of trial medication, and a third scan was performed at day 7. Other CT scans were performed if necessary. The CT scans were assessed independently of the assessment by the investigator by a CT reading panel without access to the follow-up scans of individual patients but with information about the location of symptoms. If the members of the CT reading panel disagreed, they reviewed and discussed the scan until a consensus was reached. HTs were classified according to clinical and radiological criteria. HI1 was defined as small petechiae along the margins of the infarct; HI2, as confluent petechiae within the infarcted area but no space-occupying effect; PH1, as blood clots in ≤30% of the infarcted area with some slight space-occupying effect; and PH2, as blood clots in >30% of the infarcted area with a substantial space-occupying effect. Members of the safety committee and the CT reading panel, blinded to treatment allocation, identified patients with SICH. They based their judgment on all available clinical information, autopsy reports, and the CT at the time of clinical deterioration. An intracranial hemorrhage was defined as symptomatic (SICH) if the patient had clinical deterioration causing an increase in the National Institutes for Health Stroke Scale (NIHSS) score5 of ≥4 points and if the hemorrhage was likely to be the cause of the clinical deterioration. However, in case of doubt regarding whether edema or hemorrhage was the leading pathology, an association of the hemorrhage with the deterioration was assumed.

Data Collection and Analysis
The distribution of bad outcome at day 90 was stratified according to each category of HT. Bad outcome was defined as a score of 5 (severe disability, bedridden, and incontinent, requiring constant nursing care and attention) or 6 (death) on the modified Rankin scale. Furthermore, all categories of HTs were separately tested by logistic regression analysis for their effect on so-defined bad outcome. Models included treatment with rtPA and rtPA-by-category of HT interactions.

We selected 21 candidate variables among baseline variables. Candidate variables were selected because of their biological plausibility and according to the results of a previous analysis of risk factors for HT in ECASS. Candidate variables were age, sex, body weight, history of transient ischemic attack, prior stroke, history of hypertension, history of diabetes, history of congestive heart failure, history of angina, history of myocardial infarction, aspirin use before thrombolysis, atrial fibrillation at baseline, blood glucose at baseline, diastolic blood pressure at baseline, systolic blood pressure at baseline, platelet count at baseline, consciousness at baseline (conscious or not using the definitions of the NIHSS), NIHSS score at baseline, extent of parenchymal hypoattenuation on baseline CT scan (none, ≤33%, or >33% of the middle cerebral artery territory), time from symptom onset to initiation of study treatment, and treatment with rtPA.

<table>
<thead>
<tr>
<th>Category of HT</th>
<th>Placebo Group (N=386)</th>
<th>rtPA Group (N=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HT, n (%)</td>
<td>233 (60.4)</td>
<td>217 (53.3)</td>
</tr>
<tr>
<td>HI, n (%)</td>
<td>141 (36.5)</td>
<td>142 (34.9)</td>
</tr>
<tr>
<td>PH, n (%)</td>
<td>12 (3.1)</td>
<td>48 (11.8)</td>
</tr>
<tr>
<td>SICH, n (%)</td>
<td>13 (3.4)</td>
<td>36 (8.9)</td>
</tr>
</tbody>
</table>

We used logistic regression analysis to test the main effects of these variables and rtPA-by-variable interactions for PH (PH1 or PH2) and SICH. Risk factors for HI (HI1 or HI2) are not reported because we found that HIs were not more frequent and that their severity was not increased in rtPA-treated patients. Model selection was performed by use of the stepwise selection procedure. On the first run, only treatment with tPA was included in the model as a mandatory variable. On the second run, all main effects corresponding to interaction terms included in the model as a result of the first run were forced into the model.

Results
Overall, HIs occurred in 283 (35.7%), PHs in 60 (7.6%), and SICHs in 49 (6.2%) of the patients. Most SICHs (73.5%) were PHs. HIs were not more frequent in the rtPA group than in the placebo group, whereas PHs and SICHs were associated with rtPA (Table 1).

The distribution of patients with bad outcome according to category of HT is shown in Table 2. Logistic regression analyses showed significant interactions for bad outcome between rtPA and PH (odds ratio 4.8, 95% CI 1.2 to 24.7) and between rtPA and SICH (odds ratio 6.9, 95% CI 1.8 to 30.3), suggesting that both categories of HT were not only more common but also more severe in rtPA-treated patients. In contrast, among patients with HI, the odds for bad outcome were reduced in those who had received rtPA (odds ratio 0.36, 95% CI 0.15 to 0.81).

Significant risk factors for PH were rtPA, extent of parenchymal hypoattenuation on baseline CT scan, a history of congestive heart failure, increasing age, and baseline systolic blood pressure. Two interactions were detected: rtPA-by-age interaction and rtPA-by-aspirin interaction, suggesting that PHs on rtPA were more frequent in older patients and in those who had used aspirin before stroke (Table 3). The distribution of PHs according to these variables is shown in Figures 1 and 2: 24.1% of the patients who had used aspirin before stroke and 19.7% of those aged 71 to 80 years experienced a PH on rtPA.

Significant risk factors for SICH were rtPA, a history of congestive heart failure, extent of parenchymal hypoattenuation on baseline CT scan, a history of congestive heart failure, increasing age, and baseline systolic blood pressure. Two interactions were detected: rtPA-by-age interaction and rtPA-by-aspirin interaction, suggesting that PHs on rtPA were more frequent in older patients and in those who had used aspirin before stroke (Table 3). The distribution of PHs according to these variables is shown in Figures 1 and 2: 24.1% of the patients who had used aspirin before stroke and 19.7% of those aged 71 to 80 years experienced a PH on rtPA.

<table>
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<tr>
<th>Category of HT</th>
<th>Placebo Group (N=386)</th>
<th>rtPA Group (N=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HT, n (%)</td>
<td>28 /233 (12.0)</td>
<td>21 /217 (9.7)</td>
</tr>
<tr>
<td>HI, n (%)</td>
<td>25 /141 (17.7)</td>
<td>14 /142 (9.9)*</td>
</tr>
<tr>
<td>PH, n (%)</td>
<td>3 /12 (25.0)</td>
<td>24 /48 (50.0)*</td>
</tr>
<tr>
<td>SICH, n (%)</td>
<td>5 /13 (38.5)</td>
<td>26 /36 (72.2)*</td>
</tr>
</tbody>
</table>

Bad outcome is considered a modified Rankin score of 5 to 6. Values are number of patients in category with bad outcome/number of total patients in category (n/n), with percentages in parentheses.

*Significant rtPA by category of HT interaction in a logistic regression analysis.
on baseline CT scan, and increasing age. No interaction could be detected, but aspirin use before thrombolysis could not be entered as a variable in the model because no patient on aspirin in the placebo group had experienced a SICH. However, the distribution of SICH across treatment groups suggested an rtPA-by-aspirin interaction: 18.9% of patients who had used aspirin before stroke and were given rtPA had experienced SICH (Figure 1).

**Discussion**

Severe HTs were frequent in rtPA-treated patients. Depending on which definition was used (SICH or PH), 8.8% to 11.8% of patients who were given rtPA had a severe HT. Among them, 2 or 3 patients of 4 died or were severely disabled. In contrast, as previously observed in ECASS,2,7 HIs were not more frequent in rtPA-treated patients. Furthermore, among patients with HI, the odds for bad outcome were significantly lower in those given rtPA than in those receiving placebo, suggesting that rtPA may benefit some patients despite minor degrees of HT.

The risk of a severe HT was related to the extent of cerebral ischemia as depicted by baseline CT scan. This may be interpreted as a straightforward relationship between the initial extent of ischemia and the volume of HT. Our data are consistent with such an interpretation because 8.3% of patients with the larger type of PH (PH2) and only 4.2% of patients with PH1 had parenchymal hypoattenuation in >33% of the middle cerebral artery territory on baseline CT scan. Alternatively, it is conceivable that HTs in patients with extended hypoattenuation were more severe because the mass effect of ischemic edema was added to that of the hemorrhagic component. Such a mechanism is likely in patients with HI who deteriorated and thus were classified as having SICH.

In contrast to the NINDS investigators, we could not find a significant association of the severity of neurological deficit at baseline with increased risk of SICH. This is perhaps explained by the higher proportion of HIs among SICHs in the NINDS study2 because the analysis of ECASS data has demonstrated that the severity of neurological deficit at baseline is a strong risk factor for HI but not for PH,3 which we also observed in ECASS II (data not shown).

We analyzed whether cardiac emboli were associated with severe HT. This was suggested by an autopsy study in which larger confluent hemorrhages were more common in patients with cardioembolic stroke than in patients with a noncardiac cause of stroke.8 In cardioembolic stroke, HT is postulated to occur when the distal migration of embolic fragments allows reperfusion of an ischemic-weakened vascular bed.9 We found that a history of congestive heart failure was associated with an increased risk of PH and SICH, whereas atrial fibrillation on admission and a history of myocardial infarction were not. Patients with congestive heart failure are at high risk of stroke.10 A likely mechanism of stroke in these patients is cerebral embolism from a ventricular thrombus.11 It should be noted, however, that congestive heart failure has not been previously considered a risk factor for HT. It was not included among the candidate variables in previous analyses of risk factors for HT after rtPA.2,3 Hence, this finding has to be confirmed on another data set.

High blood pressure has been related to intracranial hemorrhage after rtPA for ischemic stroke in both experimental and clinical settings.12,13 Our finding of an association of baseline systolic blood pressure with PH underscores the importance of a thorough management of blood pressure in patients who are given rtPA.14

**Table 3.** Final Logistic Model Regarding the Association of Baseline Variables With PH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtPA</td>
<td>3.61</td>
<td>1.78–7.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Attenuation of density on baseline CT</td>
<td>2.64</td>
<td>1.59–4.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>2.57</td>
<td>1.16–5.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>1.02</td>
<td>1.00–1.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00–1.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.26</td>
<td>0.55–2.92</td>
<td>0.06</td>
</tr>
<tr>
<td>Age+rtPA</td>
<td>1.07</td>
<td>0.99–1.15</td>
<td>0.05</td>
</tr>
<tr>
<td>Aspirin rtPA</td>
<td>4.99</td>
<td>0.91–27.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

P≤0.06 for enter and stay criteria.

**Figure 2.** Distribution of PH according to classes of age in both treatment groups. Percentages are shown.

**Table 4.** Final Logistic Model Regarding Association of Baseline Variables With SICH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtPA</td>
<td>3.92</td>
<td>1.62–6.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>3.71</td>
<td>1.72–8.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attenuation of density on baseline CT</td>
<td>2.03</td>
<td>1.18–3.52</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.01–1.08</td>
<td>0.02</td>
</tr>
</tbody>
</table>

P≤0.06 for enter and stay criteria.
We found that the risk of PH on rTPA was higher in older patients. In the NINDS trial, there was a significant association of age with an increased risk of SICH in univariate analysis, but this association was no longer significant after multivariable modeling. We believe that this may have resulted from a lack of power, because there were only 22 SICHs in that study. Moreover, the higher proportion of HIs among SICHs may have weakened the association of age with SICH in the NINDS trial, because the analysis of ECASS data has demonstrated that age is associated with an increased risk of PH but not of HI. Finally, our results are consistent with the fact that age is a significant risk factor for cerebral hemorrhage after thrombolysis for myocardial infarction.15

Our finding of a higher incidence of PH and SICH in rTPA-treated patients who had used aspirin before stroke is in line with the results of the Multi-Center Acute Stroke Trial-Italy (MAST-I), in which the effect of the combination of streptokinase and aspirin was assessed.16,17 In MAST-I, the addition of aspirin to streptokinase significantly increased the number of deaths from intracranial hemorrhages.13 On the other hand, aspirin was not related to the risk of severe HT either in the ECASS or NINDS trial.3,4 Thus, the association of aspirin use before stroke with an increased risk of severe HT on rTPA needs to be confirmed in an independent population.

The present study has confirmed that within 6 hours of stroke onset, time to treatment is not related to the risk of a severe HT. In ECASS, the risk of PH was not higher in patients treated between 3 and 6 hours than in those treated within 3 hours. Caution was advised in the interpretation of this result, because only 87 patients were enrolled in ECASS within 3 hours.3 In the NINDS trial, however, despite the large number of patients who were treated within 90 minutes, the rate of SICH in that group was not lower than in those treated between 90 and 180 minutes.4

The determination of risk factors for severe HT on rTPA may help the physician to estimate the risk of thrombolysis and decide whether an individual can be safely treated. External validation of our predictive models would permit the development of a predictive score that might be used in day-to-day practice to identify patients at risk. In ECASS II, the rates of severe HT on rTPA in patients aged >70 years and in those taking aspirin before stroke were very high. Approximately 1 patient of 5 suffered a severe HT in these groups. Certainly, if such high rates were confirmed by an external validation study, thrombolysis should be avoided in these patients.

The present study has several potential limitations. Although we carefully selected the candidate variables, we cannot exclude that some associations occurred simply by chance. Furthermore, the rTPA-by-age and rTPA-by-aspirin interactions were only marginally significant. We decided to maintain them in the final model because we were concerned about the possibility of a type II error, and they may have important clinical implications. However, we believe that the likelihood of spurious associations is weak because most of the associations that we report have been previously suggested by independent studies.

In conclusion, this secondary analysis of ECASS II has confirmed the importance of the extent of hypoattenuation on CT as a risk factor for severe HT. The findings also suggest that older patients and those who have used aspirin before stroke are at higher risk of a severe HT on rTPA. These risk factors need to be validated on an independent data set before they can be used in clinical practice.

Acknowledgments

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References

Risk Factors for Severe Hemorrhagic Transformation in Ischemic Stroke Patients Treated With Recombinant Tissue Plasminogen Activator: A Secondary Analysis of the European-Australasian Acute Stroke Study (ECASS II)

Vincent Larrue, Rüdiger von Kummer, Achim Müller and Erich Bluhmki

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