Hemorrhagic Transformation Within 36 Hours of a Cerebral Infarct : Relationships With Early Clinical Deterioration and 3-Month Outcome in the European Cooperative Acute Stroke Study I (ECASS I) Cohort

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Hemorrhagic Transformation Within 36 Hours of a Cerebral Infarct

Relationships With Early Clinical Deterioration and 3-Month Outcome in the European Cooperative Acute Stroke Study I (ECASS I) Cohort

Marco Fiorelli, MD; Stefano Bastianello, MD; Rüdiger von Kummer, MD; Gregory J. del Zoppo, MD; Vincent Larrue, MD; Emmanuel Lesaffre, PhD; Arthur P. Ringleb, MD; Svetlana Lorenzano, MD; Claude Manelfe, MD; Luigi Bozzao, MD; for the ECASS I Study Group

Background and Purpose—The clinical correlates of the varying degrees of early hemorrhagic transformation of a cerebral infarct are unclear. We investigated the cohort of a randomized trial of thrombolysis to assess the early and late clinical course associated with different subtypes of hemorrhagic infarction (HI) and parenchymal hematoma (PH) detected within the first 36 hours of an ischemic stroke.

Methods—We exploited the database of the European Cooperative Acute Stroke Study I (ECASS I), a randomized, placebo-controlled, phase III trial of intravenous recombinant tissue plasminogen activator in acute ischemic stroke. Findings on 24- to 36- hour CT were classified into 5 categories: no hemorrhagic transformation, HI types 1 and 2, and PH types 1 and 2. We assessed the risk of concomitant neurological deterioration and of 3-month death and disability associated with subtypes of hemorrhagic transformation, as opposed to no bleeding. Risks were adjusted for age and extent of ischemic damage on baseline CT.

Results—Compared with absence of hemorrhagic transformation, HI1, HI2, and PH1 did not modify the risk of early neurological deterioration, death, and disability, whereas, in both the placebo and the recombinant tissue plasminogen activator groups, PH2 had a devastating impact on early neurological course (odds ratio for deterioration, 32.3; 95% CI, 13.4 to 77.7), and on 3-month death (odds ratio, 18.0; 95% CI, 8.05 to 40.1). Risk of disability was also higher, but not significantly, after PH2.

Conclusions—Risk of early neurological deterioration and of 3-month death was severely increased after PH2, indicating that large hematoma is the only type of hemorrhagic transformation that may alter the clinical course of ischemic stroke. **(*Stroke*. 1999;30:2280-2284.)**

Key Words: prognosis ■ stroke, hemorrhagic ■ tissue plasminogen activator

Despite our improved understanding of the prevalence and pathogenesis of hemorrhagic transformation of an acute cerebral ischemic infarct, the prognostic implications of hemorrhage in this setting remain uncertain. Although pathological and radiological studies indicate that hemorrhagic transformation is a natural event in the evolution of a cerebral infarct,[1–4] in the clinical setting it is often considered a complication. However, recent observations suggest that the prognosis may vary with the type of hemorrhagic transformation,[4–6] challenging in particular the view that hemorrhagic infarction (HI) can be a direct cause of neurological deterioration. Regarding parenchymal hematoma (PH), daily clinical experience, as well as data from hospital cohorts[4] and clinical trials,[6,7–12] suggests that it can significantly worsen the clinical course of ischemic stroke.

The potential usefulness of thrombolytic agents in acute ischemic stroke has further increased the interest concerning the clinical correlates of hemorrhagic transformation as detected by CT and described in radiographic terms. Thrombolytic agents not only increase the risk of hemorrhage overall (systemic and central nervous system) but also tend to induce earlier hemorrhagic transformation of cerebral infarctions than is observed in spontaneous evolution, more often of the PH type.[13] The cohort of patients recruited in the European

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From the Department of Neurological Science, University La Sapienza, Rome, Italy (M.F., S.B., S.L., L.B.); Department of Neuroradiology, University of Dresden, Dresden, Germany (R. von K.); Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, Calif (G. del Z.); Department of Neurology, University of Toulouse, Toulouse, France (V.L.); Biostatistical Center for Clinical Trials, University of Leuven, Leuven, Belgium (E.L.); Department of Neurology, University of Heidelberg, Heidelberg, Germany (A.P.R.); and the Department of Neuroradiology, University of Toulouse, Toulouse, France (C.M.).

Correspondence to Marco Fiorelli, MD, PhD, Department of Neurological Sciences, University La Sapienza, Viale dell'Università 30, 00185 Rome, Italy. E-mail fiorelli@uniroma1.it

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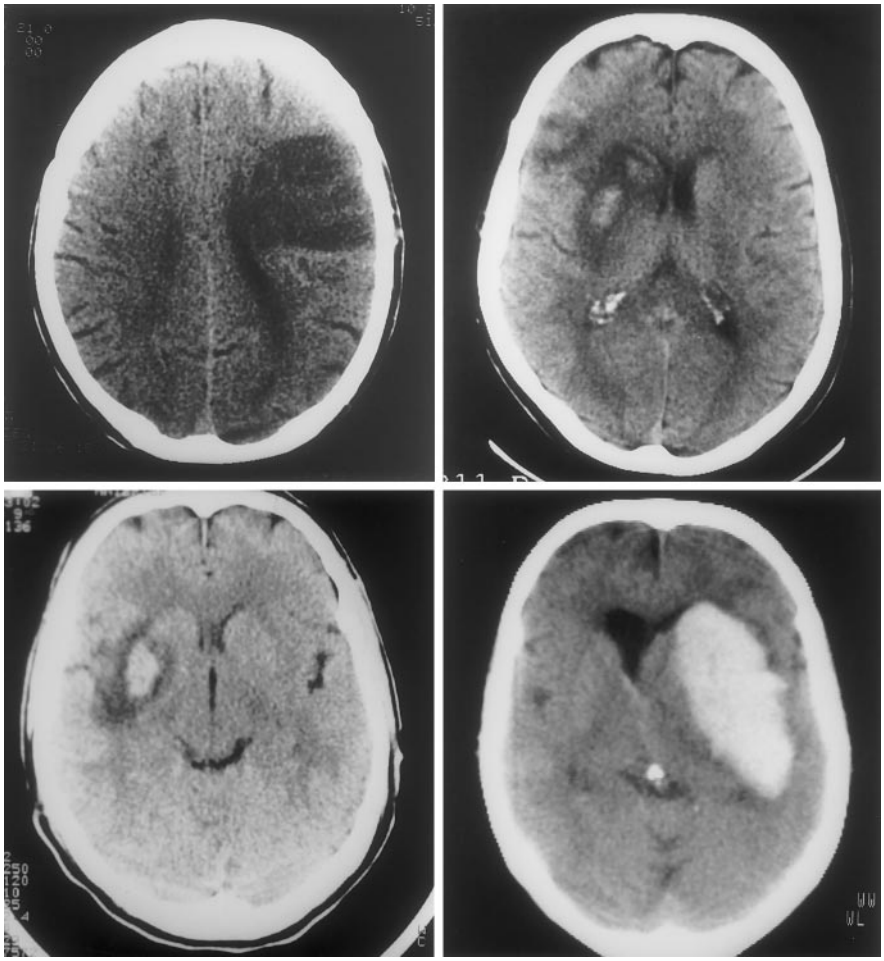

Figure 1. Subtypes of hemorrhagic transformation: HI1 (top left), HI2 (top right), PH1 (bottom left), and PH2 (bottom right).

Cooperative Acute Stroke Study I (ECASS I),[7] a placebo-controlled trial of recombinant tissue plasminogen activator (rtPA) administered intravenously within the first 6 hours of an ischemic hemispheric stroke, was the object of an extensive clinical and radiological data collection. We exploited this database to assess the relationship of hemorrhagic transformation with early evolution of the neurological presentation and final outcome in placebo and rtPA patients. The objectives of this study were to investigate the clinical correlates of different subtypes of hemorrhagic transformation occurring within the first 36 hours from the clinical onset of the infarct.

Subjects and Methods

The ECASS I study design and primary results have been reported in detail elsewhere.[7] ECASS I was a double-blind, placebo-controlled trial evaluating safety and efficacy of 1.1 mg/kg rtPA by intravenous delivery in patients presenting within 6 hours from the onset of a hemispheric acute ischemic stroke. The use of intravenous heparin or oral anticoagulants within the first 24 hours was not allowed.

According to the study protocol, all patients were submitted to a CT scan before randomization. A CT scan was repeated after 24 to 36 hours (or earlier in case of rapid and severe clinical deterioration) and again between days 4 and 10. All CT scans were read by an independent committee of 3 neuroradiologists with extensive experience in acute stroke. The 3 observers were blinded to both the rtPA/placebo allocation and the clinical course. After the exclusion of 11 patients (6 rtPA, 5 placebo) whose CT scans were judged of too poor quality to allow unequivocal assessment of hemorrhagic changes, 609 patients remained for the analysis. With the adaptation of preexisting criteria[6,14] to the purposes of ECASS I protocol, HI was defined as a petechial infarction without space-occupying effect, and PH was defined as a hemorrhage (coagulum) with mass effect. HIs were of 2 subtypes: HI1 (small petechiae) and HI2 (more confluent petechiae). Similarly, there were 2 subtypes of PH: PH1 ($\leq$30% of the infarcted area with some mild space-occupying effect) and PH2 ($>$30% of the infarcted area with significant space-occupying effect, or clot remote from infarcted area). Potential determinants of HI and PH in ECASS I patients have been investigated and reported in a companion article.[13]

The 2-by-2 interrater agreement for the diagnosis of hemorrhagic transformation (either HI or PH) compared with no hemorrhagic transformation was good,[15] with a κ of 0.77 (95% CI, 0.75 to 0.79). The diagnosis of PH compared with no PH (either HI or no hemorrhagic transformation) was also characterized by good interrater agreement (κ=0.75; 95% CI, 0.72 to 0.77). When the 5-type classification (no hemorrhagic transformation, HI1, HI2, PH1, or PH2) was used, the 2-by-2 weighted κ ranged from 0.67 (95% CI, 0.62 to 0.71) to 0.72 (95% CI, 0.67 to 0.76). The 2-by-2 agreement in diagnosis of a specific subtype (no hemorrhagic transformation, HI1, HI2, PH1, or PH2) versus any other diagnostic possibility was always $\geq$90%. For the purpose of this study, the agreement of at least 2 of the 3 raters was required to label each scan as showing no hemorrhagic transformation or a given subtype of hemorrhage.

For each patient, we retrieved from the database of the trial the following variables: age, sex, allocation to placebo/rtPA treatment, severity of neurological deficit on admission as quantified with the National Institutes of Health Stroke Scale (NIHSS) score, and presence of early focal hypodensity or swelling due to developing infarction in the baseline CT. Odds ratios (ORs) and their 95% CIs were used to evaluate the association of hemorrhagic transformation

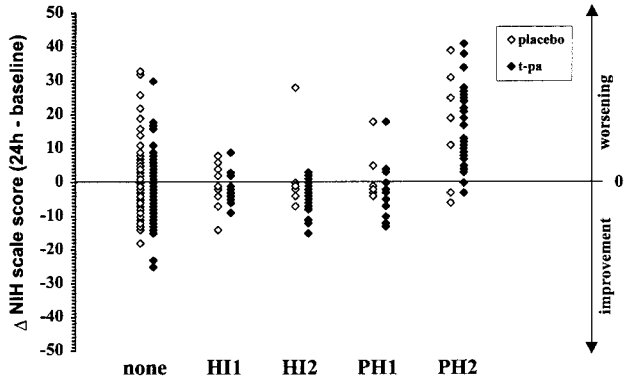

Figure 2. Scatterplot of variations of NIHSS score between baseline and 24-hour assessment according to type of hemorrhagic transformation. See text for statistical analysis.

with the risk of (1) early deterioration of neurological presentation (increase of ≥4 points on the NIHSS score after 24 hours from baseline assessment),[16] (2) death, or (3) disability (Rankin[17] score ≥1 in survivors within 3 months of stroke). ORs were adjusted by age and extent of initial ischemic damage on baseline CT scan (0=none, 1=<33% of the middle cerebral artery territory, and 2=>33% of the middle cerebral artery territory). Analyses were performed with BMDP statistical software.[18]

Results

Prototypes of the 4 subtypes of hemorrhagic transformation are presented in Figure 1. Figure 2 illustrates changes in NIHSS score at 24 hours according to presence and type of hemorrhagic transformation. Two-way ANOVA (factor 1=group, factor 2=allocation to rtPA or placebo arm) demonstrated a significant ($P<0.00001$) global difference in mean baseline-to-24-hour NIHSS score change across the 5 groups exhibiting, respectively, no hemorrhagic transformation (mean±SD change, −1.6±6.5), HI1 (−1.8±5.5), HI2 (−2.3±6.8), PH1 (−0.6±7.7), and PH2 (16.8±12.3). There was no effect of rtPA or placebo allocation ($P=0.7$) on the relationship between subtype of hemorrhagic transformation and clinical evolution. The group-by-arm interaction term was also not significant ($P=0.3$), which allowed the pooling of placebo and rtPA data for further comparisons. Two-by-two post hoc *t* tests revealed similar changes in NIHSS score at 24 hours across types of hemorrhagic transformation, except for PH2, whose score was greatly increased (indicating severe neurological deterioration) compared with each of the other 4 categories ($P=0.00001$ or lower).

The Table shows the frequency of 24-hour neurological deterioration, 3-month death, and 3-month disability in the ECASS I cohort according to presence and type of hemorrhagic transformation on 24-hour CT and according to rtPA/placebo allocation. Figure 3 shows the ORs for 24-hour neurological deterioration, 3-month death, and 3-month disability according to presence and type of hemorrhagic transformation and placebo/rt-PA allocation. ORs were adjusted for age and extent of initial ischemic damage as assessed on baseline CT. After adjustment, neither HI1 and HI2 (pooled for this analysis to avoid empty cells) nor PH1 influenced significantly the risks of early deterioration, 3-month death, or 3-month disability, whereas PH2 was still associated with a significantly increased risk of 24-hour deterioration and of 3-month death. Since here again the relationship between hemorrhagic transformation and outcome was similar in placebo and rtPA groups, it was possible to estimate the ORs and their 95% CIs in the whole cohort. Compared with patients without hemorrhagic transformation, patients with a PH2 had a strongly increased risk of 24-hour deterioration (OR, 32.3; 95% CI, 13.4 to 77.7), and of 3-month death (OR, 18.0; 95% CI, 8.05 to 40.1). PH2 survivors had a nonsignificantly higher risk of disability (placebo: OR, 1.8; 95% CI, 0.2 to 20.5; rtPA: OR, 5.4; 95% CI, 0.6 to 47.4).

Discussion

The results of this retrospective analysis confirm the clinical impression that the outcome after HI differs markedly from PH, when the events are established within the first 36 hours. Patients exhibiting an early HI did not a have a higher risk of neurological deterioration compared with patients without hemorrhagic transformation. Among patients treated with rtPA, HI was even loosely associated with early improvement. Overall, 3-month mortality and disability were also not influenced by HI. These findings may seem in contrast to the observation that hemorrhagic transformation of the HI type is often a proxy for large infarction[4,5] and hence a marker of bad outcome in ischemic stroke patients. However, a HI detected within the first 36 hours of ischemic stroke might not be comparable to a HI occurring at a later time, since early petechial changes may indicate that reperfusion occurred when the ischemic tissue was still at least partially viable. Accordingly, in a small-scale, placebo-controlled pilot trial of rtPA (duteplase) conducted by Mori et al[19] in 31 ischemic stroke patients, 8 (39%) developed early hemorrhagic transformation without influence on the clinical evolution. As summarized by Lyden and Zivin,[20] the relationships between reperfusion and hemorrhagic transformation of a cerebral infarction remain unclear. Experimental studies in the nonhuman primate clearly demonstrate a correlation between petechial (and microscopic) hemorrhage and the loss of

Outcome According to Subtype of Hemorrhagic Transformation

	None		HI1		HI2		PH1		PH2	
	Placebo (n=264)	rtPA (n=215)	Placebo (n=13)	rtPA (n=11)	Placebo (n=11)	rtPA (n=24)	Placebo (n=7)	rtPA (n=23)	Placebo (n=7)	rtPA (n=34)
24-hour deterioration	32 (12)	27 (13)	3 (23)	1 (9)	1 (9)	0 (0)	2 (29)	3 (13)	5 (71)	29 (85)
3-month death	37 (14)	31 (14)	2 (15)	0 (0)	2 (18)	3 (13)	1 (14)	6 (26)	4 (57)	26 (76)
3-month disability	147 (56)	92 (43)	10 (77)	5 (45)	7 (64)	19 (79)	3 (43)	8 (35)	2 (29)	7 (21)

Data are frequencies (%).

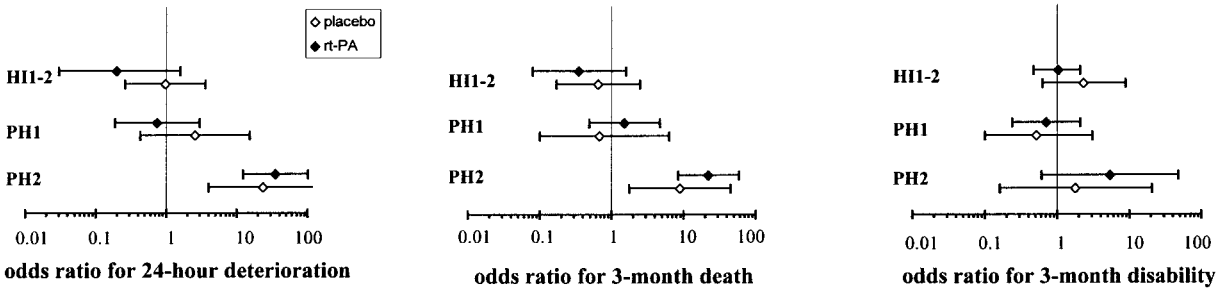

Figure 3. ORs and 95% CIs for 24-hour deterioration (decrease of the NIHSS score of ≥4 points compared with baseline), 3-month death, and 3-month disability (Rankin scale score of ≥2) in placebo and rtPA arms. ORs are adjusted for age and extent of early signs of infarct on baseline CT.

microvascular basal lamina/extracellular matrix antigens within the first 24 hours after middle cerebral artery occlusion,[21,22] providing a theoretical basis for blood extravasation. However, for a correct appraisal of the functional correlates of early HI, we need further studies on the mechanism of bleeding within the infarcted area and its relationships with reperfusion and clinical status at different times after stroke.

The univariate excess risk of 3-month death shown by patients with PH1 was neither associated with a higher risk of early deterioration nor still evident after adjustment for age and initial severity. This suggests that in most cases early small hematomas can have little if no influence on the clinical course. In contrast to the outcomes of other subtypes of bleeding, PH2 significantly increased the risk of early deterioration and 3-month death even after adjustment for possible confounders, which confirms that clinical and experimental research must focus on the prevention of this type of hemorrhagic transformation. Roughly, 3 of 4 patients with early PH2 deteriorated and died. Compared with patients without any hemorrhagic transformation, survivors from PH2 had a nonsignificantly higher risk of disability, which indicates that, taken alone, disability in survivors does not reflect faithfully the risk-benefit ratio of thrombolytics in acute ischemic stroke. These results need confirmation, since they cannot be compared with those of the retrospective review of intracerebral hemorrhages that occurred in the NINDS rt-PA Stroke Study,[23] in which HI and PH were not analyzed separately, or with the analysis made on the cohort of the Multicenter Acute Stroke Trial–Italy, in which only 5-day scans were available.[10]

Clinical deterioration during the first 24 hours was frequent in the ECASS I cohort, even among patients with no evidence of bleeding on 24-hour CT. This finding suggests that care should be taken in creating mixed clinical/CT definitions such as "symptomatic hemorrhagic transformation" since, for example, in petechial infarction this association of bleeding with clinical worsening is coincidental. A classification of hemorrhages based on radiological criteria might be a more objective tool to characterize hemorrhagic transformation after an ischemic stroke. However, although the classification used in ECASS I proved reliable in the hands of experienced neuroradiologists, its reliability in a less specialized setting has to be assessed. Additionally, if studies in different populations confirm that PH2 is the only clinically relevant subtype of hemorrhagic transformation, the number of categories of ECASS I classification might be reduced accordingly, from the original 5 to 4 or 3. For this reason, we are planning to exploit the database of ECASS II,[12] a trial that used a protocol similar to that of ECASS I but recruited patients with milder strokes on average and tested a lower dosage of rtPA (0.9 instead of 1.1 mg/kg).

In conclusion, in the ECASS I cohort, early hemorrhagic transformation after ischemic stroke was associated with a wide range of clinical patterns. Large hematomas, significantly more frequent after rtPA than after placebo, had an ominous prognosis in the vast majority of cases, whereas the clinical outcome of cerebral infarction did not appear to be modified by the occurrence of other subtypes of hemorrhagic transformation within the first 36 hours from onset.

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