Bleeding Risk Analysis in Stroke Imaging Before Thrombolysis (BRASIL)
Pooled Analysis of T2*-Weighted Magnetic Resonance Imaging Data From 570 Patients

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Background and Purpose—There has been speculation that the risk of secondary symptomatic intracranial hemorrhage (SICH) may be increased after thrombolytic therapy in ischemic stroke patients who have cerebral microbleeds (CMBs) on T2*-weighted magnetic resonance imaging. Because of this concern, some centers withhold potentially beneficial thrombolytic therapy from these patients.

Methods—We analyzed magnetic resonance imaging data acquired within 6 hours after symptom onset from 570 ischemic stroke patients treated with intravenous tissue plasminogen activator in 13 centers in Europe, North America, and Asia. Baseline T2*-weighted magnetic resonance images were evaluated for the presence of CMBs. The primary end point was SICH, defined as clinical deterioration with an increase in the National Institutes of Health Stroke Scale score by $\geq 4$ points, temporally related to a parenchymal hematoma on follow-up-imaging.

Results—A total of 242 CMBs were detected in 86 of 570 patients (15.1%). The number of CMBs ranged from 1 to 77 in the individual patient, with $\geq 5$ CMBs in 6 of 570 patients (1.1%). Proportions of patients with SICH were 5.8% (95% CI, 1.9 to 13.0) in the presence of CMBs and 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs ($P=0.170$, Fisher’s exact test), resulting in no significant absolute increase in the risk of SICH of 3.1% (95% CI, $-2.0$ to 8.3).

Conclusions—The data suggest that if there is any increased risk of SICH attributable to CMBs, it is likely to be small and unlikely to exceed the benefits of thrombolytic therapy. No reliable conclusion regarding risk in the rare patient with multiple CMBs can be reached. (Stroke. 2007;38:2738-2744.)

Key Words: hemorrhage, intracranial ■ stroke ■ stroke management ■ therapy ■ thrombolysis

Thrombolytic therapy in acute stroke patients has been shown to be beneficial in large randomized trials. Secondary postischemic symptomatic intracranial hemorrhage (SICH) remains the primary concern associated with the administration of thrombolytic drugs. In contrast, the risk of SICH after systemic thrombotic therapy in myocardial infarction is low. Several major stroke centers now use magnetic resonance imaging (MRI) as the primary imaging modality in acute stroke, which may also represent the new “gold standard” for detecting both primary brain hemorrhage and secondary hemorrhagic transformation.

The identification and exclusion of patients with increased risk for SICH are major challenges for diagnostic imaging before treatment. There is evidence that hypointense lesions on T2*-weighted MRI (“cerebral microbleeds” [CMBs]) generally indicate an increased risk of both primary brain...
hemorrhage\textsuperscript{9,10} and hemorrhagic transformation after ischemic stroke.\textsuperscript{11} Based on these observations, it has been hypothesized that CMBs may become a marker of increased risk of secondary hemorrhage after thrombolytic therapy in stroke patients.\textsuperscript{9,11-13} Secondary hemorrhagic transformation of ischemic infarction, however, is not necessarily associated with a poor prognosis,\textsuperscript{14} and the key questions are “Is there an increased risk of hemorrhagic transformation after tissue plasminogen activator (tPA) when CMBs are present?” and “Does the risk of clinically relevant intracranial hematoma exceed the benefit of thrombolytic agents in the subgroup of patients with CMBs?”

Anecdotal case reports have described patients with CMBs who developed catastrophic postischemic hemorrhage, related\textsuperscript{15} or unrelated\textsuperscript{16} to therapy. On the basis of these observations, patients with CMBs are already excluded from thrombolytic treatment.\textsuperscript{4,17} Evidence for these decisions is weak: Previous reports on CMBs in patients treated with thrombolytic therapy include a total of 27 to 70 patients with or without CMBs and differ considerably in the time points and methods of treatment, as well as on the definitions of hemorrhage.\textsuperscript{11,12,18} These series showed contradictory results for the risk of hemorrhage and allow no general conclusion for the time window of 0 to 6 hours after symptom onset. This uncertainty about the relevance of CMBs in candidates for thrombolytic therapy requires urgent clarification from a large database\textsuperscript{19,20} because exclusion from potentially beneficial therapy is a serious consequence for patients with CMBs. Because the true clinical significance of CMBs is still unknown, a study of this subject will change the planning of future clinical trials.

This article describes the protocol, methods, and outcome results of the B\textsuperscript{2}leeding Risk Analysis in Stroke by T\textsuperscript{2}w-Weighted IMaging before thromboly\textsuperscript{2}sis (BRASIL) study. BRASIL is a large, international, multicenter, nonrandomized analysis of patients from 13 centers and compares the risk of SICH after IV thrombolytic therapy in patients with and without CMBs by applying a predefined common end point. The primary objective of BRASIL was to obtain a more reliable risk estimate for clinically relevant SICH in the presence of CMB patients treated with IV thrombolytic therapy within the first 6 hours after symptom onset, which is relevant for many centers worldwide.\textsuperscript{4}

### Methods

#### Patients

We analyzed datasets of consecutive patients with ischemic stroke from 13 centers in Europe, North America, and Asia. The first MRI was obtained within 6 hours after symptom onset. Follow-up imaging (MRI or computed tomography [CT]) was done either routinely or because of any clinical deterioration up to 10 days after thrombolysis. The National Institutes of Health Stroke Scale (NIHSS) score was assessed by a stroke neurologist at each imaging time point. Criteria for thrombolytic therapy varied slightly among centers; the absence of hemorrhage on brain CT and identification of a diffusion-weighted imaging (DWI) and/or a perfusion lesion on the stroke MRI was used as the only imaging criterion at most sites within the first 3 hours. Beyond 3 hours, thrombolytic therapy was mainly based on the presence of a mismatch (DWI lesion larger than perfusion lesion by >20\%) and preferably no large DWI lesion. The presence of CMBs was not included for therapeutic decisions during the sampling period at any center. The standard dosage for IV tPA therapy was 0.9 mg/kg bodyweight and a maximum dose of 90 mg at all centers. The study was approved by the local ethics committees at all centers that performed prospective data sampling. Informed consent was obtained for all patients where required by local legislation.

#### Imaging Methods

MRI studies were performed on clinical MRI scanners equipped with a standard head coil. The imaging protocol included an axial with a DWI and perfusion-weighted imaging sequence, MR angiography, and a T2 sequence for most patients. Image acquisition time was <20 minutes for the entire protocol in the majority of cases. DEdicated T\textsuperscript{2}w-Weighted (T\textsuperscript{2}w) images (repetition time=0.8 to 2140 ms, echo time=14 to 49 ms) were acquired with a matrix of 128\times128, 256\times256, or 512\times192. The field of view ranged from 230\times230 mm to 320\times192 mm. Slice thicknesses was 5 to 7 mm; the interslice gap was 0 to 2 mm. Follow-up imaging was performed 1 to 10 days after stroke onset either because of clinical deterioration or after a predefined interval of 5 to 10 days.

#### Definition of CMBs and SICHs

Baseline T\textsuperscript{2}w images were rated locally for the presence of CMBs and the existence of subsequent hemorrhage on follow-up imaging in the case of clinical deterioration. The baseline and follow-up images were read locally, and only the follow-up images that could be considered to represent SICH (any hemorrhage temporally related to
clinical deterioration of >2 points on the NIHSS) were subject to central rereading by a neuroradiologist (J.F.) for the presence of space-occupying parenchymal hematomas to standardize the definition of parenchymal hematoma type 2 (PH2) and thus, of SICH (the Figure). Local ratings were performed by strictly adhering to predefined specifications either by an experienced neuroradiologist or a stroke neurologist. Readers were blinded to clinical and follow-up imaging data. A CMB was defined as a focal area of signal loss within the brain parenchyma within or remote from the ischemic lesion (as defined by DWI) measuring <5 mm on T2*w imaging. Areas of symmetric hypointensity of the globus pallidus and loss of signal in the middle cerebral artery and its branches were disregarded. The primary end point was the rate of SICH in patients with and without CMBs. SICH was defined as an increase of ≥4 NIHSS points in the presence of a space-occupying effect of an intracerebral hematoma (space-occupying PH2).

### Statistical Analysis

The primary end point was SICH in patients with and without CMBs. Based on the percentage of patients with CMBs in a stroke population eligible for thrombolytic therapy from the literature (range, 12.2% to 18.2%12,18) and a rate of SICH of 5.9% in CT-selected, tPA-treated patients,1 we assumed CMBs in 14% of the cohort and the risk of SICH in patients without microbleeds to be 5% for the power analysis. Based on these assumptions, a study to rule out the presence of CMBs versus patients without would require a total sample of 568 patients (80% power at the 95% level of confidence). For standard statistical analysis, we used the SPSS 13.0 for Windows software package (SPSS Inc, Chicago, Ill). Demographic data, time intervals of examinations, and clinical scale scores are given as medians with interquartile range. Fisher's exact test, or a corresponding \( \chi^2 \) test for large samples, was used for comparing categorical variables. A Mann–Whitney U test was used to compare a continuous variable with a dichotomous outcome. Mantel-Haenszel analysis was used to obtain pooled estimates of ORs for the effect of CMBs. Based on a threshold value from the literature, the ORs for SICH was used to obtain pooled estimates of ORs for the effect of CMBs.

### Patient Characteristics

Datasets from 873 patients treated consecutively with thrombolytic therapy in 13 centers in Europe, North America, and Asia were acquired for central analysis (Table 1). In a second step, all patients were excluded who had received sole or combined intra-arterial thrombolytic therapy, when local rating of CMBs was done on source images on perfusion-weighted imaging, b=0 images of DWI, or any combination of these exclusion criteria. For the final analysis presented here, only those patients who received IV tPA and were imaged with dedicated T2*w images for detection of hemorrhage were included (n=570; 341 males and 229 females). Imaging modality for follow-up in patients with SICH was CT (n=8) or MRI (n=10).

The median age of the patients was 69 years (first and third quartile, 59 and 77 years). The median time from symptom onset to MRI was 136 minutes (first and third quartile, 100 and 193 minutes), and the median initial NIHSS score was 13 (first and third quartile, 8 and 17; data available for 563 of 570 patients). Thrombolytic therapy was initiated before MRI in 29 of 570 patients (1 of these patients had a single CMB but no SICH). Therapy was initiated within 3 hours after symptom onset in 381 of 570 patients (66.8%), within 3 to 6 hours in 180 of 570 (31.6%), and at an unknown time but within 6 hours in 9 of 570 (1.6%). The NIHSS score was available at the follow-up time point only in 451 of 570 patients but was available for all patients with clinical deterioration. Therefore, the primary end point of SICH was not affected by the missing follow-up NIHSS scores.

### CMBs and ICH

A total of 242 CMBs were detected in 86 of 570 patients (15.1%). The number of CMBs ranged from 1 to 77 in individual patients (Table 2). An increase in the NIHSS score of ≥2 points, together with any type of hemorrhage on follow-up imaging, was observed in 37 patients (6.5%). Among these, a parenchymal hematoma with clinical deterioration of at least 4 points on the NIHSS (SICH) was found in 18 (3.2%) patients.
Table 2. Numbers of CMBs in Patients Without Clinical Deterioration and Hemorrhage (No HE), With Clinical Deterioration but Without PH (Any HE), and With SICH on Follow-Up Imaging

<table>
<thead>
<tr>
<th>CMB No.</th>
<th>No HE</th>
<th>Any HE</th>
<th>SICH</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>0</td>
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<td>29</td>
<td>13</td>
<td>484</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>4</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>8</td>
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<tr>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<tr>
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<td>0</td>
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</tr>
<tr>
<td>77</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>533</td>
<td>37</td>
<td>18</td>
<td>570</td>
</tr>
</tbody>
</table>

Proportions of patients with SICH were 5.8% (95% CI, 1.9 to 13.0) in the presence of CMBs and 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs (P = 0.170, Fisher’s exact test), resulting in a nonsignificant absolute increase in the risk of SICH of 3.1% (95% CI, –2.0 to 8.3). The OR for SICH in patients with CMBs versus patients without CMBs was 2.23 (95% CI, 0.67 to 6.97). The proportions of patients with any hemorrhage were 9.3% (95% CI, 4.1 to 17.5) in the presence of CMBs and 6.0% (95% CI, 4.1 to 8.5) without CMBs (P = 0.240, Fisher’s exact test). The OR for any hemorrhage in patients with CMBs versus patients without CMBs was 1.61 (95% CI, 0.66 to 3.85). The OR for SICH in the presence of CMBs when therapy was initiated ≤3 hours after symptom onset, which is recommended by many local authorities, was 2.2 (95% CI, 0.6 to 8.0) and 0.1 (95% CI, 0.0 to 23.3) in the extended time window of >3 to 6 hours.

By Mantel-Haenszel analysis, a method that better accounts for heterogeneity among centers, we also found no significant increase in the risk of SICH (P = 0.10). The overall OR for SICH was 2.76 (95% CI, 0.82 to 9.30; P = 0.1). A separate analysis for a predefined threshold of >1 CMB showed similar results: ORs of 2.60 (0.57 to 9.11, P = 0.24) and 2.38 (0.23 to 24.98, P = 0.47), respectively.

Other Variables
Because of significant variation in the prevalence of CMBs among centers (P = 0.0005), a logistic-regression analysis would have to be stratified by center and thus, was omitted owing to the lack of statistical power. Furthermore, because the presence of CMBs was not a risk factor for SICH, performing a multivariate analysis was unnecessary. No association was observed between the presence of CMBs and sex (P = 0.881, Fisher’s exact test), time from symptom onset to MRI (P = 0.770, Mann–Whitney U test), and NIHSS score (P = 0.770, Mann–Whitney U test). Patients with CMBs were significantly older (median, 72 years; first and third quartile, 65 and 79) than patients without CMBs (median, 69 years; first and third quartile, 58 and 77; P = 0.001, Mann–Wilcoxon test).

Discussion
Histopathologic studies suggest that most focal areas of MRI signal loss on T2*w imaging indicate focal hemosiderin deposits from previous small bleeds. The differential diagnosis of CMBs, however, also includes microcalcifications and even the release of prosthetic heart valve material, both of which certainly do not increase the risk for SICH. The spatial distribution of CMBs is very similar to the usual sites of ICH, and the existence of higher numbers of CMBs represents an independent factor for the overall incidence of ICH. Based on these observations, it has been hypothesized that CMBs may represent an independent risk factor for devastating hemorrhage after thrombolytic therapy. Besides anecdotal observations of devastating postischemic hemorrhages in patients with CMBs, previously published case series included 27 and 44 stroke patients who were treated with IV tPA within 6 hours, 70 patients who were treated with IV tPA within 3 to 6 hours, and 41 patients who were treated with combined IV/intra-arterial tPA within 3 hours of symptom onset or with intra-arterial thrombolitics only within 12 hours from symptom onset. The inhomogeneity of the investigated time points, the different treatment methods, and the different definitions of hemorrhagic transformation hamper both the generalization of results and the estimation of risk for SICH after tPA application within the first 6 hours, which is most relevant for several international stroke centers. This drawback has been overcome in BRASIL, wherein all 570 patients were treated with IV tPA within the first 6 hours after symptom onset, imaging evaluation was performed according to a predefined scheme, the end point of SICH was conservatively defined, and follow-up imaging was evaluated at a central reading center.

Clinical Relevance of CMBs
In any case, the risk of SICH must be balanced against the potential benefit of the withheld therapy and needs to be compared with the beneficial effects of tPA. BRASIL was not designed to evaluate the degree of benefit of tPA in MRI-selected patients. However, the rate of SICH of 5.8% (95% CI, 1.9 to 13.0) in patients with CMBs and of 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs cannot be compared with data from the literature. In studies based on CT-selected patients, the rate of favorable outcome improved from 29.2% (95% CI, 25.1 to 33.5; placebo group) to 42.3% (95% CI, 37.8 to 47.0; treated with tPA) within the first 3 hours, resulting in an absolute increase of ≈10%. The decreasing benefit of thrombolytic therapy for later time points, which is known for CT-selected patients, is not necessarily observed in patients selected according to MRI criteria. Furthermore, in line with our finding of the general rate of 3.2% for SICH, the rate of substantial hemorrhage seems to be lower in MRI-selected patients (3%) than expected from CT-based trials (5.9%) or registries (3.3% to 5.7%). Whether advanced MRI is more effective in selecting those most likely to benefit from thrombolytic therapy should be evaluated in a randomized study. Nevertheless, the aforementioned benefit of thrombolytic therapy as known from CT-based studies will exceed the risk, even for the maximum rate of SICH, which is still consistent with the BRASIL data (3.1%; 95%
CI, −2.0 to 8.3). Even if not based on a randomized trial, this information reflects the highest available level of evidence and might support clinicians in their individual therapy decisions.

Based on our data, a minor increase in hemorrhage risk cannot be ruled out. A study of 7664 patients with dedicated T2∗w MRI and IV thrombolytic therapy would be necessary to exclude an increased risk of hemorrhage with an OR of 1.5 (80% power, 95% level of confidence). We suspect that such a population has probably not yet been investigated with sufficient documentation worldwide, and funding and recruitment for such a prospective study seem virtually impossible. However, even a slight increase in the SICH rate, if indeed it exists, would not justify withholding potentially beneficial tPA therapy from patients. Thrombolysis has been proven to be effective even when the rate of hemorrhage is significantly increased.1,14

Relevance of the Number of CMBs for the Risk of SICH

The number of CMBs might be valuable for predicting subsequent hemorrhage after thrombolysis therapy, because the number of CMBs has been significantly associated with an increased risk of primary ICH. Kang et al17 reported an acute stroke patient with multiple CMBs on the pretreatment scan who developed a hemorrhage after thrombolytic therapy. These authors concluded that 2 or more CMBs should be considered a relative contraindication for thrombolytic treatment. The clinical relevance of this threshold was not confirmed in our study.

In the present study, we were able to analyze a large number of stroke patients with CMBs treated with thrombolytic therapy (n=86). Nevertheless, assessment of the association of the individual number of CMBs with bleeding risk was complicated by the low rate of patients with a large number of CMBs. In our study, only 6 of 570 patients (1.1%) had 5 or more CMBs. In contrast, the proportion of patients with >10 CMBs was reported to be 14.6% to 31.5% in patient groups predominantly presenting with primary hemorrhage, who were not the target population for our study.9,34 However, only 1 of 41 (2.4%) had >5 CMBs in a comparable sample of patients eligible for thrombolytic therapy.12

Our data allow no conclusions to be drawn concerning the rare patients with multiple CMBs in whom postischemic brain hemorrhages have been reported anecdotally after tPA therapy.15 The low number of detected CMBs in the present study may be explained by both differences among patient populations15 and the use of fast sequences in the hyperacute setting with more artifacts and lower spatial resolution.36 It must be considered that the rate of CMBs increases with age,37 which is a known risk factor for SICH.38 The first observation was confirmed in our study, indicating a possible environmental fallacy in the interpretation of a possible association of CMBs with bleeding risk.

Role of the Definition of SICH

The definition of SICH used profoundly affects its detection rate. Slight hemorrhagic transformation of ischemic brain tissue is associated with relatively small infarcts and often has a good prognosis.39,40 The space-occupying effect of the hemorrhage plays a major role in clinical worsening: Compared with absent and milder forms of hemorrhagic transformation, only space-occupying parenchymal hematomas (ie, PH2) had a devastating impact on the clinical course.22 Because even a tiny hemorrhage within a growing infarct lesion might fulfill the criterion of “SICH” (the Figure), finding of a PH2 was incorporated into the definition of SICH. Of the 37 of 570 patients with any type of hemorrhage in the presence of clinical deterioration, only 18 had a PH2-type hemorrhage (SICH).

Limitations

Limitations of the present study include possible patient selection, missing randomization, no control group without thrombolytic therapy, retrospective analysis in some centers, and no control for several clinical and laboratory variables. Therapy randomization for the presence of CMBs or some other control group without therapy could not be performed because it would have been unethical to withhold beneficial therapy (as proven in CT-based trials1) from patients with CMBs. A control group would not have profoundly enhanced the results of our analysis, because BRASIL aimed to compare the risk of SICH after thrombolytic therapy in patients with and without CMBs. Bias caused by unwanted patient selection is unlikely for 2 reasons: First, all centers provided data from a consecutive patient cohort treated with thrombolytic therapy uninfluenced by the findings on T2∗w images. Second, the rate of CMBs of 15.1% in our study is very comparable to that in other thrombolytic therapy studies (12.2% to 20.0%).11,12,26 Thus, exclusion of CMB-positive patients who would have hemorrhaged while maintaining the typical rate of stroke patients showing any number of CMBs is unlikely. Unexpected heterogeneity in the prevalence of CMBs among centers might have had an impact on the precision of the estimates of differences between CMB and non-CMB patients.

We suspect that the considerable discrepancy in the prevalence of any CMB per site can be explained in part by chance effects and other variables. We were able to control for demographic and clinical data at presentation but not for laboratory data, other imaging information like degree of leukoaraiosis,41 and clinical history, which have already been extensively analyzed by others.38 Lack of a central reading of pretreatment T2∗w images should not have influenced the analysis because interobserver agreement for reading CMBs is known to be very high.42 Heterogeneity in the prevalence of CMBs among centers also underlines the concept that translating the presence of CMBs into risk of SICH in these patients might be dependent on both the local patient population and the MRI sequence parameters and that findings from single-center studies cannot be easily transferred to other stroke centers.

Conclusions

Based on data from 13 high-volume stroke centers, BRASIL data represent the highest available level of evidence on the prognostic value of CMBs for clinically relevant secondary
bleeding complications in acute ischemic stroke patients after thrombolytic therapy. The data suggest that the risk estimate of hemorrhage in the presence of CMBS is unlikely to exclude the benefit of thrombolytic treatment in MRI-selected patients, as expected from the literature. However, a minor increase in hemorrhagic risk cannot be excluded, and conclusions concerning the rare patient with multiple CMBS cannot be drawn. Therefore, a prospective study is warranted to acquire more information on the prognostic value of single and multiple CMBS for outcome in stroke patients.

Appendix: BRASIL Coinvestigators

Disclosures
J.F. has received speaker fees from Bracco ALTANA; D.S.L. is on an Advisory Board for Coaxia Inc; J.R. received honoraria from Boehringer-Ingelheim; P.D.S. is on a speakers bureau and advisory board for Boehringer Ingelheim.

References


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