Microbleed Status and 3-Month Outcome After Intravenous Thrombolysis in 717 Patients With Acute Ischemic Stroke

Guillaume Turc, MD; Asmaa Sallem, MD; Solène Moulin, MD; Marie Tisserand, MD; Alexandre Machet, MD; Myriam Edjlali, MD; Jean-Claude Baron, ScD; Xavier Leclerc, PhD; Didier Leys, PhD; Jean-Louis Mas, MD; Charlotte Cordonnier, PhD; Catherine Oppenheim, PhD

Background and Purpose—Whether cerebral microbleeds (CMBs) detected on pretreatment magnetic resonance imaging increase the risks of symptomatic intracranial hemorrhage (sICH) and, most importantly, poor outcome in patients treated by intravenous thrombolysis for acute ischemic stroke is still debated. We assessed the effect of CMB presence and burden on 3-month modified Rankin Scale and sICH in a multicentric cohort.

Methods—We analyzed prospectively collected data of consecutive patients solely treated by intravenous thrombolysis for acute ischemic stroke, in 2 centers where magnetic resonance imaging is the first-line pretreatment imaging. Neuroradiologists blinded to clinical data rated CMBs on T2* sequence using a validated scale. Logistic regressions were used to assess relationships between CMBs and 3-month modified Rankin Scale or sICH.

Results—Among 717 patients, 150 (20.9%) had ≥1 CMBs. CMB burden was associated with worse modified Rankin Scale in univariable shift analysis (odds ratio, 1.07; 95% confidence interval, 1.00–1.15 per 1-CMB increase; \( P = 0.049 \)), but significance was lost after adjustment for age, hypertension, and atrial fibrillation (odds ratio, 1.03; 95% confidence interval, 0.96–1.11 per 1-CMB increase; \( P = 0.37 \)). Results remained nonsignificant when taking into account CMB location or presumed underlying vasculopathy. The incidence of sICH ranged from 3.8% to 9.1%, depending on the definition. Neither CMB presence, burden, location, nor presumed underlying vasculopathy was independently associated with sICH.

Conclusions—Poor outcome or sICH was not associated with CMB presence or burden on pre–intravenous thrombolysis magnetic resonance imaging after adjustment for confounding factors. An individual patient data meta-analysis is needed to determine whether a subgroup of patients with CMBs carries an independent risk of poor outcome that might outweigh the expected benefit of intravenous thrombolysis. (Stroke. 2015;46:0000. DOI: 10.1161/STROKEAHA.115.009290.)

Key Words: cerebral hemorrhage ▪ magnetic resonance imaging ▪ stroke

Cerebral microbleeds (CMBs) are small areas of signal void on T2* or susceptibility-weighted imaging (SWI), which correspond to focal hemosiderin deposits presumably due to previous leakage from small vessels.1,2 In patients with acute ischemic stroke (AIS), the reported prevalence of CMBs on pretreatment magnetic resonance imaging (MRI) ranges from 15% to 35%, depending on cohort characteristics and MRI sequences (T2* or SWI).3–5 Whether preexisting CMBs increase the risks of intravenous thrombolysis (IVT)–related symptomatic intracranial hemorrhage (sICH) and, most importantly, of poor functional outcome is still uncertain.6 Several studies have assessed the potential association between CMBs and post-IVT sICH, with conflicting results, which prevented the American Heart Association Stroke Council from making specific recommendations on IVT in patients with CMBs.7 In 2013, 2 independent systematic reviews and meta-analyses found an ≈2-fold increased risk of sICH in patients with ≥1 CMB on pre-IVT MRI, but this association failed to reach statistical significance.8–9 In view of the methodological limitations and heterogeneity of the included studies, namely different study designs, treatment modalities, and definitions of sICH, authors acknowledged that good quality data from large, prospective cohorts were lacking at that time.10 In 2014 and 2015, 3 additional studies reported results from prospectively collected data. Two found a significant association between CMB presence (or burden) and post-IVT sICH,5,11 whereas the last one did not.6 Although post-IVT sICH is an ominous event, a key clinical question remains whether the presence or burden of CMBs on pretreatment MRI independently increases the risk of poor outcome.12

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From the Departments of Neurology (G.T., J.-C.B., J.-L.M.) and Radiology (M.T., A.M., C.O.), Hôpital Sainte-Anne, Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, DHU Neurovasc, Paris, France; and Departments of Neurology (S.M., D.L., C.C.) and Radiology (A.S., M.E., X.L.), Lille University Hospital and Université de Lille, UDSL, INSERM U1171, Lille, France.

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Correspondence to Guillaume Turc, MD, Service de Neurologie, Hôpital Sainte-Anne, 1 rue Cabanis, 75014 Paris, France. E-mail g.turc@ch-sainte-anne.fr

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long-term outcome after IVT. Indeed, the benefit of IVT at 3 months may outweigh its harms even in some patients with initial sICH. We aimed to determine whether the presence and burden of CMBs on pretreatment MRI were independently associated with 3-month outcome and sICH.

Materials and Methods

Patients

We analyzed prospectively collected data of consecutive patients who underwent IVT for AIS in 2 French centers where MRI is the first-line pretreatment imaging for AIS (Sainte-Anne, Paris. November 2003 to December 2013 and Lille, October 2009 to May 2014). Patients were included (1) if they had a pretreatment MRI, including diagnostic quality T2* sequence, and (2) if they were treated by IVT alone (alteplase, 0.9 mg/kg) for an AIS ≤4.5 hours or for a wake-up stroke with diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch.12–15 High CMB burden was not an exclusion criterion for IVT in both centers. Sex, age, history of hypertension, diabetes mellitus, current smoking, atrial fibrillation, previous stroke/transient ischemic attack, baseline National Institute of Health Stroke Scale (NIHSS) score, serum glucose, blood pressure before IVT, and onset-to-treatment time were routinely collected.

In accordance with the French legislation, the study did not need approval by an Ethics Committee nor written informed consent from patients because it implied only analysis of anonymized data collected prospectively as part of routine clinical care. The article was prepared in accordance with recently proposed recommendations for studies investigating the association between CMBs and sICH or 3-month outcome.5

Imaging Methods and Definition of CMBs

In both centers, pretreatment MRI included diffusion-weighted imaging, fluid-attenuated inversion recovery, T2*-weighted gradient echo imaging, and intracranial MR angiography (total acquisition time, ≤10 minutes). The acquisition parameters of the T2* sequences remained unchanged throughout the study period: (1) Sainte-Anne center (1.5 Tesla GE Healthcare MR scanner): repetition time/echo time, 460/13 ms; flip angle, 25°; field of view, 24×18 cm2; matrix, 256×224; 6-mm contiguous slice thickness; duration, 1 minute and (2) Lille center (1.5 Tesla Philips Achieva MR scanner): repetition time/echo time, 945/32 ms; flip angle, 18°; field of view, 23×18.3 cm2; matrix, 256×205; 5-mm slice thickness (gap, 0.5–1.5 mm); duration, 2 minutes.16 A follow-up imaging (MRI including T2* sequence or computed tomographic scanner) was scheduled ≥24 hours after IVT and in the case of neurological deterioration.

Pretreatment T2* images were rated by neuroradiologists, blinded to clinical and follow-up imaging data, for the number of CMBs and their distribution, according to a validated scale.4 CMBs were defined as small areas (≤10 mm) of signal void on T2* sequence with a defined as small areas (≤10 mm) of signal void on T2* sequence with uncertain etiology.11 All available MR sequences were analyzed to exclude potential CMB mimics (vascular structures, thrombus, calcifications, iron deposits, cavernous malformation, or hemorrhagic metastases).15,16 Presumed underlying vasculopathy for CMBs was defined as cerebral amyloid angiopathy (CAA: strictly lobar distribution of CMBs in patients aged ≥55 years),15,16 hypertensive vasculopathy (strictly deep or infratentorial distribution of CMBs in hypertensive patients),15 or undetermined (all other situations).15 Existence of ICH according to published radiological classification criteria (hemorrhagic infarct or parenchymal hematoma, type 1 or 2)17 was rated on follow-up images by neuroradiologists blinded to clinical data and pretreatment CMB status.

Outcomes

Functional outcome (3-month modified Rankin Scale [mRS]) was considered as the primary end point and prospectively assessed by board-certified stroke neurologists, blinded to CMB rating, during face-to-face visits or structured telephone interviews. Occurrence of sICH was considered as the secondary end point and assessed according to 4 definitions (Table I in the online-only Data Supplement): National Institute of Neurological Disorders and Stroke (NINDS),19 European Cooperative Acute Stroke Studies 2 and 3 (ECASS-220 and ECASS-321), and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST22).

Statistical Analysis

Continuous variables were expressed as mean±SD or median (interquartile range) and compared using the t test or Mann–Whitney U test, as appropriate. Categorical variables were expressed as percentages and compared using the Pearson χ2 test or Fisher’s exact test, as appropriate. Associations between CMBs (presence or burden) and dependent variables (3-month mRS or sICH according to the 4 above-mentioned definitions) were assessed by calculations of crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) in logistic regression models. Baseline variables associated with CMB presence at a level of P<0.20 in univariable analysis were considered for inclusion into multivariable models, taking into account potential multicollinearity. CMB burden was examined as a continuous variable (per 1-CMB increase) for the main analysis. In sensitivity analysis, CMB burden was examined using the following categorization: 0 versus 1 versus 2 to 4 versus ≥5. Three-month mRS was dichotomized in binary logistic regression models (mRS score >1 versus ≤1; mRS score ≥2 versus ≤1). Because it may increase statistical power,23 shift analysis over the whole range of the mRS was also performed in ordinal logistic regression models. For multivariable ordinal logistic regression, partial proportional odds models were used because 2 explanatory variables (age and hypertension) did not meet the assumption of proportional odds.24 Statistical significance was set at P<0.05. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

During the study period, 931 patients were treated by IVT for an ischemic stroke, of which 214 (23.0%) were excluded (Figure 1 in the online-only Data Supplement), leaving 717 patients for the analysis. (Lille, n=375; Sainte-Anne, n=342). Included and excluded patients did not differ on baseline characteristics, except for NIHSS score (median, 11 versus 14; P=0.01).

Patients’ characteristics are summarized in Table 1. Median (interquartile range) age and NIHSS score were 74 (60–83) and 11 (6–18), respectively. Ninety-one (12.7%) patients had a prestroke mRS score >1, including 62 (8.6%) patients with a prestroke mRS score >2. On pretreatment imaging, 150 (20.9%) patients had ≥1 CMB (maximum 26); 92 (12.8%) had precisely 1 CMB, 33 (4.6%) had 2 to 4 CMBs, and 25 (3.5%) had ≥5 CMBs. The prevalence of CMBs did not differ across centers (P=0.78). Among patients with CMBs, presumed underlying vasculopathy was CAA in 60 (40.0%), hypertensive vasculopathy in 34 (22.7%), and undetermined in 56 (37.3%) patients. Associations between the presence of CMBs and baseline characteristics are summarized in Table 2. Follow-up imaging modality was MRI in 674 (94.0%) patients.

At 3 months, 329 (45.9%) patients had a mRS score >2 and 434 (60.5%) had a mRS score >1. With such dichotomization of the mRS score, there was no significant association between CMB presence or burden and 3-month outcome in univariable and multivariable analyses (Table 3).

Shift analysis over the entire range of the mRS showed a marginally significant association between CMB burden
and worse outcome in univariable analysis (OR, 1.07; 95% CI, 1.00–1.15 per 1-CMB increase; \( P=0.049 \)) but not in multivariable analysis (OR, 1.07; 95% CI, 0.96–1.11 per 1-CMB increase; \( P=0.37 \); Table 3). Results remained nonsignificant when (1) considering CMB burden as a categorical variable, (2) taking into account CMB location or presumed underlying vasculopathy, and (3) an alternative model, including all baseline variables, associated with mRS score >2 was considered\(^5\) (data not shown).

The rates of sICH ranged from 3.8% (ECASS-3 and SITS-MOST definitions) to 9.1% (NINDS definition). There was no significant association between CMB presence or burden (considered as a continuous variable) and sICH in univariable or multivariable analysis, irrespective of the sICH definition (Table 3). In sensitivity analyses, CMB burden, considered as a categorical variable, was only marginally associated in univariable analysis with sICH according to the NINDS definition (\( P=0.046 \)). CMB location or presumed underlying vasculopathy were not significantly associated with sICH (data not shown).

### Discussion

Capitalizing on a large sample of patients with AIS to address the clinical relevance of CMBs on pre-IVT MRI, we observed a marginally significant association between CMB burden and worse 3-month outcome in univariable ordinal logistic regression, which lost significance after adjustment for confounding factors. We found no independent association between CMB burden at baseline and sICH, irrespective of the definition used.

Most researchers assessing the clinical significance of pre-IVT CMBs have focused on sICH,\(^3,8\) as this association has pathophysiological plausibility\(^10\) and because sICH is a determinant cause of poor long-term functional outcome.\(^26\) Although our findings on the relationship between sICH and CMB burden were similar to those of the previous reports,\(^3,4\) they stand in clear distinction to those of 2 recent studies.\(^5,11\) Using the ECASS-3 definition, both studies found a significant association between sICH and a high CMB burden. We could not replicate these findings, except in univariable analysis for sICH according to the NINDS definition, when using the specific categorization proposed by Dannenberg et al.\(^5\)

### Table 1. Population Characteristics (n=717)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>351 (48.9)</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>74 (60–83)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>452 (63.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>113 (15.8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>128 (17.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>166 (23.1)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>71 (9.9)</td>
</tr>
</tbody>
</table>

### Table 2. Baseline Characteristics Associated With CMB Presence in Univariable Analysis

<table>
<thead>
<tr>
<th>CMB Presence</th>
<th>OR (95% CI)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.09 (0.76–1.56)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age, per 10-year increase</td>
<td>1.29 (1.13–1.47)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.37 (0.93–2.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.78 (0.47–1.32)</td>
<td>0.36</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.85 (0.52–1.38)</td>
<td>0.51</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.33 (0.88–2.00)</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.21 (0.68–2.16)</td>
<td>0.51</td>
</tr>
<tr>
<td>Pre-IVT mRS score, &gt;1</td>
<td>1.27 (0.79–2.07)</td>
<td>0.32</td>
</tr>
<tr>
<td>NIHSS, per 1-point increase</td>
<td>1.00 (0.97–1.03)</td>
<td>0.96</td>
</tr>
<tr>
<td>OTT, per 10-min increase</td>
<td>1.04 (1.00–1.08)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum glucose, per 1-mmol/L increase</td>
<td>0.96 (0.89–1.04)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic BP, per 10-mm Hg increase</td>
<td>1.12 (1.02–1.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP, per 10-mm Hg increase</td>
<td>1.09 (0.97–1.23)</td>
<td>0.15</td>
</tr>
<tr>
<td>Lille center</td>
<td>1.05 (0.73–1.51)</td>
<td>0.78</td>
</tr>
<tr>
<td>Sainte-Anne center</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic medication before stroke*</td>
<td>1.41 (0.82–2.41)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

\(^5\)BP indicates blood pressure; CI, confidence interval; CMB, cerebral microbleed; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; and OTT, onset-to-treatment time.

*Sainte-Anne cohort only, n=342.
This discrepancy is unlikely to be due to a lack of statistical power in our study, given its sample size and the prevalence of sICH, CMB presence, and proportion of patients with a high CMB burden, which were similar to those of the literature.3–5 Yet, differences in population characteristics could possibly explain the discrepancy across studies. Compared with our population, patients included in the study by Dannenberg et al5 were slightly older and more frequently had a presumed CAA, which might carry a higher risk of post-IVT sICH, including remote parenchymal hematoma. Although the proportion of presumed CAA in the subgroup of patients with ≥5 CMBs is not mentioned in the publication by Dannenberg et al5 it might have been higher than ours. Patients included in the study by Yan et al11 had a high proportion of patients with ≥1 CMBs (39.9%) and an important CMB burden (742 CMBs in 133 patients), which is consistent with a previous report from another Asian cohort28 but much higher than expected in a white one (401 CMBs in 150 patients in our study, in line with others3). It remains to be determined whether Asian patients carry a higher risk of post-IVT sICH in the presence of CMBs than Western patients.27

Although sICH is an important end point for patients with CMBs treated by IVT, our main end point was 3-month mRS, for several reasons. First, the incidence of sICH varies greatly depending on its definition,22 none being optimal.20,30 By contrast, 3-month mRS is a consensual, reproducible, and widely used measure of long-term functional outcome. Second, the clinical relevance of CMB burden on pretreatment MRI should be assessed taking into account the long-term outcome, as the benefit of IVT at 3 months may outweigh its harms even in patients with initial sICH.

To date, 4 studies (including the present one) assessed the relationship between pre-IVT CMBs and 3-month outcome (Table II in the online-only Data Supplement).3,5,11 We found an association between CMB burden and worse outcome in univariable shift analysis, in line with findings from the 3 other above-mentioned studies. However, this unadjusted association could be because of confounding factors, such as older age3–5 or hypertension.4,31 Indeed, in multivariable shift analysis, the association between CMB burden and worse outcome was no longer significant in our population, in line with previous findings.4,5 To date, only Yan et al11 have observed a significant association between a high CMB burden and poor outcome in multivariable analysis. These conflicting results stress the need for an individual patient data meta-analysis to determine whether CMB burden is an independent predictor of 3-month poor outcome and to estimate the effect size of the association. Such a meta-analysis could yield sufficient statistical power to identify whether there is a subgroup of patients with CMBs, which seems to have an independent risk of poor 3-month outcome so important that it might outweigh the expected benefit of IVT. If such a subgroup exists, such findings would support a widespread use of MRI for AIS and could lead to a randomized controlled trial to determine the best acute treatment for these high-risk patients. However, to date, detecting CMBs on pretreatment MRI should not prevent IVT based on current evidence, given the uncertainty about the independence of the association between CMBs and poor outcome, and the lack of a control (placebo) group in the available observational studies.

Strengths of our study include its sample size, the prospective data collection involving 2 centers, the systematic implementation of MRI as first-line pretreatment imaging in both centers, the use of a validated scale for CMBs rating,14 and the homogeneity of the cohort, as only patients solely treated by IVT were included. Our study has several potential limitations. First, 23% of the patients treated by IVT during the study period were excluded from the final analysis. However, including and excluded patients did not differ on baseline characteristics except for NIHSS score, which was not associated with CMB presence or burden in our or in previous studies.3,5,28 Second, the lack of a control group without IVT prevented us from drawing conclusions on the benefit/risk ratio of IVT in subgroups of interest. However, withholding IVT in patients otherwise eligible for this treatment may be ethically questionable.3 Third, the statistical power of our study was limited for...
specific subgroup analyses, for instance to assess the effect of presumed CAA underlying vasculopathy in patients with ≥5 CMBs. Fourth, we did not control for potentially interesting variables, such as current antithrombotic medication, volume of pretreatment diffusion-weighted imaging lesion, or leukoaraiosis. However, the 2 first variables, available in the Sainte-Anne cohort, did not reach the prespecified P<0.20 threshold for the univariable association with CMB presence, making them unlikely to be strong confounding factors. Moreover, the inclusion of >4 explanatory variables could have led to overfitting in models with a limited number of events (eg, sICH according to ECASS-3). Fifth, one may argue that potentially relevant differences between the 2 studies showing an increased risk of sICH in patients with CMBs and the present work include the imaging modalities (present study: T2*/1.5 T; Dannenberg et al12; T2*/3T; Yan et al11; SWI/3T). However, other researchers, using SWI (1.5T and 3T) did not find such an association.4 The magnetic field strength does not greatly modify the detection of CMBs,6 but SWI is more sensitive than T2* for detecting CMBs.32 Using the T2* instead of SWI may alter the detection of CMBs, which only plausible consequence would be a loss of statistical power. Of note, despite using different T2* parameters, the prevalence of CMBs was similar across our centers.

In conclusion, we found that CMB burden on pre-IVT MRI was not associated with an increased risk of poor 3-month outcome after adjustment for confounding factors, such as age and hypertension. An individual patient data meta-analysis is needed to determine whether a subgroup of patients with CMBs carries an independent risk of 3-month poor outcome that might outweigh the expected benefit of reperfusion therapies.

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Disclosures
None.

References


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SUPPLEMENTAL MATERIAL
Supplemental Table I. Definitions of symptomatic intracranial haemorrhage (sICH)

<table>
<thead>
<tr>
<th></th>
<th>Clinical worsening</th>
<th>Imaging</th>
<th>Relation</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>Any neurological worsening</td>
<td>Any ICH</td>
<td>Temporal</td>
<td>36 hours</td>
</tr>
<tr>
<td>ECASS-2</td>
<td>≥ 4 pts NIHSS increase</td>
<td>Any ICH</td>
<td>Not specified</td>
<td>7 days</td>
</tr>
<tr>
<td>ECASS-3</td>
<td>≥ 4 pts NIHSS increase</td>
<td>Any ICH</td>
<td>Presumed causal</td>
<td>7 days</td>
</tr>
<tr>
<td>SITS-MOST</td>
<td>≥ 4 pts NIHSS increase</td>
<td>PH2</td>
<td>Not specified</td>
<td>36 hours</td>
</tr>
</tbody>
</table>

NIHSS: National Institute of Health Stroke Scale; ECASS: European Cooperative Acute Stroke Studies. SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study. PH2: parenchymal haematoma type 2 (i.e. parenchymal hemorrhage with mass effect >30% of the infarcted area with significant space-occupying effect)  

Original description of each sICH definition:

NINDS: “A hemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage or any decline in neurologic status. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when any clinical finding suggested hemorrhage.”  

NB: The main reported sICH occurrence in NINDS was within the first 36 hours.  

ECASS-2: “Symptomatic intracranial haemorrhage was defined as blood at any site in the brain […] , documentation of clinical deterioration, or adverse events indicating clinical worsening or causing an increase in the NIHSS score of 4 or more points. CT scans of the brain were assessed 22–36 h after the infusion of trial medication started, and at day 7. Other CT scans were done if necessary.”  

ECASS-3: “Symptomatic intracranial hemorrhage was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.”  

SITS-MOST: “Symptomatic intracerebral haemorrhage, per the SITS-MOST protocol, was defined as local or remote parenchymal haemorrhage type 2 on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or [haemorrhage] leading to death.”
Supplemental Figure: Flow diagram of included and excluded patients

Patients treated by IVT for AIS during the study period
\textbf{n=931} (Lille center n=499, Sainte-Anne center n=432)

Patients excluded (n=214).
Reasons:
- Additional endovascular therapy (n=59)
- Pre-treatment CT instead of MR imaging (n=45)
- MR images unavailable for retrospective review (n=85)
- Missing T2* sequence on baseline MRI (n=5)
- Poor quality T2* sequence on baseline MRI (n=6)
- Missing 3-month modified Rankin Scale (n=14)

Patients included in the present study
\textbf{n=717} (Lille center n=375, Sainte-Anne center n=342)

IVT: intravenous thrombolysis; AIS: acute ischemic stroke;
CT: computed tomography; MRI: magnetic resonance imaging.
## Supplemental Table II: Characteristics of studies which assessed the association between 3-month mRS>2 and CMBs presence.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Data collection</th>
<th>Age Mean±SD or Median (IQR)</th>
<th>MRI</th>
<th>≥1 CMBs on pre-IVT MRI</th>
<th>sICH n (%)</th>
<th>3-month mRS&gt;2 n (%)</th>
<th>Prevalence of 3-month mRS&gt;2 in patients with ≥1 CMBs, compared to patients without CMBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gratz et al (2014)7</td>
<td>174</td>
<td>IVT only; 1 center</td>
<td>68.1±13.7†</td>
<td>SWI, 1,5&amp;3T</td>
<td>79 (20.2%)†</td>
<td>6 (3.4%)</td>
<td>70 (40.2%)</td>
<td>22/38 (57.9%) vs 48/136 (35.3%) Crude OR=2.52 (95%CI 1.21-5.25) P=0.01 Adjusted OR=N/A, P=0.26†</td>
</tr>
<tr>
<td>Dannenberg et al (2014)8</td>
<td>326</td>
<td>Prospective, 1 center</td>
<td>76 (68-84)</td>
<td>T2*, 3T</td>
<td>81 (24.8%)</td>
<td>10 (3.1%)</td>
<td>158 (49.4%)</td>
<td>49/80 (61.3%) vs 109/240 (45.4%) Crude OR=1.90 (95%CI 1.13-3.19) P=0.02 Adjusted OR=1.15 (95%CI 0.60-2.22) P=0.68</td>
</tr>
<tr>
<td>Yan et al (2015)9</td>
<td>333</td>
<td>Prospective, 1 center</td>
<td>66.2±13.0</td>
<td>SWI, 3T</td>
<td>133 (39.9%)</td>
<td>8 (2.4%)</td>
<td>140 (42.0%)</td>
<td>66/132 (50.0%) vs 74/201 (36.8%) Crude OR=1.68 (95%CI 1.08-2.62) P=0.02 Adjusted OR=N/A</td>
</tr>
<tr>
<td>Present study</td>
<td>717</td>
<td>Prospective, 2 centers</td>
<td>74 (60-83)</td>
<td>T2*, 1.5T</td>
<td>150 (20.9%)</td>
<td>27 (3.8%)</td>
<td>329 (45.9%)</td>
<td>54/131 (41.2%) vs 213/524 (40.6%) § Crude OR=1.02 (95%CI 0.69-1.51), P=0.90 § Adjusted OR=0.86 (95%CI 0.57-1.28), P=0.45 §</td>
</tr>
</tbody>
</table>

CMB: cerebral microbleed; MRI: magnetic resonance imaging; N: patient number; N/A: not available; IVT: intravenous thrombolysis; mRS: Modified Rankin scale; NIHSS: National Institute of Health Stroke Scale; SWI: susceptibility-weighted imaging; sICH: symptomatic intracranial hemorrhage; OR: odds ratio; CI: confidence interval; SD: standard deviation; IQR: interquartile range.

†Result based on whole cohort (392 patients, treated by IVT and/or endovascular therapy) ‡Missing data in 6 patients § 62 patients with prestroke mRS>2 were excluded for this analysis
Supplemental References


急性虚血性脳卒中患者 717 例における静脈内血栓溶解療法後の微小脳出血の状態と 3 カ月後の転帰

Microbleed Status and 3-Month Outcome after Intravenous Thrombolysis in 717 Patients with Acute Ischemic Stroke

Guillaume Turc, MD 1 ; Asmaa Sallem, MD 3 ; Solène Moulin, MD 2 , et al.

1 Departments of Neurology, Hôpital Sainte-Anne, Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, DHU Neurovasc, Paris, France; and Departments of Neurology and Radiology, Lille University Hospital and Université de Lille, UDSL, INSERM U1171, Lille, France.

背景および目的：治療開始前の磁気共鳴画像法（MRI）で微小脳出血（CMB）が検出されると症状性頭蓋内出血（sICH）のリスクが増加するのか、また最も重要な点として静脈内血栓溶解療法を受けた急性虚血性脳卒中患者で CMB が検出された場合は転帰不良となるのか否かについてはまだに議論が続いている。我々は多施設コホート研究を実施し、CMB の存在と病変数が 3 カ月後の改善 Rankin スケール（mRS）と sICH に及ぼす影響を調べた。

方法：治療前の第一選択の画像検査として MRI を施行している 2 つの医療機関において、静脈内血栓溶解療法のみの治療を受けた経過した急性虚血性脳卒中患者のデータを前向きに収集して分析した。検査された尺度で用いて、臨床データを知らない神経放射線科医が T2 画像上で CMB を評価した。ロジスティック回帰を用いて、CMB と 3 カ月後の mRS および sICH との関連を評価した。

結果：717 例中 150 例（20.9%）に 1 カ所以上の CMB が認められた。単変量シフト解析では、CMB の病変数は mRS の悪化と関連していたが（オッズ比（OR）= 1.07, 95% 信頼区間（95% CI）: CMB 1 カ所増加に付き 1.00 ～ 1.15, $P = 0.049$）、年齢、高血圧、および心房細動で調整した後は有意ではなくなった（OR = 1.03, 95% CI: CMB 1 カ所増加に付き 0.96 ～ 1.11, $P = 0.37$）。CMB の位置を考慮に入れた場合や潜在的な血管疾患を想定した場合でも、結果は依然として有意ではなかった。sICH の発生率は定義によって異なり、3.8 ～ 9.1% であった。CMB の存在、病変数、位置、潜在的な血管疾患のいずれにおいても sICH の独立した関連因子ではなかった。

結論：治療前の画像検査で CMB の存在が MRI 前の MRI における mRS の存在や数は不良転帰もしくは sICH の発症と関連しなかった。CMB を有するサブグループの患者が、静脈内血栓溶解療法で期待される有益性を回復転帰不良のリスクをもつか否かを判断するためにには、個々の患者のデータのメタ解析を行う必要がある。

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表 3 治療開始前の画像診断で認められた CMB と転帰の関係

<table>
<thead>
<tr>
<th></th>
<th>CBM の存在</th>
<th>CBM の病変数</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>単変量解析</td>
<td>多変量解析*</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>$P$ 値</td>
</tr>
<tr>
<td>3 カ月後の mRS スコア、&gt; 2†</td>
<td>1.02 (0.69～1.51)</td>
<td>0.90</td>
</tr>
<tr>
<td>3 カ月後の mRS スコア、&gt; 1§</td>
<td>1.02 (0.69～1.51)</td>
<td>0.92</td>
</tr>
<tr>
<td>3 カ月後の mRS が悪化（シフト解析）</td>
<td>1.18 (0.86～1.62)</td>
<td>0.31</td>
</tr>
<tr>
<td>sICH</td>
<td>NINDS の定義</td>
<td>1.26 (0.70～2.29)</td>
</tr>
<tr>
<td></td>
<td>ECASS-2 の定義</td>
<td>0.86 (0.45～1.66)</td>
</tr>
<tr>
<td></td>
<td>ECASS-3 の定義</td>
<td>1.08 (0.43～2.73)</td>
</tr>
<tr>
<td></td>
<td>SITS-MOST の定義</td>
<td>1.08 (0.43～2.73)</td>
</tr>
</tbody>
</table>

CI：信頼区間、CBM：微小脳出血、ECASS：European Cooperative Acute Stroke Study、mRS：改良 Rankin スケール、OR：オッズ比、sICH：症候性頭蓋内出血、SITS-MOST：Safe Implementation of Thrombolysis in Stroke-Monitoring Study。

*年齢、高血圧、および心房細動で調整。
†CMB1 カ所増加に付き
§脳卒中発症前の mRS スコアが > 2 の患者 62 例を除く。
§脳卒中発症前の mRS スコアが > 1 の患者 91 例を除く。
방법
총 3799명의 환자들이 급성혈혈뇌졸중으로 병원입원 후 모집되었다. 총 호모시스테인 수치는 처음 입원 후 24시간 내에 측정되었다. 중간값 48개월 동안 환자를 추적관찰하였다.

결과
추적관찰 기간 동안 233명(6.1%) 환자들이 사망하였다. 나이, 흡연, 당뇨병 및 다른 심혈관 위험인자들을 보정한 후에 가장 높은 호모시스테인 수치 사분위(>18.6 μmol/L)에 속해 있는 환자들은 가장 낮은 사분위(≤10 μmol/L)와 비교한 때 1.61배 높은 사망률(보정위험비[adjusted hazard ratio, aHR], 1.61; 95% 신뢰구간[confidence interval, CI], 1.03–2.53)을 보였다. 추가 하위그룹 분석에서 이러한 연관성은 단지 대혈관동맥경화증 아형의 뇌졸중(aHR, 1.80; 95% CI, 1.05–3.07)에서만 유의한 것이 확인되었고, 소혈관폐색 아형의 뇌졸중(aHR, 0.80; 95% CI, 0.30–2.12)에서는 유의하지 않았다. 뇌졸중 연관 사망 위험도는 가장 낮은 사분위에 위치한 환자들에게 비해 세 번째 사분위에 위치한 환자(aHR, 1.27; 95% CI, 1.06–4.80)에서 2.27배 더 높았고 네 번째 사분위 환자(aHR, 15.95; 95% CI, 1.01–4.63)에서는 2.15배 더 높았다. 심혈관질환 연관 사망 위험도와 허혈뇌졸중의 재발 위험도는 호모시스테인 수치와 유의한 연관성을 보이지 않았다.

결론
본 연구에서는 허혈뇌졸중의 급성기, 특히 대혈관동맥경화증 아형의 뇌졸중에서 호모시스테인 수치와 유의한 연관성을 보인다.

| Table 2. Associations of Hcy Level Quartiles With Mortality and Recurrent Ischemic Stroke |
|-----------------|-----------------|-----------------|-----------------|
|                | Quartile of Plasma Hcy Levels |                |                |
| Variables       | G1              | G2              | G3              | G4              |
| Recurrent isch. stroke, n (%) | 107 (271) | 110 (271) | 141 (271) | 164 (271) |
| Crude RR (95% CI) | 1.00 (0.84–1.16) | 1.06 (0.81–1.42) | 1.00 (0.82–1.42) |
| Adjusted RR (95% CI) | 1.23 (0.95–1.51) | 1.10 (0.84–1.43) | 1.10 (0.85–1.43) |
| Mortality, n (%) | 330 (271) | 44 (271) | 67 (271) | 84 (271) |
| Crude RR (95% CI) | 1.57 (0.93–2.64) | 1.83 (1.35–3.17) | 1.83 (1.35–3.17) |
| Adjusted RR (95% CI) | 1.25 (0.77–2.01) | 1.46 (0.92–2.33) | 1.46 (0.92–2.33) |

*G1 indicates confidence interval; HR, hazard ratio; and Hcy, total homocysteine.

**_Adjusted for age, smoking status, low-density lipoprotein cholesterol level, high-sensitivity C-reactive protein level, ApoB/ApoA1 ratio, and the presence of hypertension, type 2 diabetes mellitus, hyperuricemia, coronary artery disease, and obesity._**

Abstract 11

정맥내혈전용해 치료 후 미세출혈과 3개월 임상 결과: 급성혈혈뇌졸중 환자 717명의 분석

Microbleed Status and 3-Month Outcome After Intravenous Thrombolysis in 717 Patients With Acute Ischemic Stroke

Guillaume Turc, MD; Asmaa Sallem, MD; Solene Moulin, MD; Marie Tisserand, MD; Alexandre Machet, MD; Myriam Edjlali, MD; Jean-Claude Baron, ScD; Xavier Leclerc, PhD; Didier Leys, PhD; Jean-Louis Mas, MD; Charlotte Cordonnier, PhD; Catherine Oppenheim, PhD

(Stroke. 2015;46:2458-2463.)

**Key Words:** cerebral hemorrhage ■ magnetic resonance imaging ■ stroke

배경과 목적
정맥내혈전용해 치료 전에 촬영한 자기공명영상에서 확인된 뇌 미세출혈(cerebral microbleeds, CMBs)이 증상성뇌혈혈뇌졸중 (symptomatic intracranial hemorrhage, sICH)의 위험을 증가시키는지 그리고 가장 중요하게는 임상적 회복을 지연시키는지 여부는 아직 논란의 여지가 있다. 이 연구는 여러 병원에서 수집
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환자 코호트를 통한, CMB의 존재 및 그 양이 3개월 시점의 수정랜킨척도 및 sICH에 미치는 영향을 분석하였다.

방법
저자들은 급성혈혈뇌졸중 환자에서 경색혈혈전용해 치료만 받은 환자를 전향적으로 수집하였다. 참여한 2곳의 병원은 모두 투여 전 일차 난 영상 기법으로 MRI를 사용하였다. 임상 자료를 알지 못하는 신경영상 전문가가 T2* 영상에서 표준화한 척도를 이용하여 CMB를 정량화하였다. 로지스틱 회귀분석을 통해 CMB와 3개월 수정랜킨척도 혹은 sICH의 관련성을 평가하였다.

결과
총 717명의 환자 중 150명(20.9%)에서 1개 이상의 CMB가 발견되었다. CMB의 개수는 단변량 이동분석(univariate shift analysis)에서 수정랜킨척도의 악화와 연관성을 보였으나 (1-CMB 증가당 대응비, 1.07: 95% 신뢰구간 1.00–1.15; P=0.049), 연령, 고혈압 및 심방세동을 보정한 후에는 통계적 유의성이 소실되었다(1-CMB 증가당 대응비, 1.03: 95% 신뢰구간 0.96–1.11; P=0.37). CMB의 위치 혹은 기저혈관병을 고려하여 결과는 통계적으로 유의하지 않았다. sICH의 발생률은 정의에 따라 3.8%에서 9.1%로 다양하였다. CMB 여부, 개수, 위치 및 기저 혈관병은 sICH의 발생에 영향을 미치지 않았다.

결론
관련된 교란변수를 보정하면, 기능적 회복 지연 혹은 sICH는 경색혈혈전용해 치료 전에 발견된 CMB의 존재 여부 및 개수와 관련성을 보이지 않았다. 경색혈혈전용해 치료의 이득을 상회하는 출혈 위험 및 불량한 예후를 가질 가능성이 있는 환자군을 선정하기 위하여, 개별 환자 자료를 이용하는 메타-분석이 필요할 것이다.

Table 3. Association Between CMBs on Pretreatment Imaging and Outcome

<table>
<thead>
<tr>
<th>CMB(s) Presence</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis*</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>3-month mRS score, &gt;2</td>
<td>1.02 (0.89–1.51)</td>
<td>0.80</td>
<td>1.05 (0.86–1.15)</td>
<td>0.29</td>
</tr>
<tr>
<td>3-month mRS score, &gt;15</td>
<td>1.02 (0.89–1.51)</td>
<td>0.92</td>
<td>1.00 (0.91–1.11)</td>
<td>0.95</td>
</tr>
<tr>
<td>Worse 3-month mRS (shift analysis)</td>
<td>1.18 (0.88–1.59)</td>
<td>0.31</td>
<td>1.07 (1.00–1.15)</td>
<td>0.049</td>
</tr>
<tr>
<td>sICH</td>
<td>NINDS definition</td>
<td>1.28 (0.70–2.29)</td>
<td>0.44</td>
<td>1.03 (0.80–1.35)</td>
</tr>
<tr>
<td>ECASS-2 definition</td>
<td>0.86 (0.54–1.66)</td>
<td>0.05</td>
<td>0.72 (0.37–1.41)</td>
<td>0.34</td>
</tr>
<tr>
<td>ECASS-3 definition</td>
<td>1.65 (1.43–2.73)</td>
<td>0.06</td>
<td>0.99 (0.39–2.27)</td>
<td>0.80</td>
</tr>
<tr>
<td>STITS-MOST definition</td>
<td>1.65 (1.43–2.73)</td>
<td>0.06</td>
<td>0.47 (0.34–2.22)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

C indicates confidence interval; CMB, cerebral microbleeds; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage; and STITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
*Adjusted for age, hypertension, and atrial fibrillation.
†Per 1-microbleed increase.
‡Exclusion of 62 patients with prestroke mRS score of >2.
§Exclusion of 51 patients with prestroke mRS score of >1.

Abstract 12

급성혈혈뇌졸중에서 개인의 아스피린 혈소판 반응성의 시간에 따른 변화의 임상적 의미

Clinical Implications of Changes in Individual Platelet Reactivity to Aspirin Over Time in Acute Ischemic Stroke

Joon-Tae Kim, MD, PhD; Suk-Hee Heo, MD; Kang-Ho Choi, MD; Tai-Seung Nam, MD; Seong-Min Choi, MD; Seung-Han Lee, MD; Man-Seok Park, MD; Byeong C. Kim, MD; Myeong-Kyu Kim, MD; Jeffrey L. Saver, MD, PhD; Ki-Hyun Cho, MD

(Stroke. 2015;46:2534-2540.)

Key Words: aspirin ■ platelet function tests ■ stroke

배경과 목적
개인의 혈소판 반응성의 시간의존적인 변화를 심장동맥질환 환자에서 관찰할 수 있다. 따라서 혈혈뇌졸중 이후 급성기 동안에 아스피린에 대한 혈소판 반응성의 시간의존적인 변화를 평가하