Number of Cerebral Microbleeds and Risk of Intracerebral Hemorrhage After Intravenous Thrombolysis

Steffen Dannenberg*; Jan F. Scheitz, MD*; Michal Rozanski, MD; Hebun Erdur, MD; Peter Bruneccker, Dr rer medic; David J. Werring, PhD; Jochen B. Fiebach, MD; Christian H. Nolte, MD

Background and Purpose—Cerebral microbleeds (CMBs) are found in a substantial proportion of patients with ischemic stroke eligible for treatment with intravenous thrombolysis. Until now, there is limited data on the impact of multiple CMBs on occurrence of intracerebral hemorrhage (ICH) after intravenous thrombolysis.

Methods—Between 2008 and 2013, all patients receiving MRI-based intravenous thrombolysis were identified within our prospective thrombolysis register. Number of CMBs was rated on pretreatment T2*-weighted MRI by a rater blinded to clinical data and follow-up. Outcomes of interest were occurrence of symptomatic ICH (sICH) and parenchymal hemorrhage (PH).

Results—Among 326 included patients, 52 patients had a single CMB (16.0%), 19 had 2 to 4 CMBs (5.8%), and 10 had ≥5 CMBs (3.1%). Frequency of sICH/PH was 1.2%/5.7% in patients without CMBs, 3.8%/3.8% in patients with a single CMB, 10.5%/21.1% in patients with 2 to 4 CMBs, and 30.0%/30.0% in patients with ≥5 CMBs, respectively (each P for trend <0.01). The unadjusted odds ratio per additional CMB for sICH was 1.19 (95% confidence interval, 1.07–1.33; P<0.01) and for PH was 1.13 (95% confidence interval, 1.03–1.24; P<0.01). Compared with patients without CMBs, both patients with 2 to 4 CMBs (P=0.02/P=0.02) and patients with ≥5 CMBs (P<0.01/P<0.01) had significantly increased odds ratios for sICH and PH, whereas in patients with a single CMB, odds ratios were not significantly increased (P=0.21/P=0.59). The association of CMB burden with sICH/PH remained significant after adjustment for possible confounders (age, age-related white matter changes score, atrial fibrillation, onset-to-treatment time, prior statin use, and systolic blood pressure on admission).

Conclusions—Our findings indicate a higher risk of sICH and PH after intravenous thrombolysis when multiple CMBs are present, with a graded relationship to increasing baseline CMB number. (Stroke. 2014;45:2900-2905.)

Key Words: cerebral hemorrhage ■ cerebral microbleeds ■ cerebral small vessel diseases ■ magnetic resonance imaging ■ stroke ■ thrombolytic therapy

A pproximately 2% to 10% of the patients with ischemic stroke receiving intravenous thrombolysis (IVT) will develop symptomatic intracerebral hemorrhage (sICH) depending on the definition and cohort characteristics.1 Occurrence of sICH severely impacts functional recovery and is independently associated with higher mortality.2 Therefore, identifying predictors of sICH is a major focus of stroke research to improve estimation of risk and benefit of IVT. Besides clinical predictors such as higher stroke severity and higher systolic blood pressure, imaging predictors including the degree of leukoaraiosis and presence of cerebral microbleeds (CMBs) have emerged as possible risk factors for sICH.3,4 CMBs are small foci of perivascular blood products detectable with hemorrhage-sensitive MRI sequences,5,6 They are considered to be a marker of hemorrhage-prone small vessel disease5,7 and have been linked to occurrence of future ICH.4 Approximately 12% to 39% of patients with acute ischemic stroke eligible for IVT have incidental CMBs on pretreatment imaging, depending on study population characteristics (eg, age and history of stroke), field strengths of the scanner, and MRI sequences applied.4 Whether presence of CMBs affects risk of IVT-related sICH remains uncertain.4,9 Until now, CMBs have not been considered to be a contraindication to IVT, but clinicians with access to MRI face uncertainty, particularly when large numbers of CMBs are present. In a recent meta-analysis, individuals with pre-IVT CMBs had a sICH rate of 7.4% compared with 3.6% in those without CMBs, but this was not statistically significant (P=0.08).4 Previous
studies have not clearly established whether the number of CMBs affects sICH risk.\(^{10-17}\) Recently, Gratz et al\(^{14}\) did not find evidence that higher CMB burden affects risk of sICH in patients treated with different revascularization procedures. Of note, <50% of patients received IVT exclusively. This might be important, because other revascularization techniques carry different risks of bleeding.

Using a homogeneous cohort of consecutive patients with ischemic stroke treated with IVT, we aimed to investigate whether the number of CMBs on baseline MRI is associated with sICH, parenchymal hemorrhage (PH), or functional outcome.

Methods

Study Population and Data Collection

Between January 2008 and August 2013, all consecutive patients with ischemic stroke receiving IVT were registered in an ongoing, prospective thrombolysis registry.\(^{19}\) Recombinant tissue-type plasminogen activator (alteplase) was applied within 4.5 hours after symptom onset. Patients with unknown time of symptom onset were eligible for IVT based on fluid attenuated inversion recovery negativity on MRI.\(^{20}\) Inclusion criteria of our study were MRI-based IVT and either MRI- or computed tomography (CT)-based follow-up imaging within 36 hours after IVT. The decision whether to conduct MRI or CT examination was made according to contraindications for MRI and availability of the imaging method. MRI was available during working hours (working hours defined as 8:00 am to 5:00 pm on weekdays). Patients were excluded from analysis if quality of pretreatment T2* did not allow for reliable rating of CMBs because of movement artifacts or if they underwent additional endovascular revascularization procedures because of different treatment protocols and possible higher bleeding risk.

As described previously,\(^{21}\) baseline characteristics were extracted from medical records and included age, sex, and medical history, which comprised history of hypertension, hyperlipidemia, diabetes mellitus, previous stroke, atrial fibrillation, and medication on admission. Stroke severity was determined using the National Institutes of Health Stroke Scale (NIHSS) by certified raters. The degree of leukoaraiosis was assessed by the validated Age-related White Matter Changes score.\(^{21}\)

Imaging Protocol

MRI was performed using a 3-T Tim Trio Siemens MRI scanner. We acquired T2* (resonance time, 620 ms; echo time, 20 ms; field of view, 220 mm; matrix, 256×192; slice thickness, 5 mm) and diffusion-weighted imaging sequences (repetition time, 7600 ms; echo time, 93 ms; field of view, 230 mm; matrix, 192×192; slice thickness, 2.5 mm). Details have been reported previously.\(^{21}\)

CMB Definition and Detection

CMBs were defined according to recent consensus recommendations for MRI studies on cerebral small vessel disease.\(^{21}\) They can be visualized as round or oval, hypointense lesions with associated blooming on T2*-MRI being at least half-surrounded by brain parenchyma. Maximum diameter was defined as 10 mm. Occurrence of CMB mimics was systematically excluded.\(^{21}\)

CMBs on the pretreatment T2*-MRI were rated by a rater (S.D.) blinded for clinical data, follow-up images, and outcome measures. The number of CMBs was divided into 4 groups: no CMB, single CMB, 2 to 4 CMBs, and similar to previous studies, ≥5 CMBs.\(^{19}\) Presumed pathogenesis of CMBs was categorized in 3 groups: possible cerebral amyloid angiopathy (CAA), hypertensive, or undetermined.\(^{13,12,24}\) According to Boston criteria, pathogenesis of CMBs was considered possible CAA if a strictly lobar (cortical or corticosubcortical) distribution of CMBs was found in patients aged ≥55 years.\(^{13}\) Presumed hypertensive pathogenesis was defined if CMBs were located exclusively in deep regions, infratentorial regions, or both. Presence of CMBs, regardless of the number, is not considered a contraindication for IVT in our center.

Outcome Measures

Outcome parameters were occurrence of sICH and PH on follow-up imaging, as well as favorable outcome at 3 months. sICH was defined according to European Cooperative Acute Stroke Study (ECASS)-III criteria (ICH combined with clinical deterioration of ≥4 points on NIHSS, or death).\(^{22}\) PH was defined radiologically as hematoma with at least some mild space-occupying effect.\(^{23}\) Functional outcome at 3 months was assessed using the modified Rankin scale. A modified Rankin scale score of ≤2 was considered favorable. Occurrence of sICH, PH, and favorable outcome at 3 months were rated blinded for presence of CMBs on the pretreatment T2*-MRI.

Statistical Methods

Univariate comparisons were performed using the Fisher exact test for categorical variables and the Wilcoxon–Mann–Whitney U test for continuous variables. We calculated unadjusted and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between numbers of CMBs and presence of sICH, PH, and favorable outcome. Patients without CMBs were considered as reference. Adjustments were made using backward stepwise logistic regression and included all variables associated with sICH/PH or presence of CMBs with a P value <0.1 in univariate comparisons. Regarding favorable outcome, all variables significantly associated with favorable outcome qualified for the multiple regression analysis. All tests were 2-tailed, and statistical significance was determined at an α level of 0.05. Statistical analyses were performed using SPSS version 19.0 for windows.

Results

During the study period, 4457 consecutive patients with acute ischemic stroke were admitted to our hospital. A total of 952 patients received IVT (21.4%), including 585 patients with CT-based IVT and 367 patients with MRI-based IVT (median age, 75 years; median NIHSS score, 9; 48.8% men). Patients were excluded because they underwent endovascular procedures in addition to IVT (n=32) or because quality of pretreatment T2* did not allow for reliable rating of CMBs because of movement artifacts (n=9). Among the 326 patients analyzed, median age was 76 (interquartile range, 68–84) years, 48.8% were men (n=159), and median initial NIHSS score was 8 (interquartile range, 5–14). All baseline characteristics are shown in Table 1.

At least 1 CMB on pretreatment MRI was found in 24.8% of patients (n=81), 16.0% (n=52) had exactly 1 CMB, 5.8% (n=19) had 2 to 4 CMBs, and 3.1% (n=10) had ≥5 CMBs. Among patients with CMBs, 51.9% (n=42) had possible CAA-related pathogenesis, 27.2% (n=22) had presumed hypertensive pathogenesis, and 21.0% had undetermined pathogenesis (n=17). Lobar location of CMBs was present in 72.8% of the patients (n=59), deep location in 28.4% (n=23), and infratentorial location in 27.2% (n=22). Patients with CMBs were significantly older (median age, 80 versus 74 years; P<0.01) and had a higher degree of leukoaraiosis (median Age-related White Matter Changes score, 7 versus 5; P<0.01), whereas all other baseline characteristics were not significantly different.

The overall rate of sICH was 3.1% (n=10), and the rate of PH was 7.1% (n=23). Patients with any CMBs on pretreatment MRI were more likely to develop sICH than patients without CMBs (8.6% versus 1.2%; P<0.01). The rate of PH was not significantly higher in patients with any CMBs (11.1% versus 5.7%; P=0.13). As shown in Table 1 and Figure 1, the occurrence of sICH and PH significantly increased with higher number of CMBs when used as a categorical variable (overall P
value and $P$ for trend <0.01). Compared with patients without CMBs (reference group), the risk of sICH and PH was significantly higher in patients with presence of 2 to 4 and $\geq 5$ CMBs. In patients with a single CMB, the rates of sICH and PH did not significantly exceed those of the reference group (see also Table 2). The unadjusted OR per additional CMB (as a continuous variable) was 1.19 (95% CI, 1.01–1.57, per 10 mm Hg increase) and statin use before IVT (OR, 3.37; 95% CI, 1.33–8.54) were independently associated with occurrence of PH. Regarding sICH, only higher blood pressure (OR, 1.30; 95% CI, 1.01–1.57, per 10 mm Hg increase) remained significantly associated in addition to CMB number.

The rate of sICH was not significantly different in patients with possible CAA-related compared with patients without CMBs (4.8% versus 1.2%; $P$=0.16). Similar results were observed regarding PH (7.1% versus 5.7%; $P$=0.72). Patients with presumed hypertensive pathogenesis were not more likely to develop sICH (4.5% versus 1.2%; $P$=0.29) or PH (0.0% versus 5.7%; $P$=0.61) compared with patients without CMBs. As a consequence of definition, all patients with undetermined pathogenesis had $\geq 2$ CMBs (not exclusively lobar or exclusively non-lobar). In the undetermined group, sICH (23.5% versus 1.2%; $P$<0.01) and PH (35.3% versus 5.7%; $P$<0.01) were observed significantly more often compared with patients without CMBs. Data on functional outcome were available for 320 patients (98.2%). One hundred sixty-two patients had a favorable outcome after 3 months (modified Rankin scale score, 0–2;
Patients with any CMBs on pretreatment MRI were less likely to achieve favorable outcome (38.8% versus 54.6%; P=0.02). Compared with patients without CMBs, patients with a single CMB (OR, 0.58; 95% CI, 0.32–1.08; P=0.08) or 2 to 4 CMBs (OR, 0.75; 95% CI, 0.29–1.91; P=0.55) did not have a lower chance of favorable outcome, but those with ≥5 CMBs had a lower chance of favorable outcome (OR, 0.09; 95% CI 0.01–0.74; P=0.03). In a multiple regression analysis adjusting for variables significantly associated with functional outcome (age, sex, NIHSS, atrial fibrillation, Age-related White Matter Changes score, and sICH), presence of ≥5 CMBs did not remain significant (OR, 0.24; 95% CI, 0.02–2.61; P=0.24).

Presence of any CMBs on pretreatment MRI was not associated with functional outcome after multiple adjustment for the above-mentioned variables (OR for favorable outcome, 0.87; 95% CI, 0.45–1.68; P=0.68).

**Discussion**

The findings of our study indicate an increased risk of hemorrhagic complications after IVT in patients with multiple CMBs on pretreatment MRI. The presence of a single CMB did not substantially increase the risk of IVT-related sICH or PH.

Previous studies lacked appropriate sample sizes to allow for subgroup analyses on number of CMBs and occurrence of sICH. In a small Asian study on 65 stroke patients who predominantly underwent intra-arterial thrombolysis, a similar graded relationship of CMB number and risk of sICH was observed, although this was not significant. In the largest cohort investigating the association between CMBs and hemorrhagic complications (the Bleeding Risk Analysis in Stroke Imaging Before Thrombolysis [BRASIL] study), there was also a signal toward a higher risk of sICH in patients with multiple CMBs, because 2 of 7 patients with ≥5 CMBs experienced sICH. In a pooled analysis of the BRASIL data and the study by Kim et al including 635 patients with stroke receiving IVT or intra-arterial thrombolysis, a similar relationship of CMB burden and risk of any ICH was observed. Notwithstanding, these studies were highly heterogeneous regarding MRI acquisition, study populations, and treatment protocols. A recent study by Gratz et al did not show an association of CMB burden and occurrence of sICH in a similar sized cohort of patients with stroke treated with different revascularization strategies. Of note, in the subgroup of patients exclusively treated with IVT (44%), there was

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**Table 2. Unadjusted and Adjusted ORs for Association Between Number of CMBs and sICH, PH, and Favorable Outcome**

<table>
<thead>
<tr>
<th>Number of CMBs</th>
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<td>1 (reference)</td>
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<td>≥5 CMBs</td>
<td>34.57 (5.90–202.55)</td>
<td>42.65 (6.69–271.96)</td>
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<td>6.15 (1.29–29.40)</td>
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CI indicates confidence interval; CMB, cerebral microbleed; mRS, modified Rankin scale; OR, odds ratio; PH, parenchymal hemorrhage; and sICH, symptomatic intracerebral hemorrhage.

*Favorable outcome was defined as modified Rankin scale score of ≤2 at 3 months.
†Adjustment was made for all variables associated with sICH or PH with a P value <0.10 (age, systolic blood pressure, Age-Related White Matter Changes score, prior statin use, onset-to-treatment time, and atrial fibrillation).
‡Adjustment was made for all variables significantly associated with favorable outcome (age, sex, National Institutes of Health Stroke Scale, atrial fibrillation, Age-Related White Matter Changes score, and sICH).
a higher rate of sICH (5.3% versus 2.9%). Unfortunately, there were no data available on CMB burden in the IVT-only group.

Prevalence of ≥2 CMBs ranged from 4% to 8%, and prevalence of ≥5 CMBs ranged from 0% to 2% in previous cohorts. Because 9% of the patients in our unselected MRI-eligible cohort had ≥2 CMBs and 3% had ≥5 CMBs on pretreatment MRI, our study suggests that in patients with stroke eligible for IVT, multiple CMBs may not be as rare as previously reported. Differences in the frequency of CMBs in our cohort compared with others might be explained by median age and applied field strength (we used 3 T compared with 1.5 T in previous studies).

The increase of sICH and PH with higher baseline CMB numbers is consistent with the hypothesis that an underlying bleeding-prone vasculopathy associated with multiple CMBs promotes genesis of sICH and PH after IVT. The increased rate of hemorrhagic complications in those with a higher number of CMBs might reflect the presence of more severe vasculopathy. In the pathogenesis of CMBs, vasculopathies caused by CAA and hypertension are considered to be the most important factors. In our analyses, rate of sICH and PH was highest in the group with undetermined pathogenesis which comprised patients with accumulation of both lobar and nonlobar CMBs. This suggests that presence of a combination of both hypertensive and CAA-related pathologies may particularly promote sICH after IVT.

Although data are scarce, in a small pooled pathological analysis, 7 of 10 patients with thrombolysis-related ICH (after myocardial infarction) had autopsy-proven CAA compared with 22% in unselected populations of similar age, suggesting that CAA may be a risk factor for this complication. Because CMBs are not detectable with plain CT, our findings suggest that, if available, multimodal MRI including T2* or other susceptibility-weighted sequences might be superior for evaluation of bleeding risk compared with plain CT before IVT.

In addition to CMB number, prior statin use was associated with PH in a multivariable analysis. This is in line with recent observations that especially patients using higher statin doses might be prone to hemorrhagic complications. Moreover, higher blood pressure on admission was confirmed to be associated with thrombolysis-related ICH.

In univariate analysis, patients with presence of ≥5 CMBs were less likely to achieve a favorable outcome, but in multivariable analysis, the association did not remain significant. It is possible that a higher rate of sICH in patients with ≥5 CMBs causes less favorable outcome, but larger studies will be required to test this hypothesis. Of note, a recent study did not find an association of higher CMB burden with worse outcomes either. Momentarily, no final conclusion on effectiveness of IVT in patients with CMBs and especially multiple CMBs can be drawn.

Strengths of our study include the homogeneity of the cohort (treatment with IVT only), use of standardized MRI sequences, and prospective collection of outcome events. Limitations of our study include the overall low number of hemorrhagic complications limiting statistical power. Selection bias includes the single-center setting and patients’ ability to undergo MRI. Because of the observational and nonrandomized design, we cannot provide evidence whether the overall benefit of IVT is attenuated in patients with multiple CMBs. Furthermore, we did not control for volume of pretreatment diffusion-weighted imaging lesion, which was shown to be a relevant MRI predictor of sICH. Nevertheless, our findings indicate that future studies on CMBs in the setting of IVT should take the overall burden of CMBs into account.

In conclusion, we found that presence of multiple CMBs on pretreatment MRI is associated with an increased risk of hemorrhagic complications after IVT for acute ischemic stroke. The dose–response relationship of ICH to increasing baseline CMB number and biological plausibility suggest that an arteriopathy associated with multiple CMB may be an important contributory cause of post-IVT ICH. Although IVT is of established overall benefit in acute ischemic stroke, our data suggest that patients with multiple CMBs may have increased early bleeding risk, requiring a careful risk–benefit evaluation. However, until confirmed by further studies in other populations, it does not seem to be appropriate to...
withhold IVT based on the presence of CMBs on pretreatment MRI alone.

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**Disclosures**

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**References**

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랜미세출혈 수와 정맥내 혈전용해술 후 뇌내출혈 위험도

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배경과 목적

뇌미세출혈은 정맥내 혈전용해술을 받는 환자에서 증가하는 양상을 보였다. 그러나, 지금까지 다발성 뇌미세출혈이 혈전용해술 이후 뇌내출혈의 발생에 미치는 영향에 대한 연구는 매우 부족하다.

방법

자기공명영상 기반의 정맥내 혈전용해술을 받은 허혈뇌졸중 환자에서 임상 자료와 추적관찰 자료에 두건된 연구자에 의해서 측정되었다. 증상성 뇌내출혈과 실질출혈의 발생을 주요한 임상 결과로 확인하였다.

결과

326명의 환자 중에서 52명의 환자(16.0%)가 한 개의 미세출혈이 있었고, 19명(5.8%)은 2~4개의 미세출혈을, 10명(3.1%)은 5개 이상의 미세출혈이 있었다. 증상성 뇌내출혈과 실질출혈의 발생을 주요한 임상 결과로 확인하였다.

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결론

정맥내 혈전용해술 이후 증상성 뇌내출혈 및 실질출혈의 위험도는 다발성 뇌미세출혈이 있을 때 높았고, 뇌미세출혈 수에 따라서 증가하는 양상을 보였다.