Despite continuous improvements of intravenous thrombolysis (IVT) and endovascular therapy (EVT) for acute ischemic stroke, 7% to 10.5% of the patients experience symptomatic intracerebral hemorrhage (sICH) that deteriorates their outcome. Known risk factors for sICH are advanced age, higher baseline National Institutes of Health Stroke Scale (NIHSS) score, arterial hypertension, hyperglycemia, and signs of early infarct demarcation on computed tomography (CT) or MRI.

Background and Purpose—The question whether cerebral microbleeds (CMBs) visible on MRI in acute stroke increase the risk for intracerebral hemorrhages (ICHs) or worse outcome after thrombolysis is unresolved. The aim of this study was to analyze the impact of CMB detected with pretreatment susceptibility-weighted MRI on ICH occurrence and outcome.

Methods—From 2010 to 2013 we treated 724 patients with intravenous thrombolysis, endovascular therapy, or intravenous thrombolysis followed by endovascular therapy. A total of 392 of the 724 patients were examined with susceptibility-weighted MRI before treatment. CMBs were rated retrospectively. Multivariable regression analysis was used to determine the impact of CMB on ICH and outcome.

Results—Of 392 patients, 174 were treated with intravenous thrombolysis, 150 with endovascular therapy, and 68 with intravenous thrombolysis followed by endovascular therapy. CMBs were detected in 79 (20.2%) patients. Symptomatic ICH occurred in 21 (5.4%) and asymptomatic in 75 (19.1%) patients, thereof 61 (15.6%) bleedings within and 35 (8.9%) outside the infarct. Neither the existence of CMB, their burden, predominant location nor their presumed pathogenesis influenced the risk for symptomatic or asymptomatic ICH. A higher CMB burden marginally increased the risk for ICH outside the infarct (P=0.048; odds ratio, 1.004; 95% confidence interval, 1.000–1.008).

Conclusions—CMB detected on pretreatment susceptibility-weighted MRI did not increase the risk for ICH or worsened outcome, even when CMB burden, predominant location, or presumed pathogenesis was considered. There was only a small increased risk for ICH outside the infarct with increasing CMB burden that does not advise against thrombolysis in such patients. (Stroke. 2014;45:1684-1688.)

Key Words: mechanical thrombolysis ■ outcome assessment

Preexisting Cerebral Microbleeds on Susceptibility-Weighted Magnetic Resonance Imaging and Post-Thrombolysis Bleeding Risk in 392 Patients

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are less sensitive for CMB detection than the post processed susceptibility-weighted images (SWIs).\textsuperscript{13,14}

The aim of this study was to analyze the impact of CMB burden and predominant location as detected on pretreatment SWI sequences on the post-thrombolysis bleeding risk in a large cohort of patients treated for acute ischemic stroke.

**Methods**

**Patients and Treatment**
The present study includes patients of the Bernese stroke registry, a prospectively collected database. Some of their aspects have been reported previously.\textsuperscript{15–18} Patients were included in this analysis if (1) diagnosis of ischemic stroke was established with a pretreatment MRI that included SWI sequences; (2) they underwent IVT, EVT, or IVT followed by EVT; and (3) a post-treatment MRI or CT scan was performed within 72 hours after acute therapy.

Age, sex, medication, NIHSS score, time from symptom onset to treatment, coronary artery disease, atrial fibrillation, arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia, history of transient ischemic attack or ischemic stroke, family history of transient ischemic attack and stroke, treatment details (use of urokinase, mechanical procedures, bridging concept), and complications were recorded as baseline characteristics. The study was performed according to the ethical guidelines of the Canton of Bern and with approval of our institutional review board (Inselspital, University Hospital of Bern).

**MRI Methods and Image Analysis**
The standard stroke MRI protocol included diffusion-weighted imaging, T2-weighted imaging, time-of-flight magnetic resonance angiography, SWI, first-pass gadolinium-enhanced magnetic resonance angiography of the cervical and intracranial arteries, and perfusion imaging. The scans were acquired with a 1.5-T MRI (Magnetom Verio; Siemens, Erlangen, Germany; SWI parameters: repetition time, 49 ms; echo time, 40 ms; number of averages, 1; field of view read, 230 mm; field of view phase, 75.0%; voxel size, 0.9×0.7×1.8 mm; flip angle, 15°; and acquisition time, 2:59 minutes) or a 3-T Avanto (Siemens, Erlangen, Germany) was performed within 72 hours after treatment. Bleeding complications were graded according to the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial classification.\textsuperscript{19}

**Pretreatment Imaging Analysis**
SWIs were analyzed for the presence of CMB in accordance with a previously published guideline.\textsuperscript{9} A CMB was defined as a round or ovoid area of homogeneous signal loss on SWI with <5 mm in its largest diameter. To discern CMB from imaging mimics, the following criteria were applied: (1) the CMB had to exert a blooming effect, meaning that lesion size appeared larger on SWI than on spin echo sequences. (2) Signal drops of tubular or linear shape, most likely representing vascular structures or thrombus, as well as symmetrical hypointensities in the basal ganglia likely corresponding to calcifications or iron deposits, were not counted as CMB. (3) At least half of the lesion had to be surrounded by brain parenchyma. (4) If the hypointense SWI lesions were accompanied by a typical cavernous malformation or an adjacent vascular structure or thrombus, as well as symmetrical hypointensities, were not counted as CMB. (5) At least half of the lesion had to deposit, were not counted as CMB. (6) If the hypointense SWI lesions were applied: (1) the CMB had to exert a blooming effect, meaning a area of homogeneous signal loss on SWI with <5 mm in its largest time, 49 ms; echo time, 20 ms; number of averages, 1; field of view read, 230 mm; field of view phase, 75.0%; voxel size, 0.9×0.9×2.0 mm; flip angle, 15°; and acquisition time, 2:59 minutes). The SWI and minimum intensity projection images were generated automatically by the scanner software.

**Pre-Treatment Bleeding Complications**
For follow-up imaging either an MRI or a noncontrast CT with CT angiography (Somatom Definition Edge; Siemens, Erlangen, Germany) was performed within 72 hours after treatment. Bleeding complications were graded according to the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial classification.\textsuperscript{20}

**Statistical Analysis**
Data were analyzed using SPSS 21 (IBM Corp, Armonk, NY). Categorical variables were compared with χ^2 and Fisher exact test as appropriate and continuous variables with Mann–Whitney test. Outcome was dichotomized into favorable (modified Rankin Scale, 0–2) and poor clinical outcome (modified Rankin Scale, 3–6). Forward stepwise logistic regression including all variables with \( P < 0.2 \) in univariate analysis (age, sex, NIHSS score on admission, atrial fibrillation, diabetes mellitus, hypertension, hypercholesterolemia, previous stroke, smoking, occlusion localization, treatment type [IVT, EVT, or IVT followed by EVT], and previous treatment with any antithrombotics [including vitamin K antagonists]) was used to determine the predictors of bleeding complications and outcome. Variables coding for the existence of CMB, CMB burden (rank transformed variable because of skewed distribution pattern), predominant CMB location

**Table 1. Baseline Characteristics and Therapy of 392 Patients**
\begin{verbatim}
<table>
<thead>
<tr>
<th>Age, y (SD)</th>
<th>68.1 (13.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>169 (43.1)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>249/392 (63.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>66/398 (17)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>142/397 (46.3)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>67/380 (17.6)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>213/396 (55.2)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>41/390 (10.5)</td>
</tr>
<tr>
<td>Baseline NIHSS score, median (range)</td>
<td>9 (1–36)</td>
</tr>
<tr>
<td>Occlusion localization</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>60/392 (15.3)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>219/392 (55.9)</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>5/392 (1.3)</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>14/392 (3.6)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>7/392 (1.8)</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>24/392 (6.1)</td>
</tr>
<tr>
<td>No visible occlusion</td>
<td>63/392 (16.1)</td>
</tr>
<tr>
<td>Previous antithrombotic therapy</td>
<td>173/390 (44.4)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
</tr>
<tr>
<td>IVT (alteplase) only</td>
<td>174/392 (44.4)</td>
</tr>
<tr>
<td>Intra-arterial urokinase with or without mechanical intervention</td>
<td>58/392 (14.8)</td>
</tr>
<tr>
<td>Mechanical intervention only</td>
<td>92/392 (23.5)</td>
</tr>
<tr>
<td>Bridging therapy</td>
<td>68/392 (17.3)</td>
</tr>
</tbody>
</table>

\end{verbatim}
(lobar versus deep and infratentorial), and supposed pathogenesis of CMB were then each included in the final models to determine their impact. A P value of <0.05 was considered significant.

### Results

From January 2010 to March 2013, we treated 724 patients with IVT, EVT, or IVT followed by EVT, of whom 392 patients had SWI images and fulfilled inclusion criteria.

Baseline characteristics and treatment details are listed in Table 1. IVT or bridging therapy was performed in 242 (61.7%) of the patients and EVT in 150 (38.3%) patients. In 259 (66.1%) patients pretreatment imaging was acquired with a 1.5-T and in 133 (33.9%) with a 3-T MRI system. CMBs were detected on pretreatment MRI in 79 (20.2%) patients.

There was no significant difference in the detection rate of CMB at different MRI field strengths (1.5-T: 55 [21.2%]; 3-T: 24 [18.0%]; P = 0.507). The distribution of CMB burden, predominant location, and supposed pathogenesis is listed in Table 2. Higher age (P <0.001; odds ratio [OR], 1.051; 95% confidence interval [CI], 1.024–1.078) and arterial hypertension (P = 0.002; OR, 2.871; 95% CI, 1.462–5.638) predicted the existence of CMB in multivariable regression analysis.

A post-treatment CT scan was performed in 355 patients (90.6%) and a MRI scan in 37 patients (9.4%). Details on post-treatment ICH and outcome and the P values of univariate and multivariable regression analysis for CMB existence and burden are listed in Table 3. Any ICH was noted in 96 (24.5%) patients. Twenty-one ICHs were symptomatic (5.4%) and 75 (19.1%) asymptomatic. Symptomatic ICHs were not associated with CMB existence (multivariate regression analysis, P = 0.124) or burden (P = 0.120; predicting factor: atrial fibrillation, P = 0.009; OR, 15.1; 95% CI, 1.943–117.940).

Also, asymptomatic ICHs were not associated with CMB existence (P = 0.134) or burden (P = 0.144; predicting factors: NIHSS, P = 0.001; OR, 1.055; 95% CI, 1.021–1.089 and smoking, P = 0.003; OR, 2.557; 95% CI, 1.389–4.706).

In 35 patients (8.9%), an ICH was located outside the infarct, but in only 2 patients preexisting CMBs were located within the post-treatment ICH. There was a trend for an association between ICH outside the infarct and CMB existence (P = 0.052) and a significant association with CMB burden (P = 0.048; OR, 1.004; 95% CI, 1.000–1.008; additional predicting factor: NIHSS, P = 0.024; OR, 1.047; 95% CI, 1.006–1.089).

At 3 months, 199 of 340 (58.5%) patients had a favorable outcome and 287 (84.4%) survived. Outcome was not associated with CMB existence (P = 0.256) or CMB burden (P = 0.228; predicting factors: age, P <0.001; OR, 0.927; 95% CI, 0.906–0.949; NIHSS, P <0.001; OR, 0.850; 95% CI, 0.812–0.890; and sICH, P = 0.008–0.280). Also, survival was not associated with CMB existence (P = 0.309) or burden (P = 0.412; predicting factors: occlusion location, P = 0.024; age, P <0.001; OR, 0.938; 95% CI, 0.906–0.970; NIHSS, P <0.001; OR, 0.896; 95% CI, 0.852–0.942; sICH, P = 0.018; OR, 0.271; 95% CI, 0.192–0.797; and diabetes mellitus, P <0.001; OR, 0.217; 95% CI, 0.093–0.507).

The predominant location of CMB and their supposed pathogenesis did not influence bleeding complications or outcome (location: sICH, P = 0.188; asymptomatic ICH, P = 0.196; ICH outside infarct, P = 0.056; favorable outcome, P = 0.531; and

### Table 2. Frequency, Localization, and Supposed Pathogenesis of Cerebral Microbleeds Detected on Pretreatment Susceptibility-Weighted Imaging Sequences

<table>
<thead>
<tr>
<th>Any CMB</th>
<th>CMB burden</th>
<th>Localization</th>
<th>Presumed pathogenesis</th>
<th>CMB indicates cerebral microbleed.</th>
</tr>
</thead>
</table>

### Table 3. Post-Treatment Bleeding Complications and Outcome Depending on Existence of Pretreatment CMB With P Values for CMB Existence and Burden (First P Value Result of Univariate Analysis, Second of Multivariable Regression Analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IVT (n=174)</th>
<th>EVT (n=150)</th>
<th>NT Followed by EVT (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH (n=392)</td>
<td>21 (5.4)</td>
<td>4 (2.9)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Asymptomatic ICH (n=392)</td>
<td>75 (19.1)</td>
<td>17 (12.5)</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td>ICH outside infarct (n=392)</td>
<td>35 (8.9)</td>
<td>7 (5.1)</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>3-mo favorable outcome (mRS, 0–2; n=340)</td>
<td>199 (58.5)</td>
<td>88 (75.2)</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>3-mo survival (n=340)</td>
<td>287 (84.4)</td>
<td>103 (88)</td>
<td>28 (96.6)</td>
</tr>
</tbody>
</table>

B indicates burden; CMB, cerebral microbleed; E, existence; EVT, endovascular therapy; ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; and mRS, modified Rankin Scale.
survival, \( P = 0.111 \) and pathogenesis; sICH, \( P = 0.353 \); asymptomatic ICH, \( P = 0.221 \); ICH outside infarct, \( P = 0.165 \); favorable outcome, \( P = 0.316 \); and survival, \( P = 0.089 \).

**Discussion**

The main finding of this study is that the presence of CMB on pretreatment SWI sequences did not increase the risk for symptomatic or asymptomatic ICH or influence the outcome of 392 patients treated with IVT, EVT, or IVT followed by EVT. Only ICH outside the infarcted tissue was slightly more frequent in patients with preexisting CMB. Neither the predominant location of CMB nor their supposed pathogenesis was associated with bleeding complications or outcome. These results support the clinical practice that thrombolysis should not be withheld in patients with acute stroke and a high CMB burden.

At first glance the detection of CMB on MRI sequences sensitive to magnetic susceptibility effects may not indicate an elevated post-thrombolysis bleeding risk because CMBs are thought to be hemosiderin deposits of previous, old bleedings.\(^{2,3}\) Nevertheless, histopathologic findings of intact erythrocytes may also be a sign of recent bleeding in some CMB.\(^{21}\)

In addition, 2 studies found an increased risk for ICH in non-stroke patients with CMB, who were taking antplatelet agents or oral anticoagulation.\(^ {22,23} \)

Only few studies addressed the potential risk of CMB and thrombolysis.\(^ {4,4}\) Two recent meta-analyses including the same studies of 790 IVT-treated patients concluded differently: Shoamanesh et al.\(^ {10} \) found an increased risk for sICH in patients with CMB, whereas Charidimou et al.\(^ {11} \) did not. Of the previous studies only 1 considered the burden of CMB\(^ {4} \) and none of the studies analyzed the location of CMB and the risk of ICH. In addition, none of the previous studies used SWIs, which are more sensitive for CMB detection than T2*-weighted images.\(^ {13,14} \)

We included 392 patients in our study. A total of 174 had been treated with IVT, 150 with EVT and 68 with IVT followed by EVT. There was ≥1 CMB on pretreatment SWI in 79 (20.2%) of our 392 patients, which is <34% as previously reported in patients with ischemic stroke.\(^ {12} \) This might be explained by a lower number of lacunar strokes or different risk factors in our thrombolysed patients compared with previous reports. We identified advancing age and arterial hypertension as risk factors for CMB. Other authors additionally found lacunar stroke, male sex,\(^ {24} \) diabetes mellitus,\(^ {12} \) and Asian ethnicity\(^ {12} \) to be risk factors for CMB.

In subgroup analyses only in patients treated with IVT CMB were correlated positive with sICH (Table 3), whereas in patients receiving EVT or IVT followed by EVT there was no correlation. The risk of sICH did not increase with the presence or burden of CMB. A high CMB burden was only associated with an increased risk of ICH outside the infarct (\( P = 0.048 \)) similar to a recent study, but the risk increase was only marginal (OR, 1.004).\(^ {25} \)

There was no association of CMB with outcome and survival and no association of the predominant location and pathogenesis of CMB with bleeding or outcome. An autopsy study suggested a higher risk for ICH in patients with cerebral amyloid angiopathy,\(^ {11} \) but we did not find such an association in our patients.

The main limitation of our study is the retrospective analysis. In addition, we included patients treated with different thrombolysis techniques that might herald different risks for bleeding complications. Especially in the subgroup of 92 patients who received only mechanical thrombectomy, a lower bleeding risk can be expected, but consideration of treatment types in our subgroup analyses did not change the results. Nevertheless, we cannot rule out that our study is underpowered for the detection of a negative effect of preexisting CMB because of the low frequency of preexisting CMB, the low frequency of sICH, as well as a potential under-representation of specific groups of patients like those with extensive small vessel disease. Another potential limitation is the definition of CMB. We were using the definition suggested by Greenberg et al.\(^ {11} \) and Cordonnier et al.\(^ {12} \) but there is no consensus definition of CMB.

In conclusion, CMBs detected on pretreatment SWI were not associated with an increased risk for symptomatic or asymptomatic ICH or worse outcome in patients receiving thrombolysis. Consideration of CMB burden, predominant location, or presumed pathogenesis did not change this result. There was only a marginal risk increase for ICH outside the infarct that should not advise against thrombolysis in such patients.

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**Disclosures**

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**References**


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