Safety of Thrombolysis in Patients With Acute Ischemic Stroke and Cerebral Cavernous Malformations

Hebun Erdur, MD; Jan F. Scheitz, MD; Serdar Tütüncü, MD; Jochen B. Fiebach, MD; Matthias Endres, MD; David J. Werring, FRCP, PhD; Christian H. Nolte, MD

Background and Purpose—Data on safety of intravenous thrombolysis with recombinant tissue-type plasminogen activator for acute ischemic stroke in patients with coexisting cerebral cavernous malformations (CCMs) are scarce. We assessed the risk of thrombolysis-associated hemorrhage in these patients.

Methods—We searched our tertiary care hospital thrombolysis register for patients with CCM confirmed by MRI (3 T, Siemens, TimTrio) before thrombolysis for acute ischemic stroke. CCMs were graded into subtypes according to the Zabramski classification on the basis of their MRI appearance. The primary end point was symptomatic intracerebral hemorrhage according to European Cooperative Acute Stroke Study III (ECASS III) criteria. The secondary end point was any parenchymal hemorrhage.

Results—In a total of 350 patients (median age, 76 years; interquartile range, 68–84; median National Institutes of Health Stroke Scale score, 8; interquartile range, 5–14; 51.4% women), CCMs were found in 9 patients (2.6%). Seven patients had a single CCM, and 2 patients had multiple CCMs with a total number of 12 CCMs in all patients. The subtype of CCMs was type III in 9 cases and type I in 3 cases. Symptomatic intracerebral hemorrhage occurred in 1 of 9 patients with CCM versus 11 of 341 patients without CCM (P=0.27). Parenchymal hemorrhage occurred in 2 of 9 patients with CCM versus 27 of 341 patients (P=0.17) without CCM.

Conclusions—Given the limitations of our study (mainly low number of patients with CCM), the risk of thrombolysis-associated hemorrhage in patients with CCM remains uncertain. Although our data do not suggest an increased hazard from thrombolysis in patients with CCM, larger studies are necessary to determine definitively the influence of CCMs on parenchymal hemorrhage and symptomatic intracerebral hemorrhage. (Stroke. 2014;45:1846-1848.)

Key Words: hemangioma, cavernous ■ hemangioma, cavernous, central nervous system ■ hemorrhage ■ stroke ■ thrombolytic therapy

Arteriovenous malformations and previous hemorrhage are absolute contraindications for intravenous thrombolysis with recombinant tissue-type plasminogen activator (r-tPA) in acute ischemic stroke. However, some of the contraindications for the use of r-tPA were developed without sufficient safety data, and additional data are needed to inform on the risk of hemorrhage after thrombolysis. Cerebral cavernous malformations (CCMs), which consist of clusters of sinuses covered by a single layer of endothelium, are not explicitly named as a contraindication. The reliable diagnosis of CCMs requires use of MRI. The incremental use of MRI in acute stroke care uncovers an increasing number of CCMs in patients with acute ischemic stroke and confronts the physician with the question of their clinical relevance. We addressed this question by assessing (1) frequency of coexistent CCM in patients with acute ischemic stroke receiving intravenous r-tPA, and (2) frequency of symptomatic intracerebral hemorrhage (sICH) or parenchymal intracerebral hemorrhage (PH) in these patients.

Methods

Study Population and Data Acquisition
All consecutive patients who received intravenous r-tPA in our tertiary care hospital (Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin) between January 2008 and October 2013 were retrospectively analyzed. Baseline characteristics of our single-center thrombolysis register have been described before. Patients with additional thrombectomy or intra-arterial thrombolysis were not included because of potentially different risk for ICH. Diagnosis of CCM was based on MRI (3 T, Siemens, TimTrio) and confirmed by a neuroradiologist (J.B. Fiebach). Imaging protocol included T2*, diffusion-weighted imaging (DWI), time-of-flight MR-angiography, fluid-attenuated inversion recovery, and perfusion imaging. Based on their appearance on MRI, CCMs were classified into 4 subtypes...
Type I lesions represent subacute hemorrhage with hyperintensity on T1 and T2 sequences. Type II CCMs appear reticulated and show a mixed signal on T1 and T2 sequences. They represent varying states of organization of intralesional blood. Type III cavernomas represent chronic hemorrhage; they appear hypointense on T1 and T2 sequences and show a characteristic hypointense rim on T2* sequence. Punctate (type IV) CCMs were not included into our analysis because they are indistinguishable from cerebral microbleeds on MRI. CCM is not considered a contraindication for intravenous r-tPA at our center. All patients received follow-up imaging and 6-hourly neurological assessments. The primary end point was sICH according to European Cooperative Acute Stroke Study III (ECASS III) criteria (any intracranial hemorrhage associated with clinical deterioration, as defined by an increase of ≥2 points on the National Institutes of Health Stroke Scale, or that led to death). The secondary end point was any PH.

**Statistical Analysis**

For comparisons between patients with and without CCM, the Fisher exact test was used. For calculation of 95% confidence intervals (CI) for proportions, the Wilson method score was used. All tests were 2 sided, and a P value of <0.05 was considered as statistically significant. SPSS version 19 was used for data analysis.

**Results**

In a total of 967 patients treated with intravenous r-tPA, 350 patients underwent MRI before treatment. The median age was 76 years (interquartile range, 68–84 years), the median stroke severity measured by National Institutes of Health Stroke Scale was 8 (interquartile range, 5–14), and 51.4% were women. The median blood glucose on admission was 6.8 mmol/L (interquartile range, 6.0–8.3 mmol/L), and the median onset-to-treatment time was 122 minutes (interquartile range, 100–170 minutes).

None of the patients had a history of known CCM before the index stroke. All CCMs were found incidentally in T2* sequence before thrombolysis. At least 1 CCM was present in 9 patients (2.6%). Seven patients harbored 1 CCM, and 2 patients had multiple CCMs, with a total number of 12 CCMs in all patients. The subtype of CCMs was type III in 9 cases and type I in 3 cases. sICH occurred in 12 patients (3.4%). sICH was not observed statistically more often in patients with CCM compared with patients without CCM (1 of 9 versus 11 of 341 patients; or 11.1% [95% CI [2.0–43.5]] versus 3.2% [95% CI [1.8–5.7]]; P=0.27). PH was seen in 29 patients (8.3%). The frequency of PH was not significantly higher in patients with CCM compared with those without CCM (2 of 9 versus 27 of 341; or 22.2% [95% CI [6.3–54.7]] versus 7.9% [95% CI [5.5–11.3]]; P=0.17). Details of all patients with CCMs are described in Table I in the online-only Data Supplement.

The patient with CCM and sICH, a 93-year-old woman, had 2 type III CCMs. She was receiving insufficient anticoagulative therapy with phenprocoumon (international normalized ratio 1.52). After thrombolysis, she had a symptomatic PH into the infarced area, which was remote from both CCMs.

The patient with CCM and PH, an 81-year-old man, had 3 CCMs (1 type I and 2 type III); hemorrhage occurred at the site of the type I CCM and was associated with clinical worsening (2 points on the National Institutes of Health Stroke Scale attributable to new hemianopsia; Figure). He was receiving antithrombotic therapy with aspirin 100 mg before thrombolysis. This patient showed no hyperintensity on DWI or any arterial occlusion, but only a deficit on perfusion maps.

Thrombolysis was performed because of aphasia, which was attributed to the perfusion deficit. Imaging showed no DWI hyperintensity on follow-up MRI. Aphasia resolved after starting anticonvulsant medication.

A total of 617 patients received thrombolytic therapy after initial computed tomographic (CT) imaging. In 327 patients (53.0%), a brain MRI was performed during their later course of hospitalization. A CCM was found in 11 (3.4%) patients. None of these patients developed a sICH or a PH after thrombolysis.

**Discussion**

To our knowledge, this is the first systematic analysis on intracerebral bleeding risk attributable to r-tPA in patients with acute stroke with coexisting CCM. We did not find a significantly higher risk of sICH or PH in patients with CCM. However, the proportions of sICH or PH after thrombolysis were relatively high in patients with CCM. Considering the wide 95% CIs for sICH and PH, the risk of ICH could be higher in patients with concomitant CCM than in patients without CCM.

We found that ICH occurred at the site of the pre-existing type I CCM in a case, and led to clinical worsening. Interestingly, this patient presented clinically with new onset aphasia, which was interpreted as attributable to acute ischemic stroke because of a deficit on perfusion imaging. However, imaging did not show a DWI lesion. Aphasia resolved after

Figure. MR imaging of a patient with left occipital cerebral cavernous malformation (CCM) and thrombolysis-associated parenchymal hemorrhage at site of CCM. The patient developed a new hemianopsia. **A**, T2*-sequence image depicting a left occipital CCM (type I) before thrombolysis, and **B** T2*-sequence image showing parenchymal hemorrhage at the site of CCM after thrombolysis.
beginning anticonvulsant medication, suggesting that the clinical syndrome in this patient may have been a stroke mimic attributable to a focal seizure. Of note, seizures are among the most frequent clinical presentations of CCMs. Type I CCMs, which represent CCMs with subacute hemorrhage, are more prone to become symptomatic than type III or IV CCMs.2

To date, only 2 case reports on safety of thrombolysis in patients with CCM exist.6,7 Gattringer et al6 report a patient with CCM who developed sICH after thrombolysis. In this patient, bleeding occurred at the site of the previously diagnosed CCM. The CCM was seen on a CT scan before thrombolysis, and therefore was probably a type I or II CCM (because type III and IV CCMs are not visible on CT imaging).2 Considering that DWI on MRI after thrombolysis was negative in this patient, they also discussed the possibility of having treated a stroke mimic.6 Therefore, one may speculate that the risk of ICH is higher in patients with symptomatic type I or II CCM and that ICH preferentially occurs at the site of CCM.

Another finding of our study is the relatively high proportion of patients with CCM (2.6%) compared with the general population (0.3%–0.5%).2 The higher frequency of CCMs in our cohort may be explained by use of a 3-T MRI with T2* sequence, which increases the sensitivity for detecting CCMs.7 We additionally identified 11 patients with CCMs in MRI after initial CT-based thrombolysis. However, because inclusion of these patients into the analysis could introduce a bias, we decided not to include them in our main analysis. In patients with hemorrhage after thrombolysis, hemorrhage may conceal an underlying CCM. CCM in these patients would be overseen. Consequently, the risk of hemorrhage in patients with CCM could seem falsely lower.

The main limitation of our study is the low number of patients with CCM and ICH after thrombolysis, which might lead to a type II error. Our study may be further limited by a possible selection bias. We have previously shown that patients undergoing MRI before thrombolysis have less cardiac comorbidities and lower rates of sICH and 7-day mortality compared with patients receiving CT imaging before thrombolysis.3 However, this applies to patients with and without CCM, and this bias should not affect the relative risk for sICH and PH between both compared groups. Another limitation is the retrospective and monocentric design of our study, possibly limiting the extent to which our results could be generalized.

Conclusions
Clinical worsening attributable to thrombolysis occurred in 2 of 9 patients with CCMs. Patients with CCMs may have seizures attributable to subacute hemorrhage and present as stroke mimics. Larger multicenter registries are needed to further evaluate the risk of hemorrhage after thrombolysis in patients with CCM and to calculate the risk for dependent clinical outcome.

Disclosures
Dr Erdur received a travel grant from the manufacturer of recombinant tissue-type plasminogen activator. Boehringer Ingelheim (BI). Dr Endres receives funding from the Deutsche Forschungsgemeinschaft (Excellence cluster NeuroCure; SFB TR 43, KFO 247, KFO 213), Bundesministerium für Bildung und Forschung (Centre for Stroke Research Berlin), EU (European Stroke Network, Wake-Up, Counterstroke), Volkswagen Foundation (Lichtenberg Program); has participated in advisory board meetings of Bayer, BI, Bristol-Myers Squibb (BMS), Merck, Pfizer, and Sanofi; and has received honoraria from AstraZeneca, Bayer, BI, Boston Scientific, BMS, Ever, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi. Dr Nolte has served as a consultant for BMS and has received speaker honoraria from BI, Pfizer, and Takeda Pharma. The other authors report no conflicts.

References
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## ONLINE SUPPLEMENT

### Supplementary Table I. Overview of all patients with CCMs.

<table>
<thead>
<tr>
<th>Patient (sex and age)</th>
<th>Number of CCMs</th>
<th>CCM Type*</th>
<th>Localisation</th>
<th>NIHSS on admission</th>
<th>Blood pressure on admission in mmHg</th>
<th>Wahlund-Score</th>
<th>DWI lesion</th>
<th>Post rt-PA imaging</th>
<th>sICH (ECASS-III)</th>
<th>PH</th>
<th>Antithrombotic or anticoagulative therapy before stroke</th>
<th>Statins before stroke</th>
<th>mRS after 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1 (♀, 87)</td>
<td>1</td>
<td>III</td>
<td>Pons</td>
<td>7</td>
<td>150/90</td>
<td>4</td>
<td>Yes (left MCA)</td>
<td>MRI</td>
<td>No</td>
<td>Yes (left MCA)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No. 2 (♀, 89)</td>
<td>1</td>
<td>III</td>
<td>Right temporobasal</td>
<td>15</td>
<td>190/120</td>
<td>4</td>
<td>Yes (left MCA)</td>
<td>CT</td>
<td>No</td>
<td>No</td>
<td>Aspirin 100 mg</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>No. 3 (♀, 73)</td>
<td>1</td>
<td>I</td>
<td>Right temporal</td>
<td>7</td>
<td>183/95</td>
<td>6</td>
<td>Yes (left thalamic)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
<td>Aspirin 100 mg</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>No. 4 (♀, 90)</td>
<td>1</td>
<td>III</td>
<td>Pons</td>
<td>18</td>
<td>134/87</td>
<td>12</td>
<td>Yes (left MCA)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>No. 5 (♀, 60)</td>
<td>1</td>
<td>I</td>
<td>Left parietal</td>
<td>5</td>
<td>163/100</td>
<td>2</td>
<td>Yes (right anterior choroidal artery)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No. 6 (♀, 79)</td>
<td>1</td>
<td>III</td>
<td>Right frontal</td>
<td>8</td>
<td>127/68</td>
<td>4</td>
<td>Yes (left MCA)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
<td>Aspirin 100 mg</td>
<td>Pravastatin 30 mg</td>
<td>0</td>
</tr>
<tr>
<td>No. 7 (♀, 72)</td>
<td>1</td>
<td>III</td>
<td>Pons</td>
<td>4</td>
<td>117/60</td>
<td>16</td>
<td>Yes (left MCA)</td>
<td>MRI</td>
<td>No</td>
<td>No</td>
<td>Aspirin 100 mg</td>
<td>Simvastatin 20 mg</td>
<td>4</td>
</tr>
<tr>
<td>No. 8 (♀, 81)</td>
<td>3</td>
<td>I and III</td>
<td>Left occipital (Type I) and two left periventricular (Type III)</td>
<td>2</td>
<td>178/105</td>
<td>14</td>
<td>No</td>
<td>MRI</td>
<td>No (but new onset hemianopsia)</td>
<td>Yes (into Type I CCM)</td>
<td>Aspirin 100 mg</td>
<td>Simvastatin 10 mg</td>
<td>1</td>
</tr>
<tr>
<td>No. 9 (♀, 93)</td>
<td>2</td>
<td>III</td>
<td>Left temporal, left cerebellar</td>
<td>10</td>
<td>148/88</td>
<td>10</td>
<td>Yes (left MCA)</td>
<td>CT</td>
<td>Yes</td>
<td>Yes (remote from Phenprocoumon (INR 1.52))</td>
<td>No</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
*Classification according to Zabramski et al. Abbreviations: CCM, cerebral cavernous malformation; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion weighted imaging; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral hemorrhage; ECASS, European Cooperative Acute Stroke Study; PH, parenchymal hemorrhage; mRS, modified Rankin Scale; MCA, middle cerebral artery; MRI, magnetic resonance imaging; CT, computed tomography; INR, international normalized ratio.

References