Stroke
Journal of the American Heart Association

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

Steffen Dannenberg, Jan F. Scheitz, Michal Rozanski, Hebun Erdur, Peter Brunecker, David J. Werring, Jochen B. Fiebach and Christian H. Nolte

Stroke. 2014;45:2900-2905; originally published online August 12, 2014;
doi: 10.1161/STROKEAHA.114.006448
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

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 Brunecker, 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

Approximately 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 impairs 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 disease[5,7] and have been linked to occurrence of future ICH.[8] 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.[4,9,10] 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

Received June 12, 2014; final revision received July 16, 2014; accepted July 23, 2014.

From the Klinik und Hochschulambulanz für Neurologie (S.D., J.F.S., M.R., H.E., C.H.N.), Center for Stroke Research (J.F.S., M.R., P.B., J.B.F., C.H.N.), and Excellence Cluster NeuroCure (J.F.S.), Charité–Universitätsmedizin Berlin, Berlin, Germany; Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, London, United Kingdom (D.J.W.); and The National Hospital for Neurology and Neurosurgery, London, United Kingdom (D.J.W.).

Guest Editor for this article was Emmanuel Touzé, PhD.

*S. Dannenberg and Dr Scheitz contributed equally.

Presented in part at the European Stroke Conference, Nice, France, May 6–9, 2014.

Correspondence to Jan F. Scheitz, MD, Department of Neurology, Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany. E-mail jan-friedrich.scheitz@charite.de

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.114.006448**

studies have not clearly established whether the number of CMBs affects sICH risk.[10–17] Recently, Gratz et al[18] 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,[19] 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.[22]

CMB Definition and Detection

CMBs were defined according to recent consensus recommendations for MRI studies on cerebral small vessel disease.[23] 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.[5,23]

CMBs on the prethrombolysis 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.[10] Presumed pathogenesis of CMBs was categorized in 3 groups: possible cerebral amyloid angiopathy (CAA), hypertensive, or undetermined.[5,18,24] 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.[24] 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).[25] PH was defined radiologically as hematoma with at least some mild space-occupying effect.[26] 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 prethrombolysis 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

Table 1. Baseline Characteristics and Univariate Comparisons for sICH and PH

	All (n=326)	No sICH (n=316)	sICH (n=10)	*P* Value	No PH (n=303)	PH (n=23)	*P* Value
Age, y, median (IQR)	76 (68–84)	75 (68–84)	81 (73–90)	0.09	75 (67–84)	78 (73–85)	0.09
Male sex, % (n)	48.8 (159)	48.1 (152)	70.0 (7)	0.21	48.2 (146)	56.5 (13)	0.52
Risk factors							
Atrial fibrillation, % (n)	39.3 (128)	38.3 (121)	70.0 (7)	0.05	38.9 (118)	43.5 (10)	0.67
Diabetes mellitus, % (n)	22.7 (74)	22.5 (71)	30.0 (3)	0.70	22.1 (67)	30.4 (7)	0.44
Hyperlipidemia, % (n)	52.5 (171)	52.8 (167)	40.0 (4)	0.53	51.8 (157)	60.9 (14)	0.52
Hypertension, % (n)	85.0 (277)	85.4 (270)	70.0 (7)	0.18	85.1 (258)	82.6 (19)	0.76
Prior stroke, % (n)	24.5 (80)	24.7 (78)	20.0 (2)	1.00	23.8 (72)	34.8 (8)	0.31
Medication history							
Prior statin therapy, % (n)	22.5 (73)	22.2 (70)	30.0 (3)	0.70	20.9 (63)	43.5 (10)	0.02
Prior antiplatelet therapy, % (n)	45.7 (149)	46.5 (147)	20.0 (2)	0.12	45.9 (139)	43.5 (10)	1.00
Prior oral anticoagulation, % (n)	1.5 (5)	1.3 (4)	10.0 (1)	0.15	1.3 (4)	4.3 (1)	0.31
Clinical and imaging parameters on admission							
NIHSS score, median (IQR)	8 (5–14)	8 (4–14)	9 (7–15)	0.39	8 (4–14)	10 (5–16)	0.21
Systolic blood pressure, mm Hg, median (IQR)	155 (140–172)	155 (140–172)	160 (154–196)	0.10	155 (140–170)	160 (150–193)	0.07
Diastolic blood pressure, mm Hg, median (IQR)	85 (74–95)	84 (73–95)	91 (80–102)	0.18	84 (73–95)	90 (78–96)	0.45
Onset-to-treatment time, min, median (IQR)	140 (107–207)	138 (105–205)	205 (144–362)	0.06	135 (105–202)	180 (125–594)	0.04
Baseline glucose, mmol/L, median (IQR)	6.77 (5.99–8.19)	6.77 (5.99–8.20)	7.27 (6.44–8.27)	0.48	6.77 (5.99–8.16)	7.05 (5.84–8.28)	1.00
ARWMC score, median (IQR)	6 (4–10)	6 (4–10)	10 (4–15)	0.17	6 (4–10)	9 (4–15)	0.04
CMB parameters							
Any CMB, % (n)	24.8 (81)	23.4 (74)	70.0 (7)	<0.01	23.8 (72)	39.1 (9)	0.13
CMB number, median (IQR)	0 (0–1)	0 (0–0)	2 (0–12)	<0.01	0 (0–0)	0 (0–2)	0.03
No CMB, % (n)	75.2 (245)	76.6 (242)	30.0 (3)	<0.01*	76.2 (231)	60.9 (14)	<0.01*
1 CMB, % (n)	16.0 (52)	15.8 (50)	20.0 (2)		16.5 (50)	8.7 (2)	
2–4 CMBs, % (n)	5.8 (19)	5.4 (17)	20.0 (2)		5.0 (15)	17.4 (4)	
≥5 CMBs, % (n)	3.1 (10)	2.2 (7)	30.0 (3)		2.3 (7)	13.0 (3)	

ARWMC indicates Age-Related White Matter Changes; CMB, cerebral microbleed; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; and sICH, symptomatic intracerebral hemorrhage.

**P* for trend and overall *P* value.

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 ≥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, 1.07–1.33; *P*<0.01) for sICH and 1.13 (95% CI, 1.03–1.24; *P*=0.01) for PH. Figure 2 illustrates 2 examples of patients with multiple CMBs (both ≥5 CMBs) on pretreatment MRI who developed sICH after IVT.

The association of CMB number with sICH and PH remained significant after adjustment for age, prior statin use, systolic blood pressure on admission, atrial fibrillation, Age-related White Matter Changes score, and onset-to-treatment time (Table 2). In addition to higher CMB numbers, higher blood pressure (OR, 1.23; 95% CI, 1.03–1.46, 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 ≥2 CMBs (not exclusively lobar or exclusively nonlobar). 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;

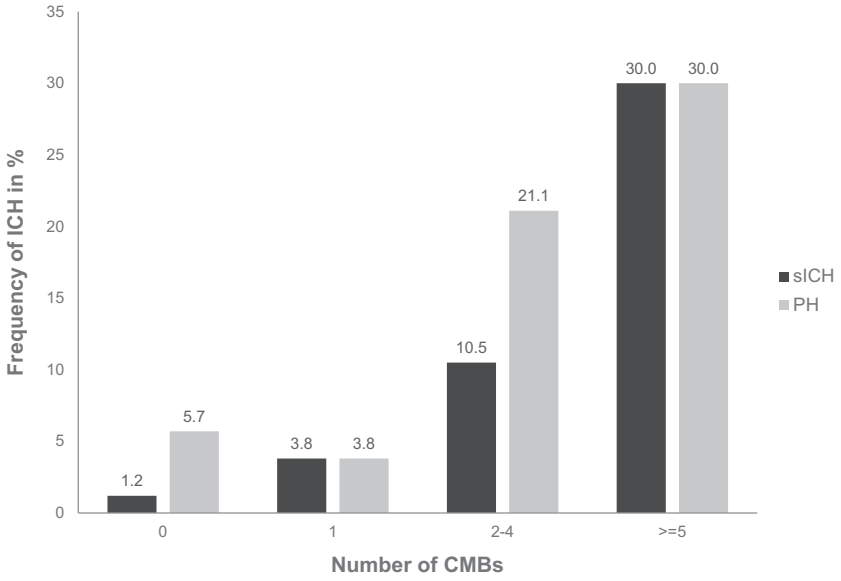

Figure 1. Frequency of symptomatic intracerebral hemorrhage (sICH) and parenchymal hemorrhage (PH) according to number of cerebral microbleeds (CMBs).

50.6%). 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.[15] 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.[10] In a pooled analysis of the BRASIL data and the study by Kim et al[15] including 635 patients with stroke receiving IVT or intra-arterial thrombolysis, a similar relationship of CMB burden and risk of any ICH was observed.[17] Notwithstanding, these studies were highly heterogeneous regarding MRI acquisition, study populations, and treatment protocols. A recent study by Gratz et al[18] 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

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

	sICH		PH		Favorable Outcome*	
	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Unadjusted OR (95% CI)	Adjusted‡ OR (95% CI)
No CMB	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1 CMB	3.23 (0.53–19.81)	3.38 (0.54–21.20)	0.66 (0.15–3.00)	0.71 (0.15–3.34)	0.58 (0.32–1.08)	0.92 (0.43–1.98)
2–4 CMBs	9.49 (1.48–60.69)	7.75 (1.17–51.44)	4.40 (1.29–15.02)	4.62 (1.26–17.02)	0.75 (0.29–1.91)	1.10 (0.33–3.63)
≥5 CMBs	34.57 (5.90–202.55)	42.65 (6.69–271.96)	7.07 (1.65–30.33)	6.15 (1.29–29.40)	0.09 (0.01–0.74)	0.24 (0.02–2.61)

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 Whiter 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 Whiter Matter Changes score, and sICH).

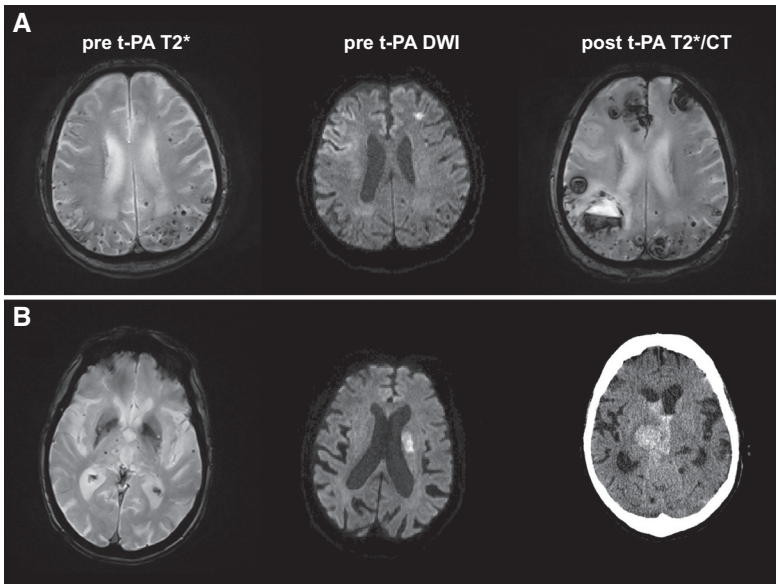

Figure 2. Imaging of 2 patients with multiple cerebral microbleeds (CMBs) who developed intracerebral hemorrhage after thrombolysis. **A**, An 84-year-old man with dysarthria, left-sided hemiparesis, and hemineglect (Age-Related White Matter Changes [ARWMC] score, 10). **Left**, Multiple CMBs in predominantly lobar distribution on pretreatment MRI. **Middle**, Diffusion-weighted imaging (DWI) shows diffusion restriction in the territory of right middle cerebral artery (MCA, frontotemporal) and left MCA (frontal). **Right**, Multiple parenchymal hemorrhages on post-thrombolysis MRI. **B**, An 89-year-old woman with sudden dysarthria and right-sided hemiparesis (ARWMC score, 15). **Left**, Multiple CMBs in predominantly deep localization on pretreatment MRI. **Middle**, Diffusion restriction in the left MCA territory on DWI. **Right**, Parenchymal hemorrhage on post-thrombolysis computed tomography (CT). t-PA indicates tissue-type plasminogen activator.

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.[10–12,14,18] 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).[10–12,15,18,27]

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.[28] 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.[29] Because CMBs are not detectable with plain CT, our findings suggests 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.[30] Moreover, higher blood pressure on admission was confirmed to be associated with thrombolysis-related ICH.[31]

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.[18] 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.[32] 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.[33] 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.

Sources of Funding

The research has received funding from the German Federal Ministry of Education and Research via the grant Center for Stroke Research Berlin (01 EO 0801). Dr Scheitz is a participant in the Charité Clinical Scientist Program funded by the Charité–Universitätsmedizin Berlin and the Berlin Institute of Health.

Disclosures

Dr Fiebach received honoraria for lectures from Boehringer Ingelheim (BI). Dr Nolte received consulting lectures and travel grants from BI. The other authors report no conflicts.

References

1. Seet RC, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. *Cerebrovasc Dis*. 2012;34:106–114.
2. Strbian D, Sairanen T, Meretoja A, Pitkäniemi J, Putaala J, Salonen O, et al; Helsinki Stroke Thrombolysis Registry Group. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology*. 2011;77:341–348.
3. Derex L, Nighoghossian N. Intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: an update. *J Neurol Neurosurg Psychiatry*. 2008;79:1093–1099.
4. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and the risk of intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013;84:277–280.
5. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165–174.
6. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. *Cerebrovasc Dis*. 2011;32:528–534.
7. Park JH, Seo SW, Kim C, Kim GH, Noh HJ, Kim ST, et al. Pathogenesis of cerebral microbleeds: in vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. *Ann Neurol*. 2013;73:584–593.
8. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts. *Stroke*. 2013;44:995–1001.
9. Charidimou A, Fox Z, Werring DJ. Do cerebral microbleeds increase the risk of intracerebral hemorrhage after thrombolysis for acute ischemic stroke? *Int J Stroke*. 2013;8:E1–E2.
10. Fiehler J, Albers GW, Boulanger JM, Derex L, Gass A, Hjort N, et al; MR STROKE Group. Bleeding risk analysis in stroke imaging before thromboLysis (BRASIL): pooled analysis of T2*-weighted magnetic resonance imaging data from 570 patients. *Stroke*. 2007;38:2738–2744.
11. Derex L, Nighoghossian N, Hermier M, Adeleine P, Philippeau F, Honnorat J, et al. Thrombolysis for ischemic stroke in patients with old microbleeds on pretreatment MRI. *Cerebrovasc Dis*. 2004;17:238–241.
12. Kakuda W, Thijs VN, Lansberg MG, Bammer R, Wechsler L, Kemp S, et al; DEFUSE Investigators. Clinical importance of microbleeds in patients receiving IV thrombolysis. *Neurology*. 2005;65:1175–1178.
13. Kato H, Izumiyama M, Izumiyama K, Takahashi A, Itoyama Y. Silent cerebral microbleeds on T2*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. *Stroke*. 2002;33:1536–1540.
14. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K, et al. Magnetic resonance imaging detection of microbleeds before thrombolysis: an emerging application. *Stroke*. 2002;33:95–98.
15. Kim HS, Lee DH, Ryu CW, Lee JH, Choi CG, Kim SJ, et al. Multiple cerebral microbleeds in hyperacute ischemic stroke: impact on prevalence and severity of early hemorrhagic transformation after thrombolytic treatment. *AJR Am J Roentgenol*. 2006;186:1443–1449.
16. Nighoghossian N, Hermier M, Adeleine P, Blanc-Lasserre K, Derex L, Honnorat J, et al. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: a gradient-echo T2*-weighted brain MRI study. *Stroke*. 2002;33:735–742.
17. Shoamanesh A, Kwok CS, Lim PA, Benavente OR. Postthrombolysis intracranial hemorrhage risk of cerebral microbleeds in acute stroke patients: a systematic review and meta-analysis. *Int J Stroke*. 2013;8:348–356.
18. Gratz PP, El-Koussy M, Hsieh K, von Arx S, Mono ML, Heldner MR, et al. Preexisting cerebral microbleeds on susceptibility-weighted magnetic resonance imaging and post-thrombolysis bleeding risk in 392 patients. *Stroke*. 2014;45:1684–1688.
19. Tütüncü S, Ziegler AM, Scheitz JF, Slowinski T, Rocco A, Endres M, et al. Severe renal impairment is associated with symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke. *Stroke*. 2013;44:3217–3219.
20. Thomalla G, Cheng B, Ebinger M, Hao Q, Tourdias T, Wu O, et al; STIR and VISTA Imaging Investigators. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurol*. 2011;10:978–986.
21. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al; European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322.
22. Hotter B, Pittl S, Ebinger M, Oepen G, Jegzentis K, Kudo K, et al. Prospective study on the mismatch concept in acute stroke patients within the first 24 h after symptom onset - 1000Plus study. *BMC Neurol*. 2009;9:60.
23. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838.
24. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology*. 2001;56:537–539.
25. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
26. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke*. 1999;30:2280–2284.
27. Stehling C, Wersching H, Kloska SP, Kirchhof P, Ring J, Nassenstein I, et al. Detection of asymptomatic cerebral microbleeds: a comparative study at 1.5 and 3.0 T. *Acad Radiol*. 2008;15:895–900.
28. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology*. 2008;70:1208–1214.
29. McCarron MO, Nicoll JA. Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. *Lancet Neurol*. 2004;3:484–492.
30. Scheitz JF, Seiffge DJ, Tütüncü S, Gensicke H, Audebert HJ, Bonati LH, et al. Dose-related effects of statins on symptomatic intracerebral hemorrhage and outcome after thrombolysis for ischemic stroke. *Stroke*. 2014;45:509–514.
31. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al; SITS Investigators. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke*. 2012;43:1524–1531.
32. Gerischer LM, Fiebach JB, Scheitz JF, Audebert HJ, Endres M, Nolte CH. Magnetic resonance imaging-based versus computed tomography-based thrombolysis in acute ischemic stroke: comparison of safety and efficacy within a cohort study. *Cerebrovasc Dis*. 2013;35:250–256.
33. Singer OC, Humpich MC, Fiehler J, Albers GW, Lansberg MG, Kastrup A, et al; MR Stroke Study Group Investigators. Risk for symptomatic intracerebral hemorrhage after thrombolysis assessed by diffusion-weighted magnetic resonance imaging. *Ann Neurol*. 2008;63:52–60.