New remote cerebral microbleeds in acute ischemic stroke: an analysis of the randomized, placebo-controlled WAKE-UP trial

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LETTER TO THE EDITORS

New remote cerebral microbleeds in acute ischemic stroke: an analysis of the randomized, placebo-controlled WAKE-UP trial

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Abbreviations

AIS	Acute ischemic stroke
CAA	Cerebral amyloid angiopathy
CMB	Cerebral microbleed
ICH	Intracranial hemorrhage
IVT	Intravenous thrombolysis
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
SD	Standard deviation

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Dear Sirs,

Cerebral microbleeds (CMB), detected as hypointense foci on blood-sensitive magnet resonance imaging (MRI), are a marker of cerebral small vessel disease [1]. Neuropathological examinations revealed that a subset of CMBs contain intact erythrocytes, indicating recent microhemorrhage [1]. In a prior observational study, new CMBs occurred in 4% of acute ischemic stroke (AIS) patients after receiving intravenous thrombolysis (IVT) with alteplase. New CMBs were associated with an increased risk for post-IVT intracerebral hemorrhage [2].

Here, we took the unique opportunity to assess the risk of IVT for the occurrence of new CMBs in AIS patients who had been randomly assigned to either alteplase (0.9 mg/kg) or placebo within the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke, ClinicalTrials.gov: NCT01525290)[3].

Eligible patients for this exploratory analysis had received two cerebral MRI examinations—one before and one after treatment (alteplase or placebo)—with the same field strength (i.e., 1.5 Tesla or 3 Tesla) and the same blood-sensitive MRI sequence (i.e., susceptibility weighted imaging (SWI) or T2*/gradient-recalled echo (GRE)). Parameters of the blood-sensitive MRI sequences varied according to center and manufacturer with slice thickness ranging from 1.5 to 7 mm, echo time (TE) from 11 to 51 ms, and repetition time (TR) from 460 to 2460 ms [4].

The CMBs were defined, according to consensus recommendations, as small (up to 10 mm in diameter), round or oval hypointense lesions with associated blooming seen on blood-sensitive MRI sequences [1]. The CMBs were rated by three raters (TBB, JV, LS) blinded to clinical information (with a very good inter-rater reliability as described previously [4]). New CMBs were categorized according to their distribution as lobar, deep (i.e., basal ganglia, thalamus) or infratentorial (i.e., brainstem, cerebellum) [4]. Newly appearing CMBs in the acute infarcted area, as seen on diffusion-weighted imaging, were not classified as new CMBs [2, 4].

Intracranial hemorrhage (ICH) was assessed on follow-up imaging 22 to 36 h after treatment.

The primary outcome was the proportion of patients with new CMBs on follow-up imaging (in the alteplase and placebo group). Secondary outcomes included symptomatic ICH according to the protocol of the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) [5] and degree of disability, quantified on the modified Rankin Scale (mRS) 90 days after treatment (excellent outcome: mRS ≤ 1, severe dependency or death: mRS 4–6) [3].

Of 503 patients included in the WAKE-UP trial, 350 patients were available for final analysis (175 with alteplase, 175 with placebo; 129 patients were not sequentially examined on the same MRI scanners, image quality of the blood-sensitive MRI sequence was too poor for analysis in 24 patients). Patients included in the final analysis did not differ regarding age and sex compared to excluded patients (mean age: 64.7 [patients included, standard deviation [SD]: 11.8] vs. 66.3 [patients excluded, SD: 10.8], $p = 0.15$, t test; female: 120/350 [34.3%] vs. 58/153 [37.9%], $p = 0.50$, chi-squared test). However, there were fewer ICH in patients included in the final analysis (76/350 [22%] vs. 47/146 [32%]; $p = 0.02$, chi-squared test).

New CMBs occurred in four patients. Noteworthy, all patients with new CMBs had received alteplase resulting in a rate of 2.3% (4/175 patients; 95% confidence interval: 0.6–5.8%). Three patients had one new CMB and one patient had two new CMBs. Distribution of new CMBs was strictly lobar in all four patients (a pattern suggestive of underlying cerebral amyloid angiopathy [1, 6]) and preexisting CMBs were present in all patients with new CMBs. One patient with new CMBs had a severe stroke with an NIHSS score of 20 on admission. Any ICH occurred in two patients with new CMBs (hemorrhagic transformation of the infarcted brain tissue (HI2, Class 1b) in one patient and intracerebral hemorrhage within and beyond the infarcted brain tissue (PH2, Class 2) in the other patient [7]). One new CMB occurred contralateral to the hemorrhagic transformation (HI2, Class 1b) in one patient, two new CMBs occurred ipsilateral to the intracerebral hemorrhage (PH2, Class 2) in the other patient. Symptomatic ICH according to SITS-MOST occurred in one patient with new CMBs. Of note, of 76 patients with any ICH, 74 ICHs occurred in patients without new CMBs. At 90 days, one patient with new CMBs achieved an excellent functional outcome (mRS ≤ 1) and two patients with new CMBs had either died or had severe disability. Further details are shown in Table 1. Due to the small number of patients with new CMBs, no inferential statistical analysis was performed.

In this exploratory analysis of the randomized, placebo-controlled WAKE-UP trial, new CMBs occurred exclusively after receiving alteplase.

In the recently published THAWS trial (THrombolysis for Acute Wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial [conducted in Japan]), new CMBs occurred in seven out of 113 AIS patients and were associated with poor neurological outcome [8]. In both study cohorts (WAKE-UP and THAWS) new CMBs occurred only in AIS patients receiving alteplase (as opposed to placebo).

The small number of outcomes, the lack of an inferential statistical analysis, a possible selection bias (ICH occurred more often in patients excluded from this analysis) as well as varying parameters of the blood-sensitive MRI sequences (e.g. slice thickness) in the different centers have to be taken into account when interpreting our findings. However, by

Table 1 Baseline characteristics and outcomes of patients with and without new cerebral microbleeds

	All ($n=350$)	No new CMBs ($n=346$)	New CMBs ($n=4$)
Demographics			
Age, mean (SD)	64.7 (11.8)	64.7 (11.9)	55, 59, 74, 74[a]
Male, % (n)	230 (65.7%)	226 (65.3%)	4/4 (100%)
Risk factors, % (*n*)			
Atrial fibrillation	40 (11.6%)	40 (11.7%)	0/4 (0%)
Diabetes mellitus, type 2	50 (14.5%)	49 (14.3%)	1/4 (25%)
Arterial hypertension	183 (52.4%)	181 (52.5%)	2/4 (50%)
History of ischemic stroke	45 (12.9%)	45 (13.0%)	0/4 (0%)
On admission			
NIHSS score, median (IQR)	5 (3;8)	5 (3;8)	1, 5, 6, 20[a]
Platelet aggregation inhibitors, n (%)	108 (30.9%)	107 (30.9%)	1/4 (25%)
Statins, *n* (%)	108 (30.9%)	105 (30.3%)	3/4 (75%)
MRI characteristics, *n* (%)			
Blood-sensitive sequence			
T2*/GRE	322 (92%)	319 (92.2%)	3/4 (75%)
SWI	28 (8%)	27 (7.8%)	1/4 (25%)
Field strength			
1.5 Tesla	175 (50%)	173 (50%)	2/4 (50%)
3 Tesla	175 (50%)	173 (50%)	2/4 (50%)
Time interval between treatment and follow-up MRI, hours, median (IQR)[b]	25.5 (23.5;28.3)	25.6 (23.5;28.3)	22.7, 24.1, 24.5, 29.6[a]
Pretreatment MRI findings			
CMB presence on pretreatment MRI, *n* (%)	68 (19.4%)	64 (18.5%)	4/4 (100%)
Number of CMBs on pretreatment MRI, median (IQR)	0 (0;0)	0 (0;0)	1, 1, 5, 5[a]
Number of CMBs on pretreatment MRI, *n* (%)			
0	282 (80.6%)	282 (81.5%)	0/4 (0%)
1	32 (9.1%)	30 (8.7%)	2/4 (50%)
2–4	23 (6.6%)	23 (6.6%)	0/4 (0%)
≥5	13 (3.7)	11 (3.2%)	2/4 (50%)
CMBs with a strictly lobar distribution on pretreatment MRI, *n* (%)	32/68 (47.1%)	29/64 (45.3%)	3/4 (75%)
CMBs with a mixed or strictly deep distribution on pretreatment MRI, *n* (%)	30/68 (44.1%)	30/64 (46.9%)	0/4 (0%)
Diffusion-weighted imaging lesion volume at baseline, mL, median (IQR)[c]	1.9 (0.7;7.1)	1.9 (0.7;7.1)	0.7, 2.6, 6.3, 18.0
Lacunar infarcts, *n* (%)	82 (23.4%)	82 (23.7%)	0/4 (0%)
Treatment, *n* (%)			
Alteplase	175 (50%)	171 (49.4%)	4/4 (100%)
Placebo	175 (50%)	175 (50.6%)	0/4 (0%)
Outcomes			
Any intracranial hemorrhage after treatment, *n* (%)	76 (21.7%)	74 (21.4%)	2/4 (50%)
Symptomatic intracranial hemorrhage after treatment (SITS-MOST), *n* (%)	3 (0.9%)	2 (0.6%)	1/4 (25%)
mRS at 90 days, median (IQR)	1 (1;3)	1 (1;3)	1, 2, 5, 5[a]
Excellent outcome (mRS ≤ 1) at 90 days, n (%)	176 (50.9%)	175 (51.2%)	1/4 (25%)
Severe dependency or death (mRS 4–6) at 90 days, *n* (%)	42 (12.1%)	40 (11.7%)	2/4 (50%)

CMBs cerebral microbleeds, *GRE* gradient-recalled echo, *IQR* interquartile range, *MRI* magnetic resonance imaging, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *SD* standard deviation, *SITS-MOST* Safe Implementation of Thrombolysis in Stroke–Monitoring Study, and *SWI* susceptibility weighted imaging

[a]Due to the small number of outcomes, quantitative variables (age, NIHSS score, time interval between treatment and follow-up MRI, number of CMBs on pretreatment MRI, diffusion-weighted imaging lesion volume at baseline, mRS at 90 days) are reported as single values in patients with new CMBs ($n=4$)

[b]The variable time interval between treatment and follow-up MRI was known in 345 patients without new CMBs

[c]The variable diffusion-weighted imaging lesion volume at baseline was known in 343 patients without new CMBs

comparing to placebo we were able to assess the effect of alteplase for the occurrence of new CMBs, thereby extending the knowledge of previous observational studies. Considering our results as well as the above-mentioned results from the THAWS trial, there is now accumulating evidence that alteplase contributes to the development of new CMBs in AIS patients. Although new CMBs occur rarely, our data call for further studies to determine if these new CMBs after receiving alteplase increase the risk of poor neurological outcome in AIS patients.

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Declarations

Conflicts of interest Dr. Braemswig is a participant in the Berlin Institute of Health-Charité Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health. Dr. Simonsen reports research grants from Novo Nordisk Foundation and Health Research Foundation of Central Denmark Region. Prof. Scheitz is participant in the BIH-Charité Advanced Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health. Prof. Fiebach reports personal fees from Abbvie, AC Immune, Artemida, Bioclinica, Biogen, BMS, Brainomix, Cerevast, Daiichi-Sankyo, Eisai, Eli Lilly, Guerbet, Ionis Pharmaceuticals, Julius clinical, jung diagnostics, Merck, Nicolab, and Tau Rx, all outside the submitted work. Prof. Endres received funding from DFG under Germany´s Excellence Strategy – EXC-2049 – 390688087, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq. Prof. Endres reports grants from Bayer and fees paid to the Charité from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work. Prof. Lemmens is a senior clinical investigator of FWO Flanders. Dr. Schlemm is a participant in the Berlin Institute of Health-Charité Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health. Dr. Schlemm reports lecture fees from Daiichi Sankyo, outside of the submitted work. Prof. Nolte is participant of the BIH-Charité Clinical Fellow Program. Prof. Nolte reports lecture fees and/or consultancies from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Pfizer, Alexion, Abbott and Gore & Ass., all outside the submitted work. All other authors declare that they have no conflict of interest.

Ethical approval This is an exploratory analysis of the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke, ClinicalTrials.gov: NCT01525290).[3] For each study site, the trial was approved by the national or local ethics committee or institutional review board, as described previously [3, 4]. Patients or their legal representatives provided written informed consent according to national and local regulations with an exception from explicit informed consent in emergency circumstances in some countries [3, 4].

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