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Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke: An Analysis of the WAKE-UP Randomized Clinical Trial

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ABSTRACT

Background and Objectives Cerebral microbleeds (CMBs) are common in acute ischemic stroke patients and are associated with increased risk of intracerebral hemorrhage (ICH) after intravenous thrombolysis. Whether CMBs modify the treatment effect of thrombolysis is unknown.

Methods We performed a pre-specified analysis of the prospective randomized controlled multicenter WAKE-UP trial including patients with acute ischemic stroke with unknown time of symptom onset and DWI-FLAIR mismatch on MRI receiving alteplase or placebo. Patients were screened and enrolled between September 2012 and June 2017 (with final follow-up in September 2017). Patients were randomized to treatment with intravenous thrombolysis with alteplase at 0.9 mg / kg body weight or placebo. CMB status (presence, number, and distribution) was assessed after study completion by three raters blinded to clinical information following a standardized protocol. Outcome measures were excellent functional outcome at 90 days, defined by modified Rankin Scale score (mRS)≤1, and symptomatic intracerebral hemorrhage (ICH) according to NINDS trial criteria 22 to 36 hours after treatment.

Results Of 503 patients enrolled in the WAKE-UP trial, 459 (91.3%; 288 [63%] men) were available for analysis; 98 (21.4%) had at least 1 CMB on baseline imaging; 45 (9.8%) had exactly 1 CMB, 37 (8.1%) had 2-4 CMBs, and 16 (3.5%) had ≥5 CMBs. Presence of CMBs was associated with a non-significant increased risk of symptomatic ICH (11.2% versus 4.2%; adjusted odds ratio 2.32 [95% CI 0.99-5.43]; P=.052), but had no effect on functional outcome at 90 days (mRS≤1: 45.8% versus 50.7%; adj. OR 0.99 [0.59-1.64]; P=.955). Patients receiving alteplase had better functional outcome (mRS≤1: 54.6% versus 44.6%, adj. OR 1.61 [1.07-2.43], P=.022) without evidence of heterogeneity in relation to CMB presence

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(P value of the interactive term .546). Results were similar for subpopulations with strictly lobar (presumed cerebral amyloid angiopathy-related) or non-strictly-lobar CMB distribution.

Discussion In the randomized-controlled WAKE-UP trial, we saw no evidence of reduced treatment effect of alteplase in acute ischemic stroke patients with one or more CMBs. Additional studies are needed to determine the treatment effect of alteplase and its benefit-harm-ratio in patients with a larger number of CMBs.

Trial registration ClinicalTrials.gov number, NCT01525290 (https://clinicaltrials.gov/ct2/show/NCT01525290); EudraCT number, 2011-005906-32 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-005906-32/GB).

Classification of Evidence This study provides Class II evidence that for patients with acute ischemic stroke with unknown time of onset and DWI-FLAIR mismatch who received IV alteplase, CMBs are not significantly associated with functional outcome at 90 days**.**

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INTRODUCTION

Background

Early treatment with intravenous thrombolysis with alteplase (recombinant tissue plasminogen activator) improves functional outcome in acute ischemic stroke patients.[1, 2] Cerebral microbleeds (CMBs), small hypointense lesions that are visible on hemorrhage-sensitive magnetic resonance imaging (MRI) sequences, are present on pre-treatment imaging in about 15% to 38% of ischemic stroke patients patients.[3, 4] CMBs, particularly if present in larger numbers, are associated with a significantly increased risk of post-alteplase symptomatic intracerebral hemorrhage (sICH).[4-6] Besides, the spatial distribution (i.e. the underlying vasculopathy[7]) of CMBs may influence the effects of CMBs on bleeding risk and functional outcome.[8] To date, no randomized controlled trials of intravenous alteplase in acute ischemic stroke patients stratified by CMB status on pre-treatment baseline MRI have been conducted and there are no studies describing the effect of CMB presence, burden, and spatial distribution or presumed pathophysiology on the risk of acute hemorrhagic complications after acute stroke without alteplase treatment. Thus, while the prognostic importance of CMBs in acute stroke patients treated with alteplase is well documented, the effect of baseline CMB status on the treatment effect of alteplase as compared to placebo is currently unknown. Reflecting this uncertainty, the American Heart Association/American Stroke Association guidelines state that treatment with IV alteplase in patients with CMBs may be associated with an increased risk of sICH, and that the benefits of treatment are uncertain in patients who have previously had a high burden of CMBs demonstrated on MRI.[3] On the other hand, an exploratory analysis of the NAVIGATE ESUS trial that compared the direct oral anticoagulant rivaroxaban to the platelet inhibitor aspirin recently showed that CMBs in ischemic stroke patients may well be a marker of worse clinical outcome in general without implying annulment of a beneficial effect of an intervention.[9]

All patients enrolled in the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke)[10], which demonstrated benefit of alteplase in imaging-

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selected acute ischemic stroke patients, underwent pre-treatment MRI showing an acute ischemic lesion. In this pre-planned exploratory analysis of the WAKE-UP trial data, we aimed to investigate (1) how presence, number, and spatial distribution of CMBs affect functional outcome and risk of hemorrhage after acute ischemic stroke and (2) whether they modify the treatment effect of alteplase.

METHODS

Study Design

We performed a pre-planned post-hoc analysis including patients enrolled in the WAKE-UP trial to provide Class II evidence for the questions whether CMBs are associated with functional outcome at 90 days in acute ischemic stroke patients with unknown time of onset and DWI-FLAIR mismatch who received IV alteplase. The WAKE-UP trial was a multicenter, two-arm, double-blind, randomized placebo-controlled clinical trial that evaluated the efficacy and safety of intravenous thrombolysis with alteplase in imaging-selected patients with acute ischemic stroke and unknown time of symptom onset. The detailed protocol has been published previously with the main results.[10] Briefly, patients aged 18-80 years with a diffusion-weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR) mismatch on acute MRI indicating lesion age ≤4.5 hours[11] were enrolled and randomized in a 1:1 ratio to treatment with either alteplase at a dose of 0.9 mg/kg body weight or placebo. Randomization was implemented by means of a Web-based procedure with a permuted-block design according to trial center. Contraindications included dependency in daily living before the stroke incident and planned mechanical thrombectomy. Presence of CMBs was not considered a contraindication for participation in the trial; however, patients could be excluded from the trial at the discretion of the local investigators if CMB burden was considered to pose a significantly increased risk of severe thrombolysis-associated bleeding. Patients were recruited in 61 experienced stroke centers in Europe.

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Patients were screened and enrolled between September 2012 and June 2017. Enrollment was stopped on June 30, 2017 due to cessation of funding.

Assessment of CMBs

All patients enrolled in the WAKE-UP trial underwent acute MRI before randomization. For the current analysis, CMBs were defined as small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.[12] Precise parameters of MRI sequences varied according to center and manufacturer; field strength was 1.5 or 3.0 Tesla, section thickness ranged from 1.5 to 7 mm, echo time (TE) from 11 to 51 ms, and repetition time (TR) from 460 to 2460 ms. Three raters (LS, TBB, JV) blinded to all clinical data independently assessed and counted the number of CMBs in separate sub-samples of patients and classified their location as either lobar, deep (i.e. in the basal ganglia/thalamus), or infratentorial (i.e. brainstem or cerebellar). Inter-rater reliability was assessed by calculating Krippendorff's alpha[13] for a randomly selected subsample of 100 scans that were assessed independently by all three raters; results were interpreted according to recommendations by Regier et al.[14] For further analysis, CMB number was discretized into the bins: 0, 1, 2-4, and ≥5 CMBs.[4]

Outcome parameters

Outcome parameters included the degree of disability and death, both 90 days after the stroke, and the occurrence of intracranial hemorrhage, assessed on follow-up imaging 22 to 36 hours after treatment. The degree of disability was quantified on the modified Rankin Scale (mRS); a score ≤1 was considered an excellent outcome, improvement of at least one point was assessed in ordinal shift analysis. Regarding intracranial hemorrhage, endpoints included the incidence of sICH according to the protocols of the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST)[15], European Cooperative Acute

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Stroke Study II (ECASS II)[16], ECASS III[17], or National Institutes of Neurological Disease and Stroke (NINDS)[18]; hemorrhagic transformation (HT; including type 1 and 2 parenchymal hematoma [PH] and type 2 hemorrhagic infarction, but not type 1 hemorrhagic infarction); and PH2 by itself. Multivariable regression analysis was restricted to SICH according to NINDS criteria in order to include sufficient numbers of events (see below). Imaging outcomes were ascertained by a central image-reading and a safety-adjudication committee within the WAKE-UP trial.

Statistical analysis

Treatment outcomes were assessed in the intention-to-treat population for all patients with available information on clinical end-points. Continuous variables are shown as median and interquartile range (IQR), proportions as absolute numbers and percentage. Associations between presence and number of CMBs and baseline characteristics were assessed using χ^2 and Wilcoxon rank-sum tests.

Associations between the presence of CMBs and binary outcome parameters were assessed using multivariable unconditional logistic regression models with a logit link function. For analyses using the ordinal mRS score as dependent variable, the proportional odds assumption was tested using a score test based on a χ^2-distribution with 12 degrees of freedom. As this assumption was not met, analyses were limited to the binary measure excellent functional outcome. For all regression analyses, independent variables included presence of CMBs (total number ≥1 versus 0), treatment group (alteplase versus placebo), the co-variates NIHSS sum score and age (selected in accordance with the study protocol of the main trial), and a facultative interactive term (presence of CMBs × treatment group). For sensitivity analyses, we also created models including variables that showed a significant univariate association with either presence or number of CMBs at the 0.05 significance level as additional co-variates. These models led to the same conclusions as the primary models, detailed results are presented in the Online Supplement (**eTable 1 and 2**).

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The relationships between clinical outcome parameters and variables of interest are expressed as odds ratios (point estimates and 95% confidence intervals [CI]).

For analyses involving the number of CMBs as an ordinal variable (0, 1, 2-4, ≥5) and/or the safety outcome parameters death and occurrence of PH2, the creation of robust multivariable models was not possible due to low event numbers (i.e. failure to obtain maximum likelihood estimates). In these cases, we provide a description of the outcome distributions and – with ordinal CMB categories – results from unadjusted non-parametric tests for linear trend (Mantel-Haenzsel test for trend). All tests were performed with a two-sided α level of .05 without adjustment for multiple testing. Analyses were performed in SAS version 9.4 (SAS Institute) and SPSS version 25.

Standard Protocol Approvals, Registrations, and Patient Consents

For each study site, the competent authorities and the corresponding ethics committee approved the trial. Written informed consent was obtained from patients or their legal representatives according to national and local regulations. There was an exception from explicit informed consent in emergency circumstances in some countries. The WAKE-UP study was pre-registered (ClinicalTrials.gov number, NCT01525290; EudraCT number, 2011-005906-32).

Data availability

Individual patients data, after de-identification, will be shared with the Virtual International Stroke Trials Archive (VISTA) and be accessible for researchers according to the VISTA rules. (http://www.virtualtrialsarchives.org/vista/).

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RESULTS

Baseline CMB results

CMB status on baseline pre-randomization MRI could be assessed for N = 459 of 503 (91.3%) patients enrolled in the WAKE-UP trial. In 23 patients (4.6%), image quality of gradient echo sequences did not allow a reliable assessment of CMBs; in 21 patients (4.2%), no gradient echo sequence at baseline was available for analysis. A flowchart is shown in **Figure 1**. The median number of CMBs across all patients was 0 (IQR 0 – 0, range 0 – 19). Of 459 patients included in the analysis, 98 (21.4%) had at least 1 CMB; 45 (9.8%) had exactly 1 CMB, 37 (8.1%) had 2-4 CMBs, and 16 (3.5%) had ≥5 CMBs. In 53 patients, CMBs were found exclusively in a lobar location; in 45 patients, CMBs were non-strictly-lobar (**Table 1**).

The inter-rater reliability between the three raters was very good or excellent (presence of CMBs, Krippendorff's alpha 0.71; total number of CMBs, alpha 0.74; distribution of CMBs [strictly lobar or non-strictly-lobar], alpha 0.85).

Baseline characteristics of patient population

Demographic and clinical characteristics at baseline according to presence and number of CMBs are shown in **Table 2**. Patients with at least 1 CMB were on average older (median age 70 [IQR 63 – 75] versus 67 [IQR 57 – 73] years; P=.024) and more often had a diagnosis of arterial hypertension (65% versus 50%; P=.006). In addition, a trend for a between-group difference was observed for the frequency of diabetes mellitus type 2 (22% versus 14%; P=.062) and atrial fibrillation (16% versus 10%; P=.067) and baseline stroke symptom severity (median NIHSS score 6 [IQR 4 – 11] versus 5 [3 – 8]; P=.084). Remaining baseline characteristics including the availability of susceptibility weighted imaging were not associated with presence or number of CMBs.

Relationship between presence of CMBs and functional outcome and safety endpoints

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Proportion of patients with excellent outcome (mRS≤1) at 90 days did not differ significantly in patients with at least 1 CMB and patients without CMBs (44 of 96 [45.8%] versus 179 of 353 [50.7%]; adjusted odds ratio 0.99, 95% CI 0.59 to 1.64; P=.955; **eFigure 1**).

Across all patients, incidence of any sICH according to NINDS criteria at follow-up imaging was numerically more than twice as frequent in patients with presence of at least 1 CMB as compared to no CMBs without reaching the predefined statistical significance threshold (11 of 98 [11.2%] versus 15 of 361 [4.2%]; adjusted odds ratio 2.32, 95% CI 0.99 to 5.43; P=.052). The occurrence of HT did not differ between groups (21 of 95 [22.1%] versus 46 of 358 [12.8%]; adjusted odds ratio 1.57, 95% CI 0.84 to 2.95; P=.158). The magnitude of the relative increase of hemorrhagic complications in patients with at least 1 CMB was similar in the placebo and in the alteplase group without evidence of heterogeneity between treatment groups (P value for interaction .522 [sICH] and .884 [HT]; **eFigure 2)**.

Modification of treatment effect of alteplase by presence of CMBs

When analyzing the group of patients with strictly lobar CMBs or no CMBs, treatment with alteplase as compared to placebo was associated with higher rates of excellent functional outcome (mRS≤1) at 90 days (112 of 205 [54.6%] versus 86 of 200 [43.0%], adjusted odds ratio 1.79, 95% CI 1.16 to 2.75, P=.008) without evidence of interaction between CMB presence and treatment group (adjusted odds $ratio_{CMB}$ 2.6, 95% CI 0.70 to 9.60, adjusted odds $ratio_{no\ CMB}$ 1.71, 95% CI 1.08 to 2.70; P value for interaction=.553). Similarly, we could not determine a modifying role of non-strictly lobar CMBs on the treatment effect of alteplase (adjusted odds $ratio_{combined\ group}$ 1.54 95% CI 1.00 to 2.37, P=.048; adjusted odds $ratio_{CMB}$ 0.65 95% CI 0.18 to 2.39, adjusted odds $ratio_{no\ CMB}$ 1.72, 95% CI 1.09 to 2.72, P value for interaction=.169; **Figure 2).**

Treatment with alteplase as compared to placebo was associated with a trend towards higher rates of sICH (18 of 233 [7.7%] versus 8 of 226 [3.5%], adjusted odds ratio 2.29, 95% CI 0.05 to 5.48, P=.064) and significantly higher rates of HT (62 of 230 [27.0%] versus 40 of

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223 [17.9%], adjusted odd ratio 1.181, 95% CI 1.02 to 3.19, P=.041). Again, there was no evidence of heterogeneity with regards to the presence or spatial distribution of CMBs (strictly lobar vs. non-strictly-lobar; all P values for interaction >.05; **Figure 3).**

Low-frequency safety endpoints: PH2 and death

For the safety endpoints PH2 and death and SICH according to SITS-MOST or ECASS II/III criteria, event numbers were too low to obtain reliable maximum likelihood estimates in adjusted regression models. PH2 and death appeared to be more frequent in patients treated with alteplase than in those receiving placebo (8 of 230 [3.5%, 95% CI 1.5% to 6.7%] versus 1 of 223 [0.5%, 95% CI 0.0% to 2.5%] and 9 of 176 [5.1%, 95% CI 2.4% to 9.5%] versus 1 of 188 [0.5%, 95% CI 0.0% to 2.9%], respectively). In addition, among patients treated with alteplase but not among patients receiving placebo, PH2 and death appeared to be more frequent in patients with at least 1 CMB than in those without CMBs (5 of 53 [9.4%, 95% CI 3.1% to 20.7%] versus 3 of 177 [1.7%, 95% CI 0.4% to 4.9%] and 4 of 43 [9.3%, 95% CI 2.6% to 22.1%] versus 5 of 133 [3.8%, 95% CI 1.2% to 8.6%], respectively; **Figure 4**). Data for SICH according to SITS-MOST or ECASS II/III criteria are presented in **eFigure 3**.

Ordinal CMB count and outcome

Among the combined group of patients treated with either placebo or alteplase, the rates of excellent functional outcome were similar for patients with 0, 1, 2-4, and ≥5 CMBs of any location (crude P values for linear trend .812 and .531, respectively; **Figure 5A and 5B**). With regards to safety endpoints, sICH, HT, and PH2, but not death appeared to be more frequent among patients with higher CMB number (crude P values for linear trend .013, .032, <.001 and .686, respectively; **Figure 5C to 5F**). Frequencies of sICH according to different definitions and sub-categories of HT by baseline CMB status are shown in **eTable 3**. Small sample sizes in groups with higher CMB burden prohibited further subgroup analyses by treatment allocation or spatial distribution, as well as adjustment for potential confounders.

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DISCUSSION

Main findings

In the current study, we analyzed data from the multicenter, double-blind, randomized WAKE-UP trial to investigate how presence, number, and spatial distribution of CMBs affect outcome after stroke and whether they may modify the treatment effect of alteplase. In line with results from the main trial,[10] we found that treatment with alteplase significantly increased the odds of excellent functional outcome in spite of a trend towards higher rates of hemorrhagic complications. We found no evidence that the beneficial effects of alteplase treatment were different in patients with one or more CMBs and those without CMB.

Interpretation

For the first time, we were able to assess the benefit and harm of intravenous alteplase in acute ischemic stroke patients with known CMB burden quantified on pre-treatment MRI in a randomized, double-blind, controlled trial. Previous observational studies that established the relationship between CMB status and increased risk of sICH after alteplase and poorer functional outcome at 90 days did not include a control group of untreated patients and therefore could not determine the isolated effect of CMBs on hemorrhagic complications and functional outcome.

In line with results from two recent meta-analyses,[4, 5] occurrence of sICH in our study population was numerically more frequent among patients with one or more CMBs than among patients without CMBs. However, this association between presence of ≥1 CMB and hemorrhagic complications was equally present in patients receiving placebo as it was in patients receiving alteplase. As a consequence, our analysis yielded similar effect size estimates for the beneficial treatment effect of alteplase on 90 day functional outcome in patients with ≥1 CMBs and patients without CMBs, indicating that presence of CMBs on MRI should not deter physicians from treating eligible patients with thrombolysis. Only in patients with one or more non-strictly-lobar CMBs lay the point estimate of the treatment

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effect of alteplase for achieving excellent functional outcome (mRS≤1) below 1; even without evidence of between-group heterogeneity, this could indicate a particular need for further studies in this patient group.

Beyond the presence of CMBs, patients with higher number of CMBs might be particularly prone to hemorrhagic complications. Although having to be interpreted with caution due to small sample sizes, our results are consistent with previous studies that have suggested an association between the number of CMBs and higher risk of hemorrhagic complications and poor functional outcome.[4, 5, 19] Similar to the models involving the presence of CMBs, however, there was no signal in our data indicating that the number of CMBs was related to functional outcome or death at 90 days.

Previous modelling work related to the treatment effect of alteplase indicated that alteplase treatment may be associated with more harm than benefit in some patients with large number (>10) of CMBs.[20] The population enrolled in the WAKE-UP trial and thereby available for the current analysis only included very few patients with >10 CMBs. Our results therefore do not exclude the possibility that alteplase is of reduced benefit in some patients with high CMB burden. Additional trials involving a sufficiently large number of patients with a large number of CMBs would be needed to answer this question.

Strictly lobar CMBs may be a sign of underlying cerebral amyloid angiopathy.[7] There is conflicting evidence whether the presumed pathophysiology of CMBs as indicated by a strictly lobar location is of prognostic importance when assessing the relationship between CMB status and outcome.[4, 8] We performed our analyses once for all patients, and separately for patients with strictly lobar CMBs and non-strictly-lobar CMBs and found no evidence of heterogeneity with regards to presumed CMB pathophysiology.

Strengths of the current study include the availability for analysis of patients treated with alteplase and placebo; MRI proven ischemic stroke in all patients; assessment of CMB burden before administration of the study drug; outcome ascertainment within the framework

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of a prospective randomized controlled trial; and the availability of medium term functional outcome data.

Limitations

First, the number of patients with high or very high CMB burden was low, precluding adjusted analyses of CMB number, raising the possibility of type 2 errors, and limiting generalizability to patients with high CMB burden. The endpoints PH2 and death could not be analyzed in adjusted regression models due to low numbers of events. Unadjusted analyses suggested that the presence of ≥1 CMB might increase the odds of these complications in patients treated with alteplase, but not in patients receiving placebo. Further studies are required to confirm or refute these observations. Second, although presence of CMBs on initial brain MRI was no formal contraindication for participation in the WAKE-UP trial, patients with many CMBs might have been excluded from participation at the discretion of local investigators due to a perceived increased risk of severe thrombolysis-associated bleeding. This could have introduced an indication bias by which our analysis could have underestimated the true bleeding risk in the CMB group. A screening log was not maintained, so the exact number of patients excluded for this reason cannot be quantified. However, 21.4% of patients in our study had at least one and 3.5% had five or more CMBs, consistent with findings from previous observational studies,[4] suggesting that preferential exclusion of patients with higher CMB burden did not play major role. Third, imaging protocols and hemorrhage sensitive sequences were not standardized across study sites, which might have introduced additional heterogeneity; however, presence and total number of CMBs were not related to field strengths nor the availability of susceptibility weighted imaging. While such associations might have been expected based on previous studies,[12] the small number of patients receiving susceptibility weighted imaging and the heterogeneity of T2* imaging protocols may have masked this effect in our study, highlighting the need for harmonized imaging protocols across study sites in future trials. Fourth, only a minority of patients in the

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WAKE-UP trial had high stroke symptom severity scores, proximal large vessel occlusions, and/or were treated with mechanical thrombectomy; therefore, our results cannot be extended to these patient groups without further study.

Conclusions

In summary, this pre-defined post-hoc analysis of the randomized controlled WAKE-UP trial data showed no evidence that treatment with alteplase is less effective or even causes harm in acute ischemic stroke patients with one or more CMBs. The effect of CMBs on hemorrhagic complications was equally present in patients receiving placebo or alteplase. Our results corroborate findings from previous observational studies indicating that in otherwise eligible patients, intravenous thrombolysis should not be withheld on the basis of a small to moderate number of CMBs alone. The study was not powered to provide direct evidence of superiority of alteplase over placebo in patients with CMBs. Additional studies are needed to determine the treatment effect of alteplase and its benefit-harm-ratio in patients with a larger number of CMBs.

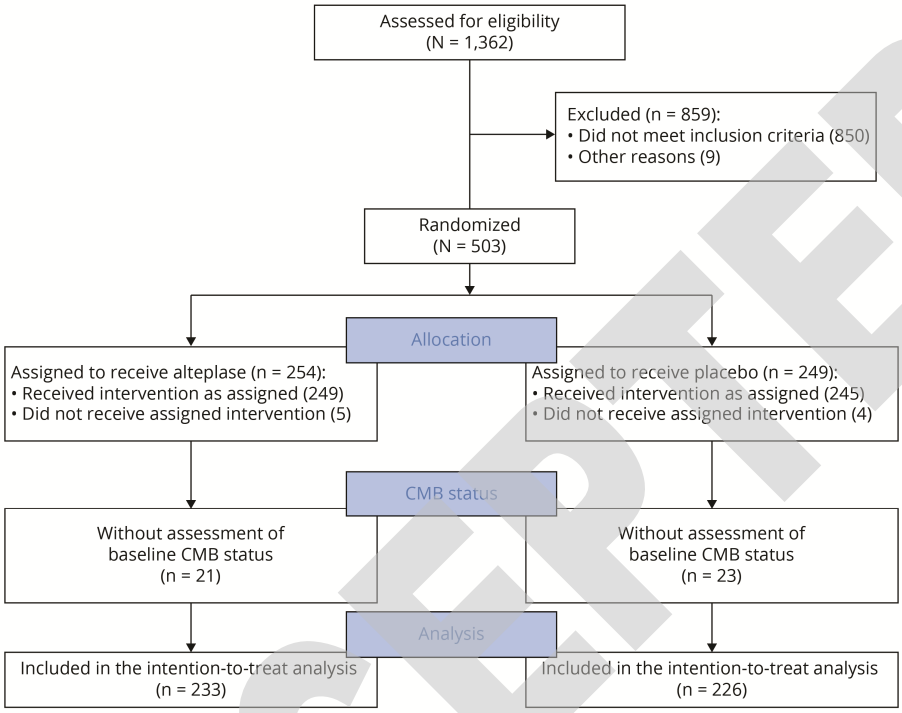
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FIGURE LEGENDS

Figure 1 Flow Diagram.

CMB indicates cerebral microbleed.



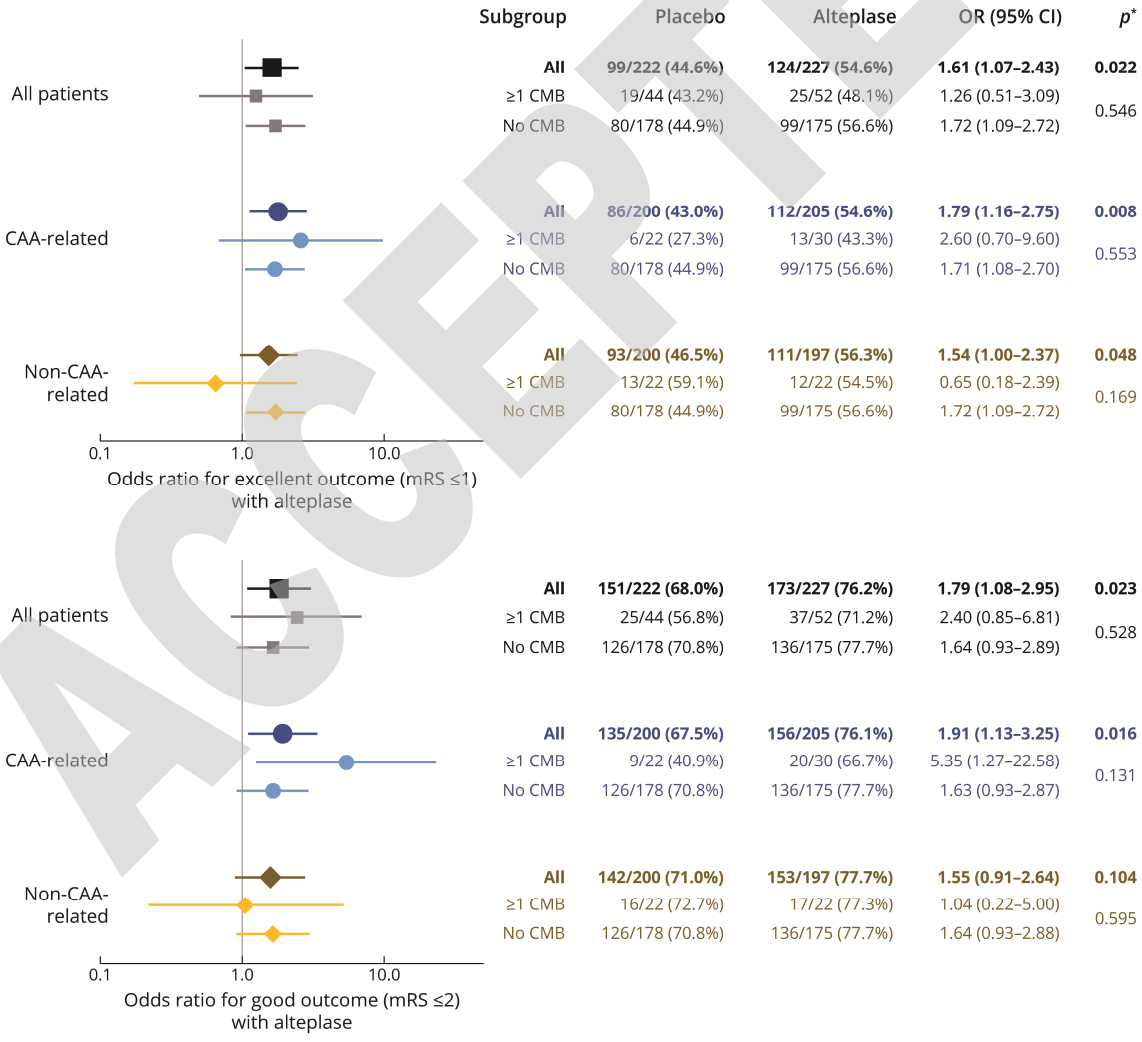
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Figure 2 Association between alteplase treatment and functional outcome at 90 days according to presence and spatial distribution of cerebral microbleeds.

Point estimates above 1 indicate better functional outcome with alteplase treatment. *First P value per group corresponds to the hypothesis that across patients with any number of CMBs, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients with no CMBs and at ≥1 CMBs, the odds ratio is identical (no interaction).

CMBs indicates cerebral microbleeds; OR, odds ratio; CI, confidence interval.



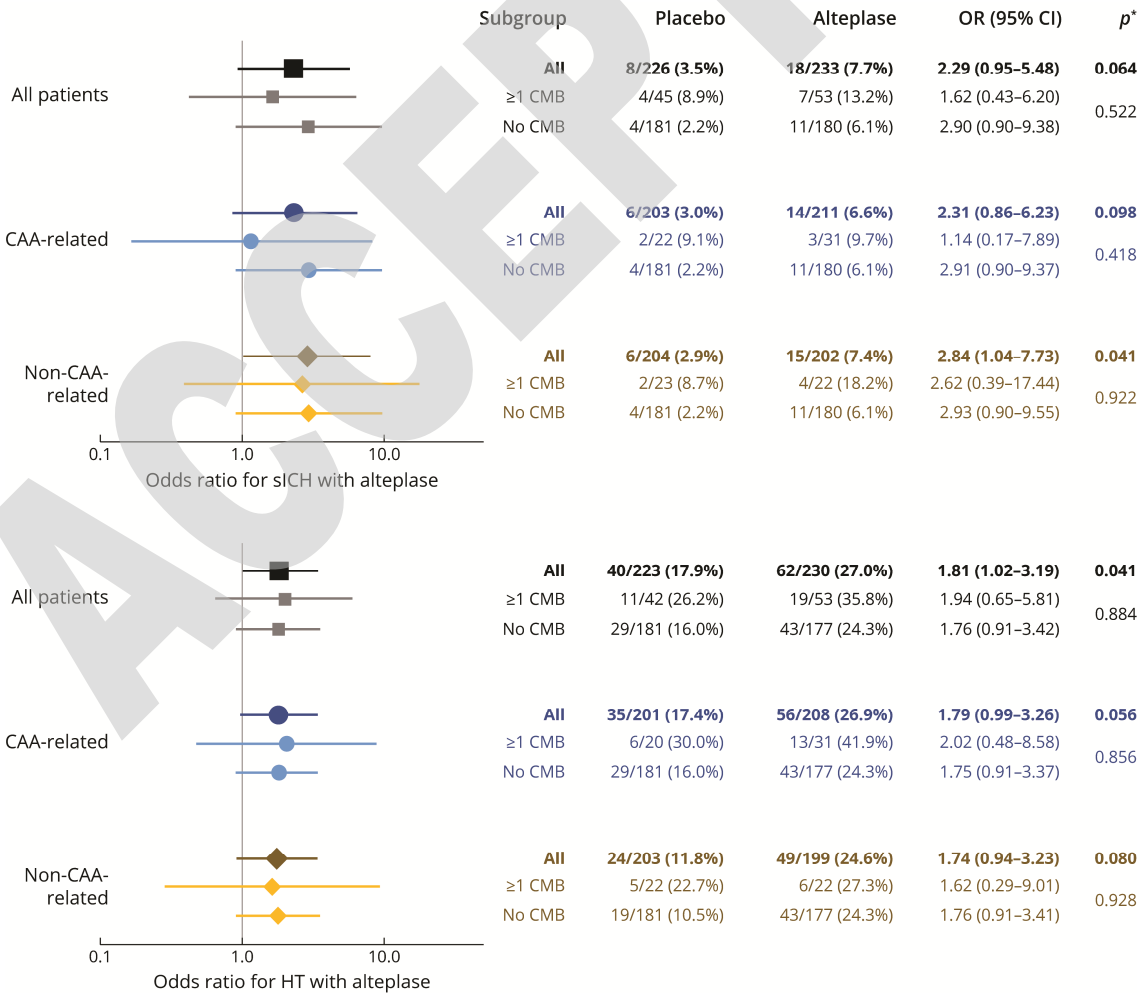
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Figure 3 Association between alteplase treatment and hemorrhagic complications according to presence and spatial distribution of cerebral microbleeds.

Point estimates above 1 indicate higher risk of hemorrhage with alteplase treatment. *First P value per group corresponds to the hypothesis that across patients with any number of CMBs, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients with no CMB and ≥1 CMB, the odds ratio is identical (no interaction).

CMB indicates cerebral microbleed; OR, odds ratio; CI, confidence interval; sICH, symptomatic intracranial hemorrhage; HT, hemorrhagic transformation.

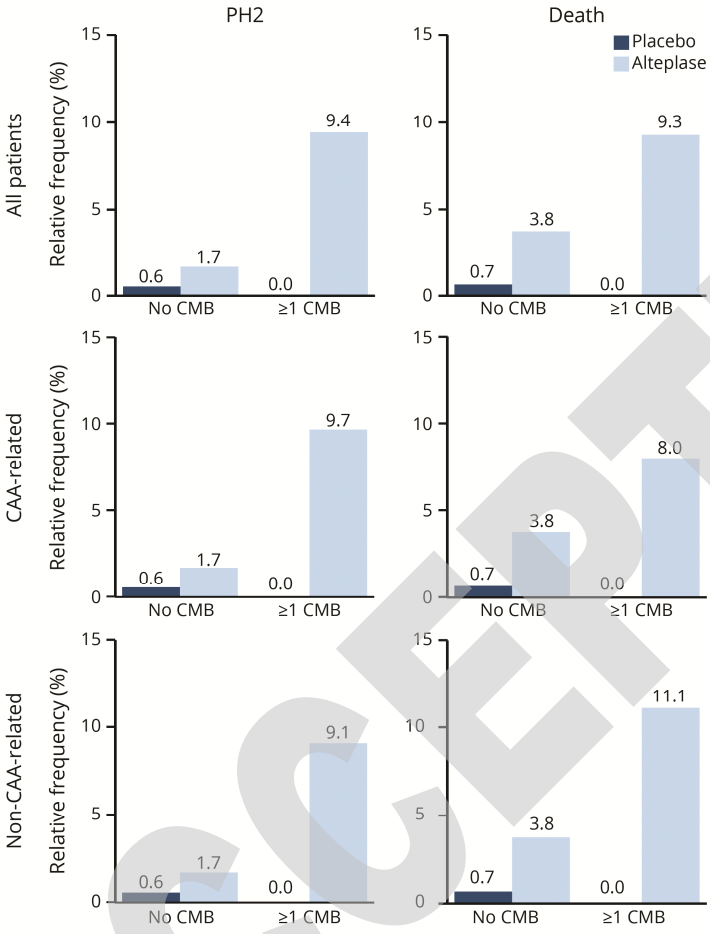


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Figure 4 Relative frequencies of low-frequency safety endpoints by treatment group and presence of cerebral microbleeds.

PH2 indicates parenchymal hematoma type 2; CMBs, cerebral microbleeds.

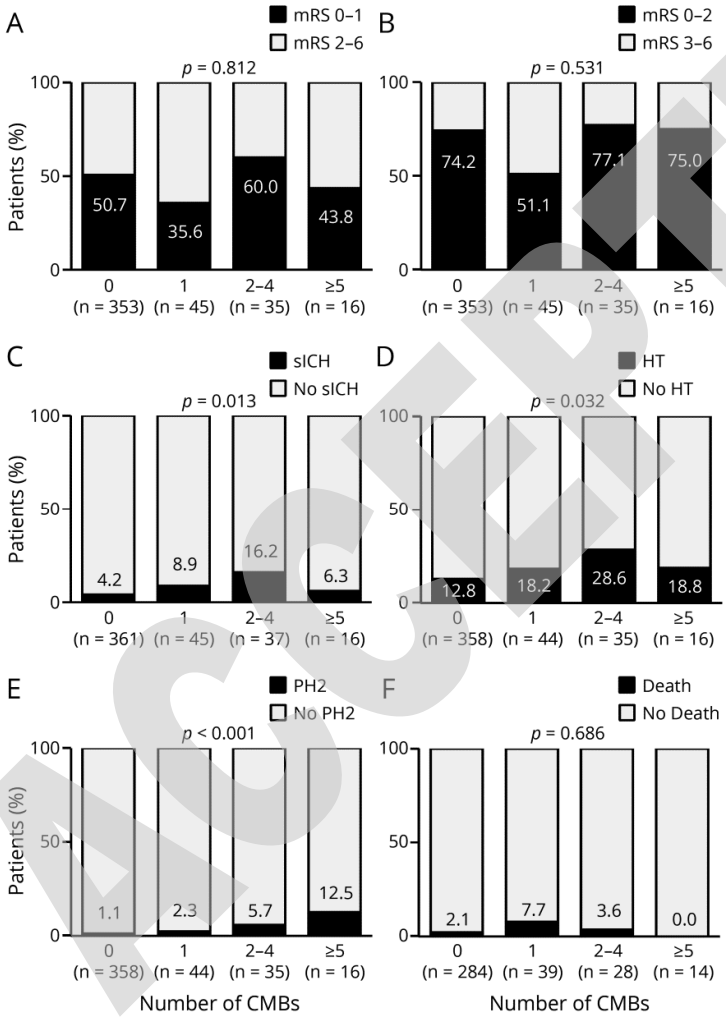


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Figure 5 Associations between number of cerebral microbleeds and functional and safety outcomes.

P values for linear association between CMB number and outcome measure (linear trend) are derived from Mantel-Haenzsel tests for trend. CMBs indicates cerebral microbleeds; mRS, modified Rankin scale; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; PH2, parenchymal hemorrhage.



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TABLES

Table 1. Spatial distribution of cerebral microbleeds

	All patients (n=459)	CMBs strictly lobar or none (n=414)	CMBs non-strictly-lobar or none (n=406)
No CMBs			
Proportion, no. (%)	361 (78.6)	361 (87.2)	361 (88.9)
Any location			
Proportion, no. (%)	98 (21.4)	53 (12.8)	45 (11.1)
Conditional frequency, median (IQR)	2 (1-3)	1 (1-2)	2 (1-5)
Lobar			
Proportion, no. (%)	73 (15.9)	53 (12.8)	20 (4.9)
Conditional frequency, median (IQR)	1 (1-3)	1 (1-2)	1 (1-4.8)
Basal ganglia			
Proportion, no. (%)	35 (7.6)	NA	35 (8.6)
Conditional frequency, median (IQR)	1 (1-2)	NA	1 (1-2)
Brain stem			
Proportion, no. (%)	8 (1.7)	NA	8 (2.0)
Conditional frequency, median (IQR)	1.5 (1-2)	NA	1.5 (1-2)
Cerebellum			
Proportion, no. (%)	15 (3.3)	NA	15 (3.7)
Conditional frequency, median (IQR)	1 (1-2)	NA	1 (1-2)

CMBs indicates cerebral microbleeds; NA, not applicable.

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Table 2. Demographic and clinical characteristics at baseline according to presence and number of cerebral microbleeds.

	All (N=459)	No CMBs (n =361)	≥1 CMBs (n=98)	1 CMB (n =45)	2-4 CMBs (n =37)	≥5 CMBs (n =16)	*P* Value, presence[a]	*P* Value, number[b]
Age, mean (IQR), years	68 (59-74)	67(57–73)	70(63-75)	72(65–76)	67(59–72)	70(65–74)	**.024**	.033
Sex–n (%)								
Female	171(37)	129(36)	32(33)	12(27)	15(41)	5(31)	.820	.561
Male	288(63)	232(64)	66(67)	33(73)	22(60)	11(69)		
Medical history, no. (%)								
Arterial hypertension	242(53)	178(50)	64(65)	32(71)	21(57)	11(69)	**.006**	**.026**
Diabetes mellitus, type 2	73(16)	51(14)	22(22)	12(27)	8(22)	2(13)	.062	.136
Hypercholesterolemia	161(37)	123(36)	38(40)	18(41)	15(42)	5(31)	.549	.788
Atrial fibrillation	50(11)	34(10)	16(16)	9(20)	7(19)	0(0)	.067	**.029**
History of ischemic stroke	58(13)	44(12)	14(14)	9(20)	3(8)	2(13)	.608	.400
Current medication, no. (%)								
Platelet aggregation inhibitors	137(30)	106(29)	31(32)	17(38)	10(27)	4(25)	.709	.634
Statines	137(30)	104(29)	33(34)	15(33)	13(35)	5(31)	.384	.812
NIHSS score, median (IQR)	5(3-8.5)	5(3–8)	6(4–11)	6(4–12)	6(4–10)	5(4–9)	**.084**	.273
NIHSS score, stratified, no. (%)								
<= 10	371(81)	298(83)	73(75)	31(69)	28(76)	14(88)	**.083**	.115
> 10	88(19)	63(18)	25(26)	14(31)	9(24)	2(13)		
Reason for unknown time of symptom onset, no. (%)								
Nighttime sleep	415(90)	325(90)	90(92)	42(93)	32(87)	16(100)	.534	.769
Daytime sleep	19(4)	17(5)	2(2)	1(2)	1(3)	0(0)		
Aphasia	16(3)	13(4)	3(3)	1(2)	2(5)	0(0)		
Confusion or other	9(2)	6(2)	3(3)	1(2)	2(5)	0(0)		
Lesion volume on diffusion-weighted imaging, median (IQR), ml	2.1(0.7-7.7)	2.1(0.6-7.3)	1.9(0.9-9.2)	2.6(1.0-12.6)	1.3(1.0-5.7)	1.1(0.8-7.5)	.531	.474
Large vessel occlusion, no. (%)	85(19)	67(19)	18(19)	10(33)	6(17)	2(13)	>.99	.820
Time intervals, median (IQR), hours								
Between symptom recognition and start of infusion	3.1(2.5-3.8)	3.1(2.5–3.8)	3.3(2.5–4.0)	3.3(2.6–4.0)	3.2(2.4–3.7)	3.3(2.5–4.2)	.433	.83
Between 'last known well' and start of infusion	10.3(8.1-12.0)	10.2(8.1-12.0)	10.4(7.3-12.0)	10.5(8.4-11.9)	10.8(7.8-12.4)	7.8(6.4–11.0)	.942	.236
Number of CMBs, median (IQR)	0(0–0)	0(0–0)	2(1–3)	1(1–1)	2(2–3)	6.5(5–9)	NA	NA

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Hemorrhage sensitive sequence, no. (%)								
Only GRE/T2*	405(88)	321(89)	84(86)	38(84)	34(92)	12(75)	.412[c]	.266[c]
Only SWI	37(8)	27(7)	10(10)	4(9)	2(5)	4(25)		
GRE/T2* and SWI	17(4)	13(4)	4(4)	3(7)	1(3)	0(0)		
Field strength, no. (%)								
1.5 T	237(52)	191(53)	46(47)	24(53)	14(38)	8(50)	.294	.373
3.0 T	222(48)	170(47)	52(53)	21(47)	23(62)	8(50)		
Treatment, no. (%)								
Alteplase	233(50.8)	180(49.9)	53(54.1)	20(44.4)	17(45.9)	8(50.0)	.459	.874
Placebo	226(49.2)	181(50.1)	45(45.9)	25(55.6)	20(54.1)	8(50.0)		

[a]Comparing between "no CMBs" and ≥1 CMBs. [b]Comparing between CMBs as categorical variable (0, 1, 2-4, ≥5). P-values not adjusted for multiple testing. [c]P-value calculated for dichotomization "SWI performed: yes/no".
CMBs indicates cerebral microbleeds; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; GRE, gradient echo; SWI, susceptibility weighted imaging; NA, not applicable

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Appendix 2: Coinvestigators

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REFERENCES

1. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-1935.

2. Lees KR, Emberson J, Blackwell L, et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. Stroke 2016;47:2373-2379.

3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

4. Charidimou A, Turc G, Oppenheim C, et al. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis. Stroke 2017;48:2084-2090.

5. Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis in Patients With Acute Ischemic Stroke and High Cerebral Microbleed Burden: A Meta-analysis. JAMA Neurol 2016;73:675-683.

6. Fiehler J, Albers GW, Boulanger JM, et al. 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.

7. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009;8:165-174.

8. Choi KH, Kim JH, Kang KW, et al. Impact of Microbleeds on Outcome Following Recanalization in Patients With Acute Ischemic Stroke. Stroke 2018:STROKEAHA118023084.

9. Shoamanesh A, Hart RG, Connolly SJ, et al. Microbleeds and the Effect of Anticoagulation in Patients With Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Randomized Clinical Trial. JAMA Neurol 2020.

10. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med 2018;379:611-622.

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11. Thomalla G, Cheng B, Ebinger M, et al. 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.

12. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822-838.

13. Hayes AF, Krippendorff K. Answering the call for a standard reliability measure for coding data. Communication methods and measures 2007;1:77-89.

14. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry 2013;170:59-70.

15. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-282.

16. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251.

17. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.

18. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.

19. Dannenberg S, Scheitz JF, Rozanski M, et al. Number of cerebral microbleeds and risk of intracerebral hemorrhage after intravenous thrombolysis. Stroke 2014;45:2900-2905.

20. Schlemm L, Endres M, Werring DJ, Nolte CH. Benefit of Intravenous Thrombolysis in Acute Ischemic Stroke Patients With High Cerebral Microbleed Burden. Stroke 2020;51:232-239.

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Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke: An Analysis of the WAKE-UP Randomized Clinical Trial

Ludwig Schlemm, Tim Bastian Braemswig, Florent Boutitie, et al.

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