Cerebral microbleeds and postthrombolysis intracerebral hemorrhage risk

Updated meta-analysis

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ABSTRACT

Objective: We performed a systematic review and meta-analysis to assess whether the presence of cerebral microbleeds (CMBs) on pretreatment MRI scans of patients with acute ischemic stroke treated with thrombolysis is associated with an increased risk of symptomatic intracerebral hemorrhage (ICH).

Methods: We searched PubMed for relevant studies and calculated pooled odds ratios (ORs) for symptomatic ICH, using the Mantel–Haenszel fixed-effects method, among individuals with vs without CMBs on pretreatment MRI scans. To minimize potential bias, sensitivity analysis was performed including studies providing data on patients treated only with IV thrombolysis.

Results: Ten eligible studies including 2,028 patients were pooled in meta-analysis. The overall prevalence of CMBs was 23.3%. Among patients with CMBs, 40 of 472 (8.5%; 95% confidence interval [CI]: 6.1%–11.4%) experienced a symptomatic ICH after thrombolysis compared with 61 of 1,556 patients (3.9%; 95% CI: 3%–5%) without CMBs. The pooled OR of ICH across all studies was 2.26 (95% CI: 1.46–3.49; $p < 0.0001$). Eight studies, including 1,704 patients (n = 401 with CMBs), provided data on patients treated with IV thrombolysis only; OR for the presence of CMBs and the development of symptomatic ICH was 2.87 (95% CI: 1.76–4.69; $p < 0.0001$).

Conclusions: Our meta-analysis of the available published data demonstrates an increased risk of symptomatic ICH after thrombolysis for acute ischemic stroke in patients with CMBs. However, we cannot fully exclude bias or confounding, so our results should be considered hypothesis-generating. Detecting CMBs should not prevent thrombolytic treatment based on present evidence. Further analyses, taking into account CMB number and location, as well as measures of functional outcome, are needed. ***Neurology*® 2015;85:927–934**

GLOSSARY

CI = confidence interval; **CMB** = cerebral microbleed; **ICH** = intracerebral hemorrhage; **OR** = odds ratio; **rtPA** = recombinant tissue plasminogen activator; **SWI** = susceptibility-weighted imaging.

IV thrombolysis with recombinant tissue plasminogen activator (rtPA) remains the cornerstone of acute ischemic stroke treatment.[1] Early intracerebral hemorrhage (ICH) is the most serious yet unpredictable complication of thrombolysis.[2,3] Emerging evidence suggests that neuroimaging markers of cerebral small vessel disease (e.g., leukoaraiosis) might be a risk factor for thrombolysis-related ICH, together with age, early ischemic CT changes, high blood pressure, hyperglycemia, clinical stroke severity, and large infarct volume.[2,4]

Cerebral microbleeds (CMBs), detected as small, rounded, hypointense lesions on blood-sensitive MRI sequences, including T2*-weighted gradient-recalled echo and susceptibility-weighted imaging (SWI), are commonly found in stroke patients. CMBs are small perivascular hemosiderin deposits usually attributed to leakage through pathologically fragile hemorrhage-prone small vessels.[5,6] In the setting of acute ischemic stroke thrombolysis, previous studies have given conflicting results regarding the possible risk of ICH in patients with CMBs.[7,8] In 2012,

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Supplemental data at Neurology.org

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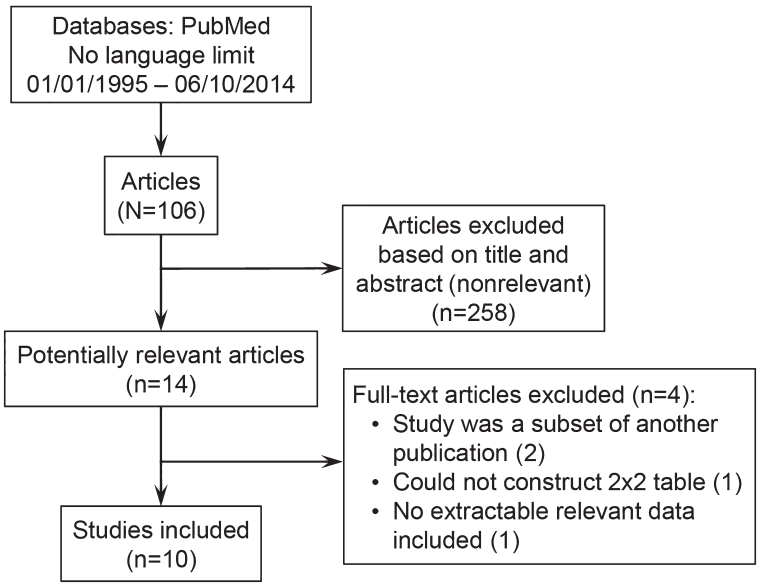
Figure 1 Study selection



Flowchart of literature search and study selection.

meta-analyses pooling data from a total of 790 patients from 5 studies demonstrated a trend toward increased risk of postthrombolysis ICH in patients with CMBs (relative risk: 1.90; 95% confidence interval [CI]: 0.92–3.93; $p = 0.082$).[9,10] Of note, none of the 5 included studies reached statistical significance; however, all studies, including the meta-analyses, were underpowered to appropriately address the question.[9,10]

Given new recently published studies on the topic, including larger cohorts, we performed an updated systematic review and meta-analysis to assess whether the presence of CMBs on prethrombolysis MRI scans of patients with acute ischemic stroke is associated with an increased risk of symptomatic ICH.

METHODS

Search strategy and selection criteria. We searched PubMed between January 1, 1995, and October 6, 2014, using the following search terms: "micro(-)bleed*," or "micro(-)h(a)emorrhag*, or "gradient-echo," or "susceptibility-weighted" in association with "thromboly*" or "tPA," or "tissue plasminogen activator." Reference lists from all included articles, review papers on the topic, and the authors' own files were also searched for relevant studies. Case reports were excluded and articles not published in English were translated where needed. Two authors (A.C. and D.W.) identified potentially relevant studies, resolving any uncertainties with a third author (A.S.).

Studies were eligible for inclusion if they had (1) defined and assessed symptomatic ICH risk (the outcome of interest) in patients with acute ischemic stroke treated with thrombolysis, and (2) quantified this risk in relation to the presence of CMBs on pretreatment MRI scans.

Data extraction. Two authors (A.C. and A.S.) reviewed all articles selected as potentially relevant and extracted data independently. For each study, we extracted information on study design, number and characteristics of participants (including mean age and sex), blood-sensitive MRI parameters used, thrombolytic treatment and dosage, duration of follow-up, number of participants with at least one CMB, and number of participants with the outcome of interest (symptomatic ICH clearly defined according to standard criteria). Disagreements were resolved by discussion and consensus.

All included studies were critically appraised against a checklist of key quality indicators that we developed,[9–11] with reference to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement and the ideal characteristics for a study of CMBs[12] (study sample size, clearly defined CMB criteria, clear definition of the study population, standardized MRI parameters, ICH criteria clearly defined, awareness of >2 CMB mimics, standardized rating scale or trained observer agreement [inter- and intrarater], classification of CMB distribution, and adjusted results for other risk factors).

Statistical analysis. Because of the relatively small number of studies and outcome events, we used a fixed-effects model. We quantified the strength of the association between CMBs and ICH using odds ratios (ORs) and their corresponding 95% CIs, with the inverse variance method for weighting. To account for methodologic variability in the route of thrombolysis treatment among the included studies, a subgroup analysis was performed including only studies that provided relevant data on patients treated only with IV tPA. We assessed statistical heterogeneity using I^2 statistics and also visually through inspection of the forest plot. We explored publication bias with funnel plots. We used meta-regression to explore whether certain baseline characteristics of the included patient populations could have affected our results. We also performed fixed-effect univariable meta-regression analyses to evaluate whether certain methodologic characteristics of the studies (including key quality indicators and MRI sequence parameters, i.e., SWI vs T2*-weighted gradient-recalled echo, echo time, field strength, and slice thickness) could be confounders in the relationship between CMBs and ICH. As a sensitivity analysis, we investigated the influence of each study on the overall meta-analyses estimates (using the "metaninf" command) and inspected the results graphically with meta-analyses estimates computed, omitting one study in each turn. We repeated all analyses using random-effects models. Meta-analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX). We prepared this report with reference to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[13] and MOOSE (Meta-analysis of Observational Studies in Epidemiology)[14] guidelines.

RESULTS

Ten studies including a total of 2,028 patients met our inclusion criteria and were pooled in meta-analysis (figure 1).[7,8,15–22] A summary of the characteristics of included studies, methodologic key issues, and quality indicators are noted in tables 1 and 2 as well as in tables e-1 and e-2 on the *Neurology*® Web site at Neurology.org. There was no evidence of publication bias in the funnel plot. From inspection of each of the studies, the CMB (+) vs

Table 1 Characteristics and methodologic aspects of included studies

Study reference	Study design	No. of patients (% men)	Mean age, y	Initial stroke severity (NIHSS)	Blood-sensitive MRI parameters				CMB prevalence (95% CI), %	Thrombolysis regimen	FU time, d	ICH definition
					Sequence	Field strength, T	Echo time, ms	Section thickness, mm				
15	Retrospective, single center	225 (67.6)	66.29	11.4	SWI	3	4.5	2	36.1	IV rtPA	90	ICH with worsening of ≥4 points on NIHSS
16	Prospective, single center	392 (56.9)	68.1	9	SWI	1.5/3	20/40		20.2	IV rtPA, endovascular therapy, or both	3	ICH with worsening of ≥4 points on NIHSS or ≥1 point on NIHSS consciousness level
17	Prospective, single center	326 (48.8)	76	8 (IQR 5–14)	T2*-GRE	3	20	5	24.8	IV tPA within 4.5 h or normal FLAIR if unknown time	2.5	ICH combined with clinical deterioration of ≥4 points on NIHSS, or death
18	Retrospective, single center	71 (70.4)	73	15.1	T2*-GRE	1.5	—	—	19.7	IV rtPA	7	ICH with worsening of ≥3 points on NIHSS
19	Prospective, single center	224 (54)	76.2	13.4	T2*-GRE	1.5	20	6	32.1	IV tPA within 3 h	1	Local or extraischemic parenchymal hemorrhage type 2 with worsening of ≥4 points on NIHSS within 24 h of thrombolysis
8	Prospective, multicenter (13)	570 (—)	69 (59–77)[a]	13 (IQR 8–17)	T2*-GRE	—	14–49	5–7	15.1 (9.1–19.7)	IV tPA within 6 h	10	ICH with worsening of ≥4 points on NIHSS
20	Retrospective, single center	65 (57)	67	—	T2*-GRE	—	30	5	15.7 (8.1–26.4)	IV tPA within 3 h (n = 12); IA UK within 6 h (n = 53)	7	Symptomatic hemorrhage, any neurologic deterioration within 48 h that could be attributed to hemorrhage presence on follow-up MRI
21	Prospective, multicenter (3)	70 (44.3)	70.5	Mean ± SD: 11 ± 9.2, 13 ± 9.8, CMB (+)/(−)	T2*-GRE	1.5	14–47	5	38.5 (26.7–51.4)	IV tPA within 6 h	30	ICH with worsening of ≥2 points on NIHSS
22	Retrospective, single center	44 (—)	63.2 ± 14.1	14 ± 5.8 (mean ± SD)	T2*-GRE	1.5	26	5	18.2 (8.2–32.7)	IV tPA at 2 different doses within 7 h	7	ICH with worsening of ≥4 points on NIHSS or ≥1 point on NIHSS consciousness level
7	Retrospective, single center	41 (—)	—	—	T2*-GRE	1.5	15	7	12.2 (4.1–26.2)	IV/IA tPA within 3 h; IA UK or tPA mechanical clot disruption during IA thrombolysis	7	ICH with worsening of ≥4 points on NIHSS or ≥1 point on NIHSS consciousness level

Abbreviations: CI = confidence interval; FLAIR = fluid-attenuated inversion recovery; FU = follow-up; IA = intra-arterial; ICH = intracerebral hemorrhage; IQR = interquartile range; NIHSS = NIH Stroke Scale; SWI = susceptibility-weighted imaging; T2*-GRE = T2*-weighted gradient-recalled echo; rtPA = recombinant tissue plasminogen activator; tPA = tissue plasminogen activator; UK = urokinase.
[a] First and third quartile, 59 and 77 years.

Table 2 Ascertainment of risk of bias: Summary of study quality indicators

Study reference	Study size (>100)	Clear definition of study population	Standardized MRI parameters	CMB criteria clearly defined	ICH criteria clearly defined	Awareness of >2 CMB mimics	Standardized rating scale or trained observer agreement reported (inter- and intrarater)	Classification of CMB distribution	Adjusted results for other risk factors	Quality score (no. of quality indicators fulfilled)
15	✓	✓	✓	✓	✓	✓	✓	✓	✓	9/9
16	✓	✓	✓	✓	✓	✓	✓	✓	✓	9/9
17	✓	✓	✓	✓	✓	✓	✓	✓	✓	9/9
18	✗	✓	✓	✗	✓	✗	✗	✗	✓	4/9
19	✓	✓	✓	✗	✓	✗	✗	✗	✓	5/9
8	✓	✓	✗	✓	✓	✓	✓	✗	✗	6/9
20	✗	✓	✓	✓	✗	✓	✓	✓	✓	8/9
21	✗	✓	✓	✓	✓	✓	✓	✗	✓	8/9
22	✗	✓	✓	✓	✓	✓	✓	✗	✓	8/9
7	✗	✓	✓	✓	✓	✓	✓	✗	✓	8/9

Abbreviations: CMB = cerebral microbleed; ICH = intracerebral hemorrhage.

CMB (−) groups were not significantly different in basic characteristics (including age, sex, or stroke severity) except that in 2 studies, higher age was associated with CMBs.[8,17] The crude prevalence of CMBs on pretreatment MRI scans was 472 of 2,028 (23.3%).

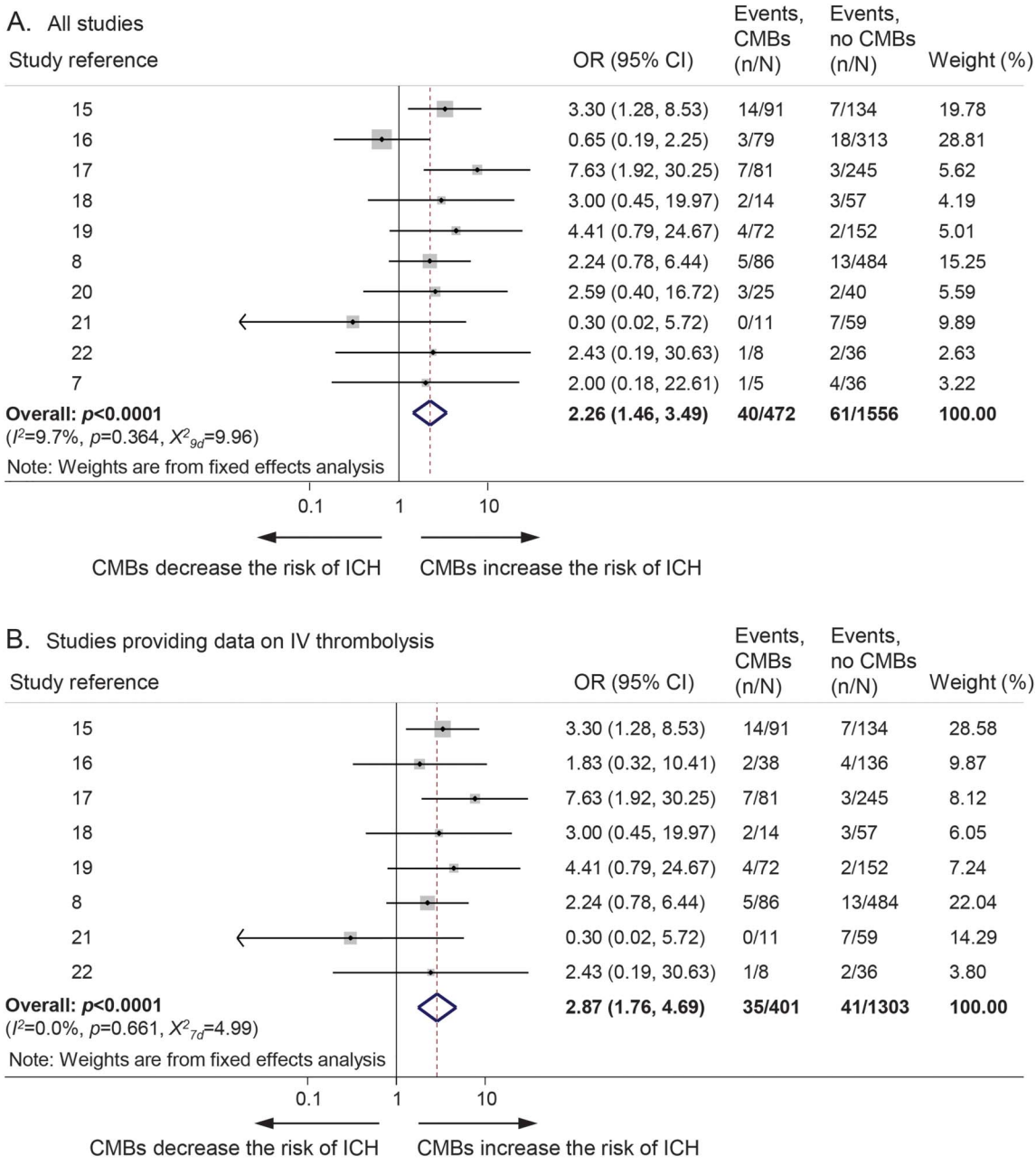
Symptomatic ICH occurred in 5% (95% CI: 4.1%–6.2%) of the entire population. Among patients with CMBs, 40 of 472 (8.5%; 95% CI: 6.1%–11.4%) experienced a symptomatic ICH after thrombolysis compared with 61 of 1,556 patients (3.9%; 95% CI: 3.0%–5.0%) without CMBs. The OR of ICH across all pooled studies was 2.26 (95% CI: 1.46–3.49; $p < 0.0001$) (figure 2). Eight studies, including 1,704 patients (n = 401 with CMBs), provided data on patients treated with IV thrombolysis only.[8,15–19,21,22] Pooled analysis of these studies demonstrated OR for the presence of CMBs and the development of symptomatic ICH to be 2.87 (95% CI: 1.76–4.69; $p < 0.0001$) (figure 2). These results remained consistent when only the 4 largest studies (including >100 patients)[8,15–17] were pooled in meta-analysis.

No significant heterogeneity was noted between studies (that provided relevant data) according to age, sex, hypertension, or initial stroke severity (NIH Stroke Scale score) for any of the outcomes (all p values >0.1). In further meta-regression analyses, none of the key methodologic characteristics of included studies (i.e., total quality score as presented in table 2 and MRI parameters) reached statistical significance for the association with postthrombolysis ICH occurrence (table 3). In all pooled analyses, the results were of similar effect size when exploring the influence of each individual study on the overall meta-analysis summary estimates (data not shown). All analyses (including the IV thrombolysis only subanalysis) were consistent using a random-effects model.

DISCUSSION Our updated meta-analysis in more than 2,000 patients with acute ischemic stroke shows that CMB presence on pretreatment MRI scans is associated with an approximate doubling of the risk of symptomatic ICH following thrombolytic treatment. These results remained consistent in predefined subgroup pooled analyses including only patients treated with IV rtPA.

CMBs may heighten the risk of thrombolysis-related ICH either as the direct source of the ICH or, more likely, as a general marker of hemorrhage-prone pathologic state due to severe small vessel disease. It seems plausible that small vessel disease (including cerebral amyloid angiopathy and hypertensive arteriopathy), causing the blood vessel walls to become brittle and fragile, may interact with other factors that potentially increase bleeding risk after rtPA, such as upregulation of matrix metalloproteinases, disruption of the blood-brain barrier, hyperglycemia, and hypertension,[2,23] lowering the threshold for postthrombolysis ICH.[24] The relationship of cerebral small vessel disease with an increased risk of developing ICH after thrombolysis is also supported by studies showing an association between moderate to severe leukoaraiosis (another neuroimaging correlate of microangiopathy) and postthrombolysis ICH.[24] However, these studies did not adjust for presence of concurrent CMBs, and the extent to which leukoaraiosis in itself can be used as a reliable predictor of ICH is questionable, since it lacks pathologic specificity and may reflect mainly ischemic aspects of microangiopathy.[24] Compared with leukoaraiosis, which can also be assessed on CT, CMBs, which can only be detected on MRI, may be a more

Figure 2 Forest plots of CMB presence and risk of postthrombolysis symptomatic ICH



Meta-analysis of the association between symptomatic ICH risk in patients with acute ischemic stroke treated with thrombolysis, in relation to the presence of CMBs on pretreatment MRI scans. Pooled analysis results in all studies/entire study population (A) and in studies providing data on patients treated with IV thrombolysis only (B). CI = confidence interval; CMB = cerebral microbleed; ICH = intracerebral hemorrhage; OR = odds ratio.

specific marker of a bleeding-prone form of small vessel disease.[5] Indeed, the role of CMBs as reliable predictors of ICH risk in other clinical scenarios outside acute stroke and thrombolysis (including incident and recurrent spontaneous ICH) is supported by recent data.[25–28] Furthermore, higher rates of future spontaneous ICH have been observed in patients with CMBs treated with aspirin.[29,30] It is important to note that patients with moderate to severe leukoaraiosis appear to still obtain clinical benefit from IV rtPA despite the increased risk of symptomatic ICH.[31] Accordingly, in the absence of comparative data demonstrating lack of functional benefit from thrombolysis in CMB-positive acute ischemic stroke patients vs those without CMBs, our results do not justify withholding IV rtPA from otherwise eligible candidates solely on the basis of CMB presence on MRI.

A small number of autopsy cases also support a direct role of preexisting small vessel pathology, particularly cerebral amyloid angiopathy, in some cases of thrombolysis-related ICH.[32] In a small PET study

Table 3 Ascertainment of risk of confounding in univariable meta-regression analyses evaluating the association between important methodologic characteristics of included studies and the occurrence of postthrombolysis intracerebral hemorrhage

Potential confounder	OR	95% CI	*p* Value
Total study quality score (see table 2)	0.57	0.02–20.67	0.726
SWI vs T2*-GRE	0.58	0.14–2.35	0.394
Field strength, T/alternative	1.08/2.06	0.29–4.01/0.73–5.89	0.890/0.140
Section thickness, mm	0,95	0.65–1.39	0.753
Echo time for T2*-GRE, ms	0.94	0.81–1.08	0.274

Abbreviations: CI = confidence interval; OR = odds ratio; SWI = susceptibility-weighted imaging; T2*-GRE = T2*-weighted gradient-recalled echo.

using Pittsburgh compound B to detect cerebral β-amyloid burden, cortical Pittsburgh compound B retention was higher among patients with thrombolysis-related parenchymal hemorrhages compared with thrombolysed acute stroke patients without hemorrhage and normal controls.[33] Finally, an increased risk of ICH was associated with IV thrombolysis in cerebral amyloid angiopathy transgenic mice, which display the typical findings of human amyloid angiopathy.[9,34,35] Given this circumstantial evidence suggesting a link between thrombolysis-related ICH and cerebral amyloid angiopathy, multiple strictly lobar CMBs (a characteristic marker of the disease)[36] may be of particular prognostic value, but, limited by the available data, we were unable to address this question in our meta-analysis. It should be noted that preexisting cerebral small vessel disease pathology might be specifically related with remote postthrombolysis ICH distinct from the acute infarct area.[37,38]

Several methodologic aspects of the included studies and limitations of our analyses deserve consideration. First, the MRI parameters used varied between studies, and this is likely to affect the prevalence of CMBs: it has been demonstrated that among others, field strength, echo time, and the use of SWI have a significant effect on CMB detection.[39] For example, the relative low prevalence of CMBs in the 2002 study by Kidwell et al.[7] may be explained by the short echo time and low field strength used. Second, slightly different definitions for postthrombolysis ICH and different follow-up strategies were used. However, most definitions included ICH (both hemorrhagic transformation and parenchymal hemorrhage) that was likely to be clinically relevant and associated with clinical deterioration. Third, different thrombolysis protocols were used across the cohorts, but we accounted for this methodologic heterogeneity by presenting a sensitivity analysis including only patients treated with IV tPA. It is reassuring that studies that included both IV and intraarterial thrombolysis patients did not find any significant difference in the occurrence of hemorrhagic complications.[20,22] Although published data suggest further increased symptomatic ICH rates in patients with higher CMB counts,[10,17] the studies overall have not systematically reported on ICH risk in relation to CMB number and anatomical distribution using uniform definitions, precluding any meaningful pooled analysis without individual patient data available. Finally, there is a clear possibility of selection bias, since not all acute stroke patients undergo MRI, and such patients were excluded from all study cohorts. The limitations highlighted above would tend to bias our analysis toward a null result (no group differences between patients with vs without CMBs), suggesting that CMB burden, or a certain CMB cutoff, may in fact be a stronger predictor of postthrombolysis ICH than we have been able to demonstrate here.[10]

Although our analysis does show that the presence of CMBs on pretreatment MRI increases the risk of early symptomatic ICH after thrombolysis, these results should be treated with caution and considered preliminary and hypothesis-generating. Despite our best efforts, differences in key methodologic aspects in the available studies might still be confounding the relationship under investigation. Since MRI is often not the first-line routine imaging modality, our results cannot yet be translated into clinical practice. In addition, data are limited on CMBs and interventional endovascular treatments in acute stroke, especially without prior IV thrombolysis; only 2 of the studies included in our meta-analysis included such data. Based on present evidence, detecting CMBs should not prevent thrombolytic treatment, given the clear benefit of this treatment on longer-term outcomes in large randomized controlled trials. Moreover, the extra information about ICH risk provided by MRI needs to be carefully balanced against any potential to delay thrombolysis by using pretreatment MRI protocols. Our study, however, raises the question of whether the balance of risk vs benefit may not favor intervention in certain patient subgroups, for example elderly individuals with known cognitive

impairment who might be more likely to harbor multiple or lobar CMBs and could potentially be targeted for MRI. Data presented here thus reinforce the need to further evaluate CMBs in individual patient meta-analyses and large multicenter studies, not only for the risk of postthrombolysis early symptomatic ICH, but also for long-term functional outcome.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. A. Charidimou and Dr. Z. Fox. A. Charidimou: study concept and design, systematic review, data extraction, data analysis, write-up. A. Shoamanesh: study concept, systematic review, data extraction, critical revisions. D. Wilson: systematic review, data extraction, critical revisions. Q. Gang: translation of non-English papers, critical revisions. Z. Fox: statistical analysis, critical revisions. H.R. Jäger: critical revisions. O.R. Benavente: critical revisions. D.J. Werring: study concept and design, critical revisions, funding.

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Medical marijuana: Between a plant and a hard place (see the August 2015 issue of Neurology® Clinical Practice)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the September 15, 2015, issue of *Neurology*. In the second segment, Dr. Matthew Wong talks with Dr. David Gloss about his paper on medical marijuana. Dr. Sarah Wesley reads the e-Pearl of the week about arterial retinal ischemic disease. In the next part of the podcast, Dr. Andy Southerland focuses his interview with Dr. Bert Vargas on the topic of teleconcussion.

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