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Postthrombolysis intracranial hemorrhage risk of cerebral microbleeds in acute stroke patients: a systematic review and meta-analysis

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Abstract

It has been questioned whether patients with cerebral microbleeds are at a greater risk for the development of symptomatic intracerebral hemorrhage following thrombolytic therapy in the management of acute ischemic stroke. Thus far, observational studies have not shown a statistically significant increased risk; however, these have been limited by small sample size. The aim is to better quantify the risk of postthrombolysis intracerebral hemorrhage in patients with acute ischemic stroke and cerebral microbleeds on magnetic resonance imaging. A systematic review of controlled studies investigating the presence of microbleeds on magnetic resonance imaging as a risk factor for intracerebral hemorrhage following thrombolysis in acute stroke patients was conducted. A random effects model meta-analysis was performed. In pooled analysis of five studies totaling 790 participants, the prevalence of microbleeds was 17%. The presence of microbleeds revealed a trend toward an increased risk of postthrombolysis symptomatic intracerebral hemorrhage [odds ratio: 1·98 (95% confidence interval, 0·90 to 4·35; $P = 0·09$), $I^2 = 0\%$]. Adjusted analysis minimizing potential bias resulted in an increased absolute risk of 4·6% for the development of symptomatic intracerebral hemorrhage in patients with cerebral microbleeds [odds ratio: 2·29 (95% confidence interval, 1·01 to 5·17), $I^2 = 0\%$] reaching borderline significance ($P = 0·05$). A significant relationship between increasing microbleed burden and symptomatic intracerebral hemorrhage ($P = 0·0015$) was observed. Isolated analysis of studies using exclusively intravenous tissue plasminogen activator was insignificant. Our data suggest that patients with cerebral microbleeds are at increased risk for symptomatic intracerebral hemorrhage following thrombolysis for acute ischemic stroke. However, current data are insufficient to justify withholding thrombolytic therapy from acute ischemic stroke patients solely of the basis of cerebral microbleed presence.

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Keywords

complications; hemorrhage; microbleeds; microhemorrhages; thrombolysis; tPA; urokinase

Introduction

Cerebral microbleeds (CMBs) on T2*-weighted gradient echo (GRE) imaging are believed to represent hemosiderin deposition from previous blood degradation and are associated with surrounding microangiopathy. However, histopathological analyses of CMBs have also demonstrated the presence of intact erythrocytes, which puts into question the chronicity of all lesions (1).

From the outset of their appearance within the literature, it was suggested that CMBs were strongly associated with intracerebral hemorrhage (ICH) (2-4). This led investigators to question whether CMBs could serve as predictors of ICH following antithrombotic and thrombolytic interventions in stroke patients. A recent systematic review has shown that among antithrombotic users with CMBs, the odds ratio (OR) of subsequent ICH is 12·1 [95% confidence interval (CI), 3·4 to 32·5; $P = 0·001$] (5).

Postthrombolysis ICH is the most concerning complication of acute stroke management. Determining risk factors for postthrombolysis ICH in individual patients is an essential step in weighing the risks and benefits of thrombolytic therapy. In recent years, the use of magnetic resonance imaging (MRI) for the management of acute stroke has been raised for the purpose of, among others, possibly excluding patients with CMBs (6,7). Although anecdotal case reports have suggested an association between postthrombolysis ICH and CMBs (8), a small number of nonrandomized observational studies have yet to produce a statistically significant association. However, all of these studies were confounded by small sample sizes, leaving the matter unresolved (9).

The aim of this study is to assess whether CMBs on baseline MRI of acute ischemic stroke patients receiving thrombolytic therapy resulted in an increased risk of ICH and/or symptomatic ICH (sICH). We performed a systematic review and pooled meta-analysis of all controlled studies.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (10).

Eligibility criteria

Randomized controlled trials or controlled observational studies (retrospective or prospective) that report on the risk of CMBs on MRI for the development of ICH following intravenous (IV) or intra-arterial thrombolysis in acute ischemic stroke patients were isolated. Articles meeting the following criteria were included: provided information on the methodology of thrombolytic therapy (agent, dosage, route, time to treatment, etc.); and ascertainment of ICH based on neuroimaging and/or autopsy with clinical evidence of

deterioration on neurological examination as part of the definition for sICH. Exclusion criteria included failure to define sICH and rating of CMBs on imaging obtained following the administration of thrombolysis. Outcome measures of interest were any postthrombolysis ICH and sICH.

Search strategy

Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, and Cochrane Central Register of Controlled Trials searches with no date limitations or language restrictions were conducted on June 2010 using the following broad search terms: microbleed$, microhaemorrhage$, and microhemorrhage$ (1 or 2 or 3). In order to identify unpublished studies, the same search terms were applied to conference abstract databases from the International Stroke Conference, the European Stroke Conference, and the American Academy of Neurology Annual Meeting between 2008 and 2010. The references of included trials and recent review articles up to April 2011 were checked for relevant studies.

Study selection and data extraction

Two unblinded reviewers (A. S. and C. S. K.) considered all titles and abstracts for eligibility in a systematic manner. Discrepancies were reviewed by three investigators (A. S., P. A. L., and O. B.), and a collaborative decision was made to include or exclude the study. A. S., C. S. K., and P. A. L. independently extracted information on study design, MRI parameters, treatment and dosage, patient demographics, follow-up period, ascertainment of outcomes, and outcome measures onto a spreadsheet. Disagreements were resolved by consensus. Journal authors were contacted for data needing clarification.

Assessment of risk of bias

Two reviewers (A. S. and C. S. K.) independently assessed the individual studies' risks of bias in accordance with previously published tools (11), noting methodology for participant selection, methodology for measuring exposure and outcomes, blinding, loss to follow-up, methods for controlling confounding, and declaration of conflicts of interest. Conference abstracts were searched in an attempt to reduce the possibility of publication bias.

Statistical analysis

RevMan 5·022 (Nordic Cochrane Centre, København, Denmark) was used to estimate pooled ORs based on a random effects model meta-analysis (dichotomous). Since adjusted data were not available, raw outcome data were used to yield unadjusted ORs. Statistical heterogeneity was assessed using I^2 statistic, with values of 30–60% representing a moderate level of heterogeneity (12).

In the presence of statistical heterogeneity, a sensitivity analysis was performed by comparing random effects to fixed effects meta-analysis and subgroup analysis. Irrespective of statistical heterogeneity, in order to account for methodological variability in the route of thrombolysis treatment among the included studies, a subgroup analysis was performed to isolate studies that only treated with IV tissue plasminogen activator (tPA). A data-driven adjusted analysis was performed to minimize potential sources of bias. CMB burden was

graded as either absent, one to two CMBs, three to 10 CMBs, or >10 CMBs as per Kim *et al*. (13). Chi-square test was used to assess the relation between increasing CMB burden and postthrombolysis ICH.

Results

Five studies (all published) that met our predetermined criteria were identified (Fig. 1). Study characteristics are summarized in Table 1 (13-18). The upper limit of time to treatment was six-hours for most studies. All studies used either IV tPA or urokinase. Three studies used only IV tPA (14-16). Each study had a prespecified follow-up schedule that included both neuroimaging and clinical assessment using the National Institute of Health Stroke Scale (NIHSS). Definitions of sICH were broadly similar across the studies but differed mostly with respect to the allotted timeframe from thrombolysis to ICH (range: 24 h to 10 days). The upper limit of CMB diameter was five-millimeters in all studies. Four studies used conventional GRE (13-16), whereas Kidwell *et al*. (17) used both conventional GRE (seven patients) and susceptibility-weighted imaging (all patients). They, however, reported that CMB detection rate did not differ between the two sequences in patients who underwent both of them. Study demographics are summarized in Table 2. Collectively, the five studies were composed of 790 patients (study sample size range: 41–570), 135 (17·1%) of which had CMBs.

The main source of bias within all the studies was the lack of adjusted data (Table 3). Four studies (13,14,16,17) found no statistically significant difference with respect to age and history of hypertension between patients with CMBs and those without. Only one (16) of these studies reported baseline blood pressure prior to treatment. Four studies (14-17) documented no statistically significant difference in baseline NIHSS scores between the two groups. Although all of the studies had blinded rating of neuroimaging, none of the studies mentioned whether the clinicians administering the NIHSS were blinded to patient information (i.e. CMB status). Lastly, Kakuda *et al*. (16) lost 18·6% of their sample population (eight deaths and seven refusals) to follow-up.

Any ICH developed in 14·9% of the entire population and occurred in 19·3% of patients with CMBs in comparison with 14·0% of those without CMBs (Fig. 2). Pooled analysis demonstrates OR for the presence of CMBs and the development of any postthrombolysis ICH to be 1·38 (95% CI, 0·77 to 2·48; $P = 0·28$) with a low level of statistical heterogeneity ($I^2 = 11\%$). sICH developed in 4·8% of the total population and occurred in 7·4% of patients with CMBs in comparison with 4·3% of patients without CMBs. The OR for the presence of CMBs and the development of sICH is 1·98 (95% CI, 0·90 to 4·35; $P = 0·09$) with no evidence of statistical heterogeneity ($I^2 = 0\%$). Exclusion of the Kakuda *et al*. (16) study from this analysis due to potential loss to follow-up bias (Fig. 3) yields an OR of 1·73 (95% CI, 0·97 to 3·09; $P = 0·07$; $I^2 = 0\%$) for the presence of CMBs and the development of any ICH (18·5% in CMB-positive vs. 10·6% in CMB-negative patients) and a borderline significant OR of 2·29 (95% CI, 1·01 to 5·17; $P = 0·05$; $I^2 = 0\%$) for the development of sICH (8·1% in CMB-positive vs. 3·5% in CMB-negative patients).

In subgroup analysis of studies that only used IV tPA (Fig. 4), any ICH developed in 12·6% of the 684 patients and occurred in 15·2% of patients with CMBs in comparison with 12·1% of patients without CMBs [OR 1·28 (95% CI, 0·44 to 3·72; $P = 0·65$), $I^2 = 54\%$]. sICH developed in 4·1% of these patients and occurred in 5·7% of patients with CMBs in comparison to 3·8% of patients without CMBs [OR 1·85 (95% CI, 0·73 to 4·68; $P = 0·19$), $I^2 = 0\%$].

The number of CMBs per individual patient is summarized in Table 4. Two of these studies (13,15) provided adequate information to allow for the analysis of the risk of both any postthrombolysis ICH and sICH according to CMB burden. In pooled analysis of these 635 patients (Fig. 5), any ICH occurred in 7·3% (38/524) of patients without CMBs, 9·9% (8/81) of patients with one to two CMBs, 17·4% (4/23) of patients with three to 10 CMBs, and 57·1% (4/7) of patients with >10 CMBs ($P < 0·0001$). The OR for the development of any ICH in patients with >10 CMBs in comparison with those without is 7·41 (95% CI, 1·51 to 36·40; $P = 0·01$; $I^2 = 0\%$). sICH (Fig. 6) occurred in 2·9% (15/524) of patients without CMBs, 4·9% (4/81) of patients with one to two CMBs, 8·7% (2/23) of patients with three to 10 CMBs, and 28·6% (2/7) of patients with >10 CMBs ($P = 0·0015$). The OR for the development of sICH in patients with >10 CMBs in comparison with those without is 12·18 (95% CI, 1·67 to 88·70; $P = 0·01$; $I^2 = 7\%$). Incorporating Kakuda *et al*.'s data, which only provide adequate information to assess sICH according to CMB burden, alters the previous distribution to 3·8% (22/583), 4·4% (4/90), 8·0% (2/25), and 28·6% (2/7) for zero CMBs, one to two CMBs, three to 10 CMBs, and >10 CMBs, respectively ($P = 0·01$, $n = 705$). Their study did not have any patients with >10 CMBs to allow inclusion within the random effects model meta-analysis.

Discussion

Our study is the first meta-analysis examining the risk of CMBs for the development of postthrombolysis sICH. Pooled analysis of 790 acute stroke patients receiving thrombolytic therapy demonstrated a nonsignificant trend toward an increased rate of sICH in patients with CMBs ($P = 0·09$). However, repeat analysis excluding the Kakuda *et al*. study, which eliminated the possibility of loss to follow-up bias and reduced statistical heterogeneity, led to a borderline significant increased absolute risk of 4·6% ($P = 0·05$) for the development of sICH in patients with CMBs. There was also a significant relationship between increasing CMB burden and the risk of developing any ICH ($P < 0·0001$) and sICH ($P = 0·0015$). This risk was most substantial in patients with >10 CMBs, with 57% experiencing any ICH [OR 7·41 (95% CI, 1·51 to 36·40; $P = 0·01$), $I^2 = 0\%$] and 29% experiencing sICH [OR 12·18 (95% CI, 1·67 to 88·70; $P = 0·01$), $I^2 = 7\%$]. Our findings would coincide with the increased risk of postthrombolysis sICH found in association with increasing severity of leukoaraiosis, another radiological marker of small vessel disease (19). Similarly, a correlation between increasing CMB burden and an increased risk of ICH while on antithrombotic therapy has been previously reported (20). As none of the studies within the analysis were designed to determine long-term clinical outcome measures and it is still unclear whether sICH (a potential misnomer) independently leads to poor outcomes (21), whether CMBs are a marker of poor functional outcome in tPA-treated individuals remains uncertain.

The overall rates of 14·9% for any ICH and 4·8% for sICH within the analysis population are similar to findings from a previously published meta-analysis on the safety of thrombolytic therapy in acute ischemic stroke (11·5% and 5·2% respectively) (22). However, only 17·1% of the patients within our analysis had CMBs, which is less than the expected rate within an ischemic stroke population (33·5%) (23). This discrepancy may be explained by the observation that lacunar strokes, which have the highest prevalence of CMBs among ischemic stroke subtypes (23), are underrepresented in acute stroke patients undergoing thrombolytic therapy (24).

Limitations

The most notable limitations of our analysis are the inherent biases associated with the use of observational studies, the use of unadjusted data that render our analysis vulnerable to confounding variables, and a small sample size. However, despite its lack of power, our analysis was still able to demonstrate a borderline significant increased OR of 2·29 for the development of sICH in patients with CMBs and a significantly increased risk in patients with higher CMB burden.

There was also significant methodological heterogeneity among the studies. We attempted to minimize this by performing a subgroup analysis of only IV tPA studies at the cost of a lower sample size and a greater weight distribution to Kakuda *et al*.'s data, which was the most prone to bias. The use of IV tPA outside of conventional time windows also limits our findings.

Future research

Future prospective studies with much larger sample sizes are required to clarify the significance of the association between CMBs and the development of postthrombolysis sICH. Extrapolating from the data of our adjusted analysis for sICH, a study would require a total sample of 1278 patients to assess an OR of 2·29 for the risk of sICH in patients with CMBs in comparison with those without (power 80%, significance level 0·05). In view of the inevitable multicenter nature of such an undertaking, an attempt to standardize imaging parameters for CMB detection across centers is encouraged. Rating of CMBs should be performed in a systematic and reproducible manner utilizing one of the two currently available CMB rating scales (25,26). This will allow further characterization of sICH risk in association with the number of CMBs among patients, and with CMB topography, as purely lobar/cerebellar CMBs indicative of cerebral amyloid angiopathy may have a higher inherent risk (27-29). Intraobserver and interobserver reliability for CMB rating should also be provided. Studies should initially focus on patients receiving IV tPA as it is the most widely used form of thrombolysis with the largest supporting body of evidence. To allow for comparison of study results with previously published data, analysis of rates of sICH should be performed with the use of other previously published sICH definitions in addition to the study's primary definition of sICH. Studies should determine clinical outcome measures at 90 days follow-up to elucidate the influence of CMBs on functional outcome. Lastly, data should be adjusted for potential confounding variables previously associated with increased sICH risk (19,30).

Conclusions

Our data suggest an increased risk of sICH following thrombolysis in patients with CMBs, particularly in patients with higher CMB burden, but it is unclear whether this is an independent association. Current data do not, however, justify withholding IV tPA, a standard of care, from acute ischemic stroke patients solely of the basis of CMB presence. Future large and well-designed prospective studies are required to better characterize this association.

Acknowledgments

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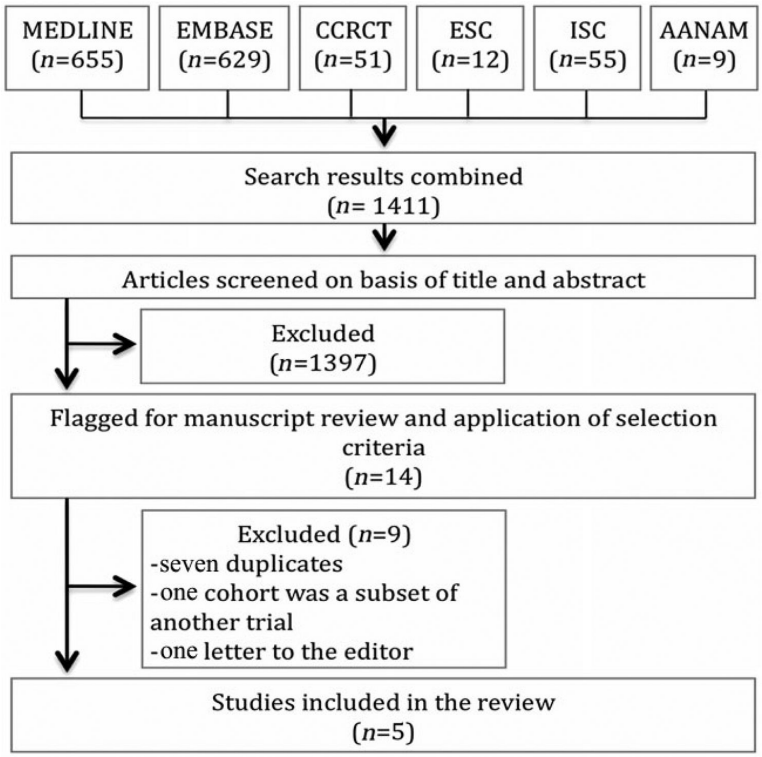

Fig. 1.

Literature search and study selection. AANAM, American Academy of Neurology Annual Meeting, CCRT, Cochrane Central Register of Controlled Trials; ESC, European Stroke Conference; ISC, International Stroke Conference.

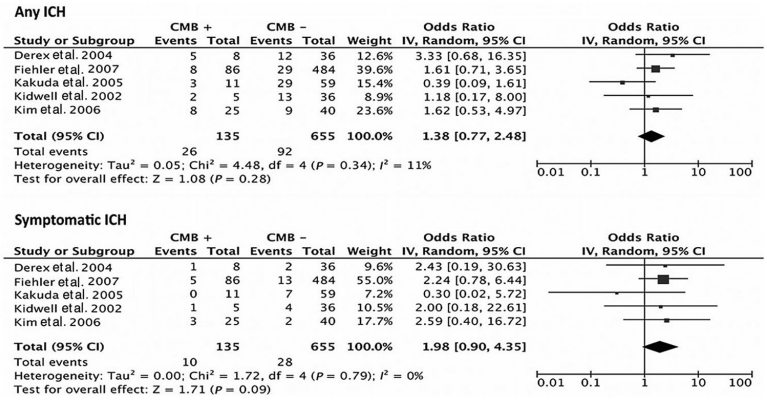

Fig. 2.

Pooled analysis for the risk of any ICH and sICH following IV and/or IA thrombolysis (n = 790). IA, intra-arterial; ICH, intracerebral hemorrhage; IV, intravenous; sICH, symptomatic ICH.

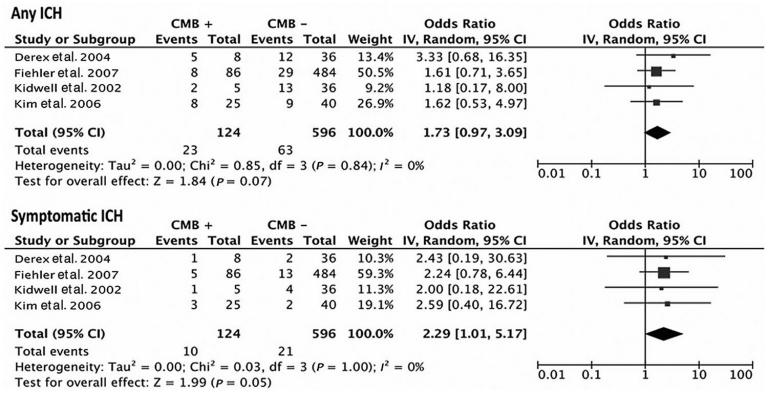

Fig. 3.

Pooled analysis for the risk of any ICH and sICH following IV and/or IA thrombolysis adjusted for potential bias (n = 720). IA, intra-arterial; ICH, intracerebral hemorrhage; IV, intravenous; sICH, symptomatic ICH.

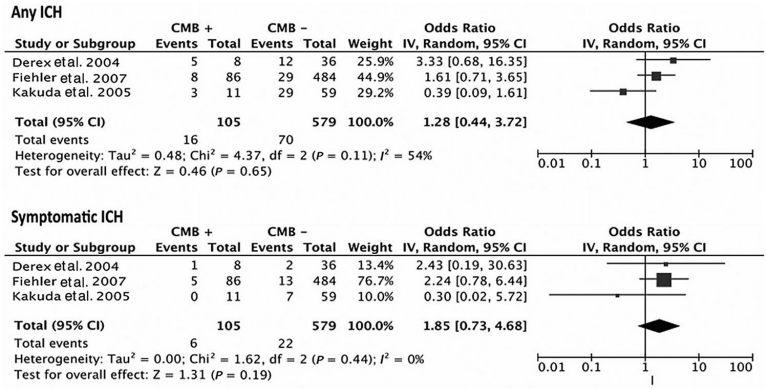

Fig. 4.

Risk of any ICH and sICH following IV tPA (*n* = 684). ICH, intracerebral hemorrhage; IV, intravenous; sICH, symptomatic ICH; tPA, tissue plasminogen activator.

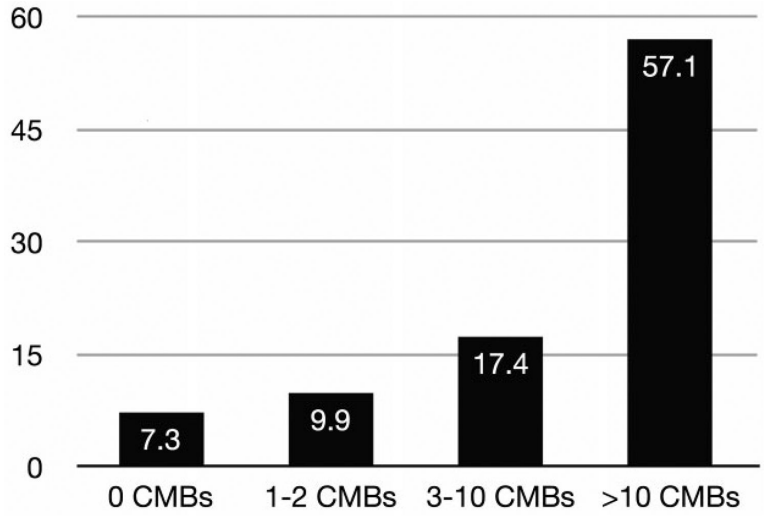

Fig. 5.

Percentage distribution of any ICH according to CMB burden; χ^2 test: $P < 0{\cdot}0001$ ($n = 635$). ICH, intracerebral hemorrhage; CMB, cerebral microbleed.

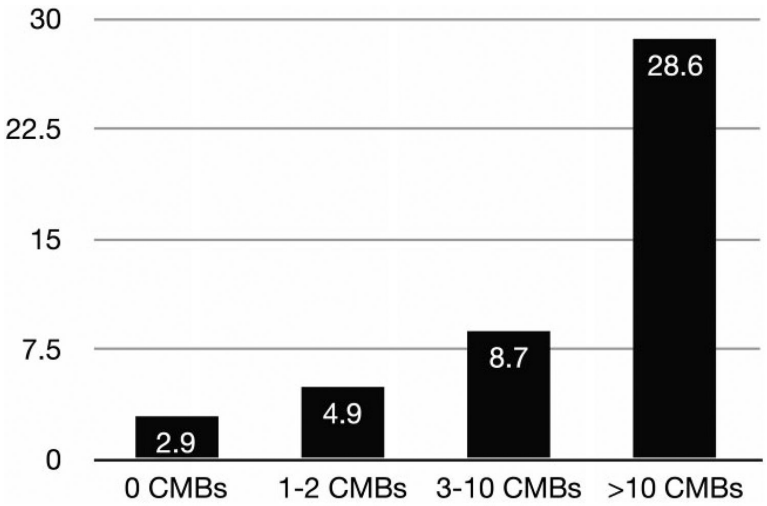

Fig. 6.

Percentage distribution of sICH according to CMB burden; χ^2 test: $P = 0{\cdot}0015$ ($n = 635$). ICH, intracerebral hemorrhage; CMB, cerebral microbleed.

Table 1

Study characteristics

Study	Design; country; sample size	Inclusion criteria	Treatment	Dose	Follow-up schedule	T2* GRE parameters [TR/TE (ms)/flip angle (°)]	Outcome measures	Definition of symptomatic ICH
Derex *et al.* 2004 (14)	Retrospective; France; 44	• Acute ICA stroke • Symptom duration of <seven-hours	IV tPA	• 0·9 mg/kg over 60 mins (10% bolus, maximum dose: 90 mg), or • 0·8 mg/kg over 90 mins (10% bolus, maximum dose: 90 mg)	• NIHSS at 24 h and seven-days • CT at 24 h and seven-days • CT if acute deterioration	800/26/20	• Asymptomatic ICH • Symptomatic ICH	ICH associated with at least a four-point worsening on the NIHSS or at least a one-point worsening on the NIHSS LOC score within seven-days of thrombolysis
Fiehler *et al*. 2007 (15)	Prospective/retrospective (center-dependent) nonrandomized; multicenter (EU, NA, South Korea); 570	• Acute ischemic stroke within six-hours • DWI and/or perfusion lesion on MRI • Diffusion/perfusion mismatch for patients within three- to six-hours	IV tPA	0·9 mg/kg (maximum dose 90 mg)	• NIHSS with every imaging. • CT or MRI at predefined interval within five-to 10 days • CT or MRI within one- to 10 days if acute deterioration	0·8–2140/14–49/na	• Any ICH • Symptomatic ICH	ICH (PH2*) associated with at least a four-point worsening on the NIHSS within 10 d of thrombolysis
Kakuda *et al*. 2005 (16)	Prospective nonrandomized; multicenter (NA, Belgium); 70	• Acute ischemic stroke within three- to six-hours • >18 years of age • NIHSS >5	IV tPA	0·9 mg/kg over 60 mins (10% bolus)	• NIHSS within three- to six-hours and 30 d • MRI within three- to six-hours and 30 d • CT if acute deterioration	450–800/14–47/60	• Asymptomatic ICH • Symptomatic ICH	ICH associated with at least a two-point worsening on the NIHSS within 36 h of thrombolysis
Kidwell *et al*. 2002 (17)	Prospective nonrandomized; United States; 41	• Acute ischemic stroke with large vessel occlusion on angiography • Pretreatment GRE or SWI performed	• Combined IV/IA tPA ± mechanical clot disruption within three-hours of symptom onset, or • IA thrombolysis (urokinase or tPA) ± mechanical clot disruption within three- to six-hours of symptom onset for AC events or three-hours to 12 h for PC events.	• Within three-hours: IV tPA at 0·6 mg/kg (10% bolus) followed by 10 mg/h IA infusion of tPA until recanalization or max IA dose of 22 mg • Within three-hours to 12 h: IA tPA until recanalization or max of 22 mg or IA urokinase until recanalization or max dose of one million U	• NIHSS 24 h and seven-days • CT immediately and 24 h	Conventional GRE (n = 7): 800/15/30; SWI (n = 41, all participants): 2000/60/na	• Any ICH • Symptomatic ICH	ICH associated with at least a four-point worsening on the NIHSS or at least a one-point worsening on the NIHSS LOC score within 24 h of thrombolysis

Study	Design; country; sample size	Inclusion criteria	Treatment	Dose	Follow-up schedule	T2* GRE parameters [TR/TE (ms)/flip angle (°)]	Outcome measures	Definition of symptomatic ICH
Kim *et al*. 2006 (13)	Retrospective; South Korea; 65	• Acute AC stroke within six-hours • No history of previous ICH • Thrombolysis immediately following initial MRI • Follow-up MRI one- to three-days following thrombolysis.	• IV tPA within three-hours, or • IA urokinase within six-hours	u • IV tPA 0·9 mg/kg, or • IA urokinase until recanalization or max dose of one million U	• NIHSS 24 h and seven-days • MRI one- to three-days	400/30/20	• Hemorrhagic transformation (any ICH) • Symptomatic ICH	ICH associated with any neurological deterioration within 48 h of thrombolysis

EU, Europe; NA, North America; ICA, internal carotid artery; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; GRE, gradient echo; SWI, susceptibility-weighted imaging; AC, anterior circulation; IV, intravenous; tPA, tissue plasminogen activator; IA, intra-arterial; PC, posterior circulation; min, minutes. TR, repetition time; TE, echo time; SWI, susceptibility weighted imaging; na, information not provided; NIHSS, National Institute of Health Stroke Scale; CT, computed tomography; ICH, intracerebral hemorrhage; LOC, level of consciousness; PH2, parenchymal hematoma type 2; U, units.

*As defined by the European Cooperative Acute Stroke Study (18).

Table 2

Study demographics and outcomes

Study	Derex *et al*. 2004 (14)	Fiehler *et al*. 2007 (15)	Kakuda *et al*. 2005 (16)	Kidwell *et al*. 2002 (17)	Kim *et al*. 2006 (13)	Total
Population size	44	570	70	41	65	790
Age	63 (mean)	69 (median)	71 (mean)	NA	67 (mean)	
Male (%)	52	60	44	NA	57	
Patients with cerebral microbleeds (%)	8 (18)	86 (15)	11 (16)	5 (12)	25 (39)	135 (17)
National Institute of Health Stroke Scale at presentation	14 (mean)	13 (median)	13 (mean)	NA	NA	
Time to treatment (minutes)	Mean of 263	67% within 180; 32% 180–360; 2% unknown but within six-hours	Mean of 321	NA	NA	
Number of patients with any intracerebral hemorrhage (%)	17 (39)	37 (6)	32 (46)	15 (37)	17 (26)	118 (15)
Number of patients with symptomatic ICH (%)	3 (7)	18 (3)	7 (10)	5 (12)	5 (8)	38 (5)

NA, information not provided.

Table 3

Ascertainment of risk of bias

Study	Adequate selection of participants	Adequate ascertainment of exposure/outcomes	Rating of neuroimaging blinded	Loss to follow-up (<10%)	Data adjusted for confounding variables	Funding/ conflicts of interest disclosed
Derex *et al*. 2004 (14)	Y	Y/Y	Y	retrospective	N	N
Fiehler *et al*. 2007 (15)	Y	Y/Y	Y	Y	N	Y
Kakuda *et al*. 2005 (16)	Y	Y/Y	Y	N (57/70 had follow-up imaging)	N	Y
Kidwell *et al*. 2002 (17)	Y	Y/Y	Y	Y	N	Y*
Kim *et al*. 2006 (13)	Y	Y/Y	Y	retrospective	N	Y*

*Designates studies where sources of funding were disclosed but lacked conflict of interest disclosures for individual authors. Y, yes, N, no.

Table 4

Number of cerebral microbleeds per individual patients

Study	Patients with one to two cerebral microbleeds (CMBs) (*n*)	Patients with three to 10 CMBs (*n*)	Patients with >10 CMBs (*n*)
Derex *et al*. 2004 (14)	7	1	0
Fiehler *et al*. 2007 (15)	69	15	2
Kakuda *et al*. 2005 (16)	9	2	0
Kidwell *et al*. 2002 (17)	4	0	1
Kim *et al*. 2006 (13)	12	8	5
Total (% of 135 patients with CMBs)	101 (75)	26 (19)	8 (6)