Original Investigation

Risk of Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis in Patients With Acute Ischemic Stroke and High Cerebral Microbleed Burden
A Meta-analysis

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IMPORTANCE Cerebral microbleeds (CMBs) have been established as an independent predictor of cerebral bleeding. There are contradictory data regarding the potential association of CMB burden with the risk of symptomatic intracerebral hemorrhage (sICH) in patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT).

OBJECTIVE To investigate the association of high CMB burden (>10 CMBs on a pre-IVT magnetic image resonance [MRI] scan) with the risk of sICH following IVT for AIS.

DATA SOURCES Eligible studies were identified by searching Medline and Scopus databases. No language or other restrictions were imposed. The literature search was conducted on October 7, 2015. This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.

STUDY SELECTION Eligible prospective study protocols that reported sICH rates in patients with AIS who underwent MRI for CMB screening prior to IVT.

DATA EXTRACTION AND SYNTHESIS The reported rates of sICH complicating IVT in patients with AIS with pretreatment MRI were extracted independently for groups of patients with 0 CMBs (CMB absence), 1 or more CMBs (CMB presence), 1 to 10 CMBs (low to moderate CMB burden), and more than 10 CMBs (high CMB burden). An individual-patient data meta-analysis was also performed in the included studies that provided complete patient data sets.

MAIN OUTCOMES AND MEASURES Symptomatic intracerebral hemorrhage based on the European Cooperative Acute Stroke Study–II definition (any intracranial bleed with ≥4 points worsening on the National Institutes of Health Stroke Scale score).

RESULTS We included 9 studies comprising 2479 patients with AIS. The risk of sICH after IVT was found to be higher in patients with evidence of CMB presence, compared with patients without CMBs (risk ratio [RR], 2.36; 95% CI, 1.21-4.61; $P = .01$). A higher risk for sICH after IVT was detected in patients with high CMB burden (>10 CMBs) when compared with patients with 0 to 10 CMBs (RR, 12.10; 95% CI, 4.36-33.57; $P < .001$) or 1 to 10 CMBs (RR, 7.01; 95% CI, 3.20-15.38; $P < .001$) on pretreatment MRI. In the individual-patient data meta-analysis, high CMB burden was associated with increased likelihood of sICH before (unadjusted odds ratio, 31.06; 95% CI, 7.12-135.44; $P < .001$) and after (adjusted odds ratio, 18.17; 95% CI, 2.39-138.22; $P = .005$) adjusting for potential confounders.

CONCLUSIONS AND RELEVANCE Presence of CMB and high CMB burdens on pretreatment MRI were independently associated with sICH in patients with AIS treated with IVT. High CMB burden may be included in individual risk stratification scores predicting sICH risk following IVT for AIS.

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Cerebral microbleeds (CMBs) as visualized on gradient echo T2* or susceptibility-weighted magnetic resonance imaging (MRI) are considered markers of bleeding-prone cerebral vessel microangiopathies and constitute both significant and independent predictors of future cerebral bleeding.[1-3] Several clinical studies have associated CMB presence with hemorrhagic stroke and hemorrhagic complications following antithrombotic medications.[4]

The potential association of CMB presence with the risk of symptomatic intracerebral hemorrhage (sICH) in patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT) remains controversial.[5-7] Moreover, the relationship of CMB burden with an increased risk of sICH complicating IVT for AIS remains to be determined.[5,6] A previous comprehensive meta-analysis[5] that has attempted to systematically evaluate this specific research question has included patients with AIS treated both with intravenous and intra-arterial reperfusion therapies including mechanical thrombectomy. However, this implies inclusion of a relevant patient group that has received no thrombolytic agent and inclusion of patients receiving both intravenous and intra-arterial thrombolytic therapy.[5] Notably, in this meta-analysis, high CMB burden (defined as >10 CMB) was associated with an excessive risk of sICH.[5] Moreover, the other meta-analysis on the topic[6] evaluated the risk of sICH in the presence of CMBs in patients with AIS treated with systemic thrombolysis without investigating the effect of CMB burden (stratified according to CMB number) on the risk of sICH.[6]

In view of these considerations, we conducted a systematic review and meta-analysis of individual patient data and sought to investigate the association of CMB presence (≥1 CMB vs 0 CMB) and CMB burden (>10 CMBs vs 1-10 CMBs) on pretreatment MRI with sICH risk, using all available data from prospective observational studies including patients with AIS treated solely with systemic thrombolysis.

Key Points

Question What is the association of high cerebral microbleed (CMB) burden (>10 CMBs) with the risk of symptomatic intracerebral hemorrhage following intravenous thrombolysis in patients with acute ischemic stroke?

Findings In this meta-analysis, higher risk for symptomatic intracerebral hemorrhage after intravenous thrombolysis was detected in patients with high CMB burden when compared with patients with 0 to 10 or 1 to 10 CMBs on pretreatment magnetic resonance imaging. High CMB burden was associated with increased likelihood of symptomatic intracerebral hemorrhage before and after adjusting for potential confounders.

Meaning High CMB burden on pretreatment magnetic resonance imaging is independently associated with symptomatic intracerebral hemorrhage in patients with acute ischemic stroke treated with intravenous thrombolysis.

Methods

Trial Identification and Data Abstraction

This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.[9] Eligible prospective study protocols reporting rates of sICH after IVT in patients who underwent CMB screening prior to the administration of IVT were identified by searching Medline and Scopus. The combination of search strings that was used in all database searches included the terms *cerebral microbleeds*, *intravenous thrombolysis*, *alteplase*, and *tissue plasminogen activator*. No language or other restrictions were imposed. The literature search was conducted on October 7, 2015. The complete search algorithm that was used in the Medline search is available in the eMethods in the Supplement. Reference lists of all articles that met our inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search. All retrieved studies were scanned independently by 2 reviewers (G.T. and A.H.K.). In case of disagreement regarding the literature search results between the aforementioned 2 authors, a third coauthor (R.Z.) was consulted, and disagreement was resolved with consensus. We also included available data from a pilot study that was performed in our institution on whether the feasibility of MRI screening for stroke mimics identification among patients with AIS eligible for IVT administration.[10]

The outcome event of interest was sICH that was ascertained using standard definitions combining neuroimaging and/or autopsy information with clinical evidence of deterioration on neurological examination.[6,7] The reported rates of sICH after IVT in patients with AIS undergoing CMB screening prior to alteplase administration were extracted independently by the 2 authors who performed the literature search (A.H.K. and G.T.) for the following subgroups of patients: (1) CMB absence (no CMBs on pre-IVT MRI), (2) CMB presence (1 or more CMBs on pre-IVT MRI), (3) low/moderate CMB burden (1-10 CMBs on pre-IVT MRI), and (4) high CMB burden (>10 CMBs on pre-IVT MRI).

The cutoff of CMBs to define high microbleed burden was selected a priori based on the findings of a previous meta-analysis[5] that also suggested an excess risk of sICH in patients with more than 10 CMBs, but the study had low statistical power owing to the low number (n = 7) of patients with a CMB count of more than 10 included[5] and the corresponding wide confidence intervals. Cerebral microbleeds were defined as small (generally 2-5 mm in diameter but up to 10 mm), hypointense, homogenous, round, or oval lesions that were visible on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted sequence imaging (SWI) and not seen on computed tomography or on fluid-attenuated inversion recovery, T1-weighted, or T2-weighted sequences.[11] In those studies providing sufficient data, the corresponding risk ratios (RRs) were calculated to express the relative risk of sICH after IVT in AIS between patients with CMB presence and CMB absence and the relative risk of sICH after IVT in AIS between patients with low/moderate CMB presence and high CMB burden. For the purpose of our meta-analysis, we also contacted all authors of eligible studies to provide complementary, nonpublished data regarding sICH in the 4 prespecified CMB subgroups.

After the overall analyses regarding the number of CMBs on pre-IVT MRI, we performed additional subgroup analyses using the magnetic resonance sequence for microbleed detection (GRE vs SWI) and the field strength of the MRI scan (1.5 T vs 3.0 T) as potential confounders both in individual-patient data meta-analysis and in the pairwise meta-analysis.

Meta-analysis of Individual-Patient Data

We attempted to capture the individual-patient data regarding the association of CMB number on pretreatment MRI and risk of sICH in patients with AIS treated with IVT by directly contacting the corresponding authors of all studies that were included in the initial pairwise meta-analysis. We confirmed all data that had been received for all appropriate individuals by checking that the numbers supplied were consistent with the original publications and that no obvious omissions or duplicates in the sequence of patient record or study identifier numbers were present.[12] Finally, data supplied were either recoded or transformed to reflect common definitions (eg, sICH definition) and common units of measurement (eg, serum glucose) across the generated individual-patient database.

Statistical Analyses

Extracted RRs from the included study protocols were pooled separately using the random-effects model (DerSimonian Laird) owing to the presumed heterogeneity between individual study estimates. The equivalent *z* test was performed for each pooled RR, and a *P* value of less than .05 was considered statistically significant. Heterogeneity between studies was assessed with the Cochran *Q* and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity per the Cochrane Handbook for Systematic Reviews of Interventions.[13] Publication bias (ie, assessment of bias across studies) was evaluated both graphically using a funnel plot[14] and with the Egger statistical test.[15]

In the individual-patient database, we divided patients, according to the CMB count in neuroimaging that was performed prior to IVT, into 3 subgroups: (1) CMB absence (0 CMBs); (2) low/moderate CMB burden (1-10 CMBs); and (3) high CMB burden (>10 CMBs). Continuous variables with a normal distribution were described as mean (SD) and nonnormally distributed variables were described as median and interquartile range (IQR), respectively. Categorical variables were presented as percentages. All variables between the 3 different subgroups were compared by means of analysis of variance or the Kruskal-Wallis test in variables with no evidence of normal distribution. Statistical significance for all tests was assumed if $P < .05$. Univariable and multivariable analyses were performed using logistic regression to identify predictors of sICH. Those factors that contributed to the outcome in the initial univariable analyses at *P* values of less than 0.1 were considered as candidate variables for the multivariable model. In the final multivariable analyses, statistical significance was achieved if *P* was less than .05, calculated by the likelihood ratio test. Associations in logistic regression analysis were presented using odds ratios (ORs) with their corresponding 95% CIs. We also performed again all univariable and multivariable analyses after dichotomizing the continuous variables according to the median value of their corresponding distribution.

Pairwise meta-analyses were conducted using Review Manager version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration) and the Comprehensive Meta-analysis version 2 software (Biostat). Individual-patient data analysis was performed with the Stata Statistical Software Release 13 for Windows (StataCorp LP).

Results

Study Selection and Study Characteristics

Systematic search of the Medline and Scopus databases yielded 43 and 39 results, respectively. After removing duplicates, the titles and abstracts from the remaining 57 studies were screened, and 12 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 12 studies, 4 studies were excluded because they reported treatment with intra-arterial thrombolysis,[16] mixed study population (treatment with intra-arterial thrombolysis or IVT),[17] no data on sICH rates,[18] or MRI acquisition not solely before IVT administration.[19] The excluded studies with the corresponding reasons for exclusion are presented in eTable 1 in the Supplement. In the final presentation of the literature search results, there was no conflict or disagreement between the 2 reviewers, and the 8 studies that met the study protocol's inclusion criteria,[20-27] together with the data from our institution,[10] were included both in the qualitative and quantitative synthesis (eFigure 1 in the Supplement). The authors of 1 study[26] provided nonpublished data regarding sICH incidence in the 4 CMB subgroups that have been included in this meta-analysis.

The characteristics of the included studies, comprising a total of 2479 patients, are summarized in eTable 2 in the Supplement. All study protocols provided sICH events according to the European Cooperative Acute Stroke Study–II (ECASS II) definition (any intracranial bleed with ≥4 points worsening on the National Institutes of Health Stroke Scale score within 7 days).[28] Thus, we selected the ECASS II definition because this was the most common definition used across different centers. Only 2 of the study protocols used SWI for the detection of CMBs prior to tissue plasminogen activator administration,[23,27] while the remaining 7 used the GRE sequence.[10,20-22,24-26] Similarly, 3-T MRI scans were performed in 2 study protocols,[20,27] 1 research group[10,23] used both 1.5- and 3-T MRI scans for pre-IVT screening, and 1.5-T MRI scans were performed in the remaining 5 studies.[21,22,24-26]

Pairwise Meta-analyses

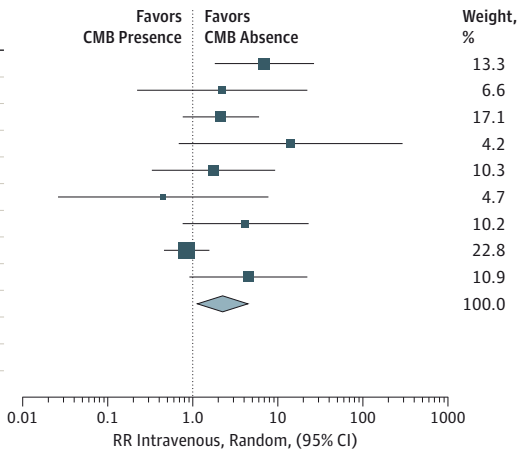
The risk of sICH after IVT was found to be higher in patients with evidence of CMB presence when compared with patients without CMBs on MRI prethrombolysis screening (RR, 2.36; 95% CI, 1.21-4.61; $P = .01$; **Figure 1**). No evidence of substantial heterogeneity was found ($I^2 = 46\%$; *P* for Cochran *Q* statistic, .06), while the visual inspection of the funnel plots

Figure 1. Forest Plot Comparing the Risk of Symptomatic Intracranial Hemorrhage Following Intravenous Thrombolysis In Patients With Acute Ischemic Stroke With and Without Cerebral Microbleeds (CMBs) on Pretreatment Magnetic Resonance Imaging

Study or Subgroup	CMB Present Events	CMB Present Total	CMB Absent Events	CMB Absent Total	RR Intravenous, Random, (95% CI)	Weight, %
Dannenberg et al[20]	7	81	3	245	7.06 (1.87-26.66)	13.3
Derex et al[21]	1	8	2	36	2.25 (0.23-21.89)	6.6
Fiehler et al[22]	5	86	13	484	2.16 (0.79-5.92)	17.1
Goyal et al[10]	1	3	0	18	14.25 (0.70-290.12)	4.2
Gratz et al[23]	2	38	4	136	1.79 (0.34-9.40)	10.3
Kakuda et al[24]	0	11	5	59	0.45 (0.03-7.69)	4.7
Kimura et al[25]	4	72	2	152	4.22 (0.79-22.52)	10.2
Turc et al[26]	12	150	52	567	0.87 (0.48-1.59)	22.8
Yan et al[27]	6	132	2	201	4.57 (0.94-22.29)	10.9
Total (95% CI)		**581**		**1898**	**2.36 (1.21-4.61)**	100.0
Total events	38		83			

Heterogeneity: $\tau^2 = 0.42$; $\chi^2 = 14.79$, $df = 8$ ($P = .06$); $I^2 = 46\%$

Test for overall effect: $Z = 2.52$ ($P = .01$)



RR indicates risk ratio.

(eFigure 2 in the Supplement) and the Egger statistical test ($P = .22$) revealed no evidence of publication bias. More specifically, random-effects pooled incidence of sICH was 3.2% (95% CI, 1.7%-6.1%) for patients with CMB absence and 6.9% (95% CI, 5.1%-9.4%) for patients with 1 or more CMBs present on pre-IVT MRI screening (eFigure 3 in the Supplement).

The prevalence of low/moderate (1-10 CMBs) and high (>10 CMBs) CMB burden was 18.9% (n = 343) and 0.8% (n = 15), respectively, in the 5 studies that reported CMB count on baseline neuroimaging. An even higher risk for sICH after IVT was found in those patients with evidence of high CMB burden (>10 CMBs) when compared with both patients with 0 to 10 CMBs (RR, 12.10; 95% CI, 4.36-33.57; $P < .001$; **Figure 2**A) and 1 to 10 CMBs (RR, 7.01; 95% CI, 3.20-15.38; $P < .001$; Figure 2B). No evidence of heterogeneity was found in both analyses (I^2 <50%, P for Cochran Q statistic >.10). The random-effects pooled incidence of sICH was 6.4% (95% CI, 4.2%-9.5%) for patients with 1 to 10 CMBs and 46.9% (95% CI, 22.8%-72.5%) for patients with more than 10 CMBs on pre-IVT screening (eFigure 4 in the Supplement).

In subgroup analyses, no differences were found when studies were stratified according to the imaging protocol used for the detection of CMBs in the MRI scan (GRE vs SWI; eFigures 5-7 in the Supplement) performed prior to the administration of IVT. The higher field strength (3 T) of the MRI scan was associated with a higher risk of sICH in patients with 1 or more CMBs in comparison with patients without CMB (RR, 5.90; 95% CI, 2.13-16.33; $P < .001$), but this association did not reach statistical significance ($P = .29$) in studies including a field strength of 1.5 T (RR, 1.42; 95% CI, 0.74-2.72; $P = .02$ for subgroup differences between studies using 3- and 1.5-T MRI; eFigure 8 in the Supplement). However, in the subgroup analyses evaluating the risk of sICH in patients with high CMB burden (>10 CMBs) in comparison with the groups with 1 to 10 or 0 to 10 CMBs, no heterogeneity was detected between studies with 3-T and those with 1.5-T MRI imaging protocols (eFigures 9 and 10 in the Supplement).

The exclusion of our pilot study[10] that has been published only as an abstract did not alter the reported associations between high CMB count and risk of sICH in patients with AIS treated with IVT (eTable 3 in the Supplement): RR for more than 10 CMBs vs 0 to 10 CMBs = 10.41 (95% CI, 3.20-33.87) and RR for more than 10 CMBs vs 1 to 10 CMBs = 7.32 (95% CI, 3.21-16.65).

Meta-analysis of Individual-Patient Data

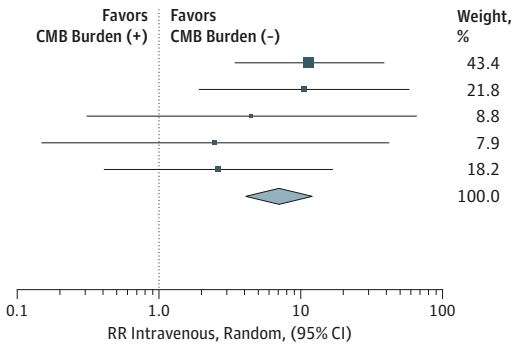
Together with our single-center data,[10] individual-patient data were provided from the corresponding authors of 2 other study protocols.[20,23] The baseline characteristics of our study population (n = 521), stratified by the count of CMBs on pre-IVT imaging, are presented in **Table 1**. The prevalence of low/moderate (1-10 CMBs) and high (>10 CMBs) CMB burden was 21.9% (n = 114) and 1.5% (n = 8), respectively, in the study population of the individual-patient data meta-analysis. Patients with high CMB burden (>10 CMBs) were older ($P < .001$) than patients with low/moderate CMB burden and patients with CMB absence, but did not differ from the other 2 groups in terms of other baseline characteristics. The rates of sICH differed ($P < .001$) between the groups as follows: 2.2% (95% CI, 1.2%-4.3%) in patients with 0 CMBs, 6.1% (95% CI, 3.0%-12.3%) in patients with 1 to 10 CMBs, and 50.0% (95% CI, 21.5%-78.5%) in patients with more than 10 CMBs on pretreatment MRI scan. A total of 7 patients (35% of all patients with sICH) had evidence of CMB on pretreatment MRI located in the same area where symptomatic intracranial bleeding occurred following IVT.

In the individual-patient data meta-analysis, high CMB burden (>10 CMBs) was associated with increased likelihood of sICH in comparison with the reference group of 0 to 10 CMBs before (unadjusted OR, 31.06; 95% CI, 7.12-135.44; $P < .001$) and after adjusting (adjusted OR, 18.17; 95% CI, 2.39-138.22; $P = .005$) for potential confounders (demographics, vascular risk factors, baseline stroke severity, pretreatment serum glucose, onset-to-treatment time, MRI field

Figure 2. Forest Plots Comparing the Risk of Symptomatic Intracranial Hemorrhage Following Intravenous Thrombolysis in Patients With Acute Ischemic Stroke With Evidence of Cerebral Microbleed (CMB) Burden (>10 CMBs)

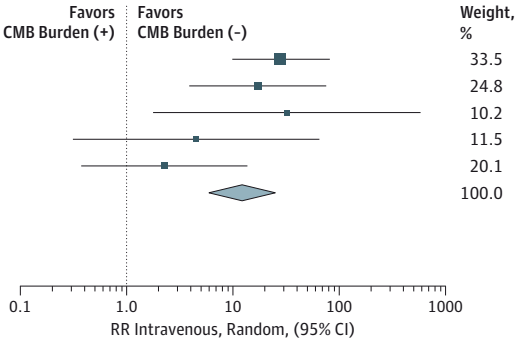
A Patients with 1 to 10 CMBs

Study or Subgroup	>10 CMBs Events	>10 CMBs Total	1-10 CMBs Events	1-10 CMBs Total	RR Intravenous, Random, (95% CI)	Weight, %
Dannenberg et al[20]	3	5	4	76	11.40 (3.46-37.57)	43.4
Fiehler et al[22]	1	2	4	84	10.50 (1.95-56.56)	21.8
Goyal et al[10]	1	1	0	2	4.50 (0.32-63.94)	8.8
Gratz et al[23]	0	2	2	36	2.47 (0.15-40.53)	7.9
Turc et al[26]	1	5	11	145	2.64 (0.42-16.65)	18.2
Total (95% CI)		**15**		**343**	**7.01 (3.20-15.38)**	100.0
Total events	6		21			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.58$, $df = 4$ ($P = .63$); $I^2 = 0\%$						
Test for overall effect: $Z = 4.86$ ($P < .001$)						



B Patients with 0 to 10 CMBs

Study or Subgroup	>10 CMBs Events	>10 CMBs Total	0-10 CMBs Events	0-10 CMBs Total	RR Intravenous, Random, (95% CI)	Weight, %
Dannenberg et al[20]	3	5	7	321	27.51 (9.88-76.62)	33.5
Fiehler et al[22]	1	2	17	568	16.71 (3.87-72.14)	24.8
Goyal et al[10]	1	1	0	20	31.50 (1.82-546.26)	10.2
Gratz et al[23]	0	2	6	172	4.44 (0.32-62.18)	11.5
Turc et al[26]	1	5	63	712	2.26 (0.39-13.25)	20.1
Total (95% CI)		**15**		**1793**	**12.10 (4.36-33.57)**	100.0
Total events	6		93			
Heterogeneity: $\tau^2 = 0.54$; $\chi^2 = 6.84$, $df = 4$ ($P = .14$); $I^2 = 41\%$						
Test for overall effect: $Z = 4.79$ ($P < .001$)						



A, Compared with patients with 1 to 10 CMBs. B, Patients with 0 to 10 CMBs on pretreatment magnetic resonance imaging. RR indicates risk ratio.

Table 1. Baseline Characteristics of Patients Included in the Individual-Patient Data Meta-analysis

	Cerebral Microbleeds			
	None	1-10	>10	*P* Value
Patients, No.	399	114	8	
Age, mean (SD), y	70.7 (13.3)	77.7 (10.1)	83.1 (7.6)	<.001
Male, No. (%)	179 (44.9)	51 (44.7)	4 (50.0)	.96
NIHSS score at admission, median (IQR)	7 (4-13)	8 (5-14)	8.5 (8-12.5)	.52
HTN, No. (%)	312 (78.2)	99 (86.8)	7 (87.5)	.11
AF, No. (%)	144 (36.2)	51 (44.7)	2 (25)	.26
DM, No. (%)	81 (20.3)	31 (27.2)	1 (12.5)	.24
Smoking, No. (%)	74 (18.6)	16 (14.0)	1 (12.5)	.34
CAD, No. (%)	71 (17.9)	21 (18.4)	3 (37.5)	.46
OTT, mean (SD), min	161.7 (63.5)	159.0 (58.7)	151.5 (29.7)	.87
Glucose level, mean (SD), mg/dL	130.2 (41.6)	131.9 (42.4)	117.8 (28.2)	.67
sICH, No. (%) [95% CI]	9 (2.2) [1.2-4.3]	7 (6.1) [3.0-12.3]	4 (50.0) [21.5-78.5]	<.001

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; sICH, symptomatic intracerebral hemorrhage.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

strength, and MRI sequence) in logistic regression models (**Table 2**). The former association persisted in the subgroup of patients with presence of CMB on pretreatment MRI. More specifically, high CMB burden (>10 CMB) was associated with higher likelihood of sICH in comparison with low/moderate CMB burden (1-10 CMBs) in univariable (unadjusted OR, 3.91; 95% CI, 1.77-8.63; *P* = .001) and multivariable (adjusted OR, 3.15; 95% CI, 1.13-8.73; *P* = .03) logistic regression analyses (**Table 3**).

In additional analyses, CMB presence was independently associated with an increased risk of sICH after IVT (OR, 3.28; 95% CI, 1.07-10.06; *P* = .04), after adjusting for potential confounders in multivariable logistic regression. However, we detected no association between CMB numbers entered as a

Table 2. Univariable and Multivariable Logistic Regression on the Risk of Symptomatic Intracerebral Hemorrhage in the Patients Included in the Individual-Patient Meta-analysis

	Univariable Analysis OR (95% CI)	*P* Value	Multivariable Analysis OR (95% CI)	*P* Value
Age, per 1-y increase	1.06 (1.02-1.11)	.007	1.05 (0.99-1.12)	.10
Male sex	1.88 (0.76-4.69)	.17	NA	NA
NIHSS score at admission, per 1-point increase	1.01 (0.94-1.08)	.80	NA	NA
HTN	1.41 (0.41-4.92)	.59	NA	NA
AF	2.42 (0.90-6.46)	.08	2.35 (0.70-7.92)	.17
DM	1.21 (0.43-3.40)	.72	NA	NA
Smoking	1.18 (0.38-3.62)	.77	NA	NA
CAD	0.80 (0.17-3.70)	.76	NA	NA
OTT, per 1-min increase	1.01 (0.99-1.01)	.05	1.01 (1.00-1.02)	.03
Glucose level	1.00 (0.99-1.01)	.97	NA	NA
High CMB burden[a]	31.06 (7.12-135.44)	<.001	18.17 (2.39-138.22)	.005
SWI	0.85 (0.32-2.25)	.74	NA	NA
3-T MRI	1.11 (0.44-2.84)	.82	NA	NA

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CMB, cerebral microbleed; DM, diabetes mellitus; HTN, hypertension; MRI, magnetic resonance imaging; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; SWI, susceptibility-weighted imaging.

[a] More than 10 CMBs on MRI.

Table 3. Univariable and Multivariable Logistic Regression Analysis in Patients Who Have Evidence of CMB Presence Prior to IVT Administration

	Univariable Analysis OR (95% CI)	*P* Value	Multivariable Analysis OR (95% CI)	*P* Value
Age	1.03 (0.96-1.10)	.40	NA	NA
Male sex	3.63 (0.91-14.42)	.07	5.33 (0.97-29.19)	.05
NIHSS score at admission	0.97 (0.87-1.09)	.65	NA	NA
HTN	0.35 (0.08-1.50)	.16	NA	NA
AF	2.08 (0.55-7.81)	.28	NA	NA
DM	0.60 (0.12-2.93)	.53	NA	NA
Smoking	2.60 (0.61-10.97)	.19	NA	NA
CAD	0.55 (0.06-4.84)	.59	NA	NA
OTT	1.01 (0.99-1.02)	.08	1.01 (0.99-1.02)	.062
Glucose level	0.99 (0.97-1.01)	.48	NA	NA
High CMB burden[a]	3.91 (1.77-8.63)	.001	3.15 (1.13-8.73)	.03
Cortical CMB presence	1.41 (0.35-5.62)	.63	NA	NA
SWI	0.46 (0.09-2.25)	.34	NA	NA
3-T MRI	1.39 (0.35-5.54)	.64	NA	NA

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CMB, cerebral microbleed; DM, diabetes mellitus; HTN, hypertension; IVT; intravenous thrombolysis; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; SWI, susceptibility-weighted imaging.

[a] More than 10 CMBs on MRI.

continuous variable in the logistic regression models and risk of sICH in patients with AIS with 1 or more CMB on pretreatment MRI (OR per 1-CMB increase, 1.00; 95% CI, 0.99-1.02; *P* = .79). Similarly, no significant association was detected between location of CMB (cortical vs subcortical) and the risk of sICH in patients with AIS treated with IVT in initial univariable logistic regression analyses (OR, 1.41; 95% CI, 0.35-5.62; Table 3).

Discussion

Our pairwise and individual-patient data meta-analyses showed that high CMB burden (>10 CMBs) on pretreatment MRI was independently associated with sICH risk in patients with AIS treated with IVT. High CMB burden was only more prevalent in older patients and was not associated with other risk factors. We consistently detected an increased incidence of sICH in this subgroup in comparison with the subgroups with CMB absence or low/moderate CMB burden on pretreatment MRI. More specifically, high CMB burden was related to a 3-fold and 7-fold increase in the risk of sICH in comparison with AIS with low/moderate CMB burden (1-10 CMBs) in the individual patient data and the pairwise meta-analyses, respectively. The excessive sICH rate (50.0% [95% CI, 21.5%-78.5%] in the individual-patient data and 46.9% [95% CI, 22.8%-72.5%] in the pairwise meta-analyses) in the subgroup of patients with AIS with high CMB burden, when combined with the low prevalence of high CMB burden (1.5%) among consecutive patients with AIS treated with IVT, indicate that systemic thrombolysis should be administered with extreme caution in this AIS subgroup and necessitate the inclusion of CMB burden in individual risk stratification scores predicting the likelihood of postthrombolysis sICH. Finally, our pairwise meta-analysis indicated that CMB presence on pretreatment MRI was associated with an approximately 2-fold higher likelihood of sICH in patients with AIS treated with IVT.

Our findings are in line with the previously published meta-analyses on this topic, which both suggested an increase in the risk of postthrombolysis sICH in the presence of CMBs.[5,6] However, to our knowledge, our study was the first to highlight that the aforementioned risk is significantly more pronounced in patients with a high CMB burden. Moreover, we included more patients in our pairwise meta-analysis (2479 patients with AIS) compared with the prior studies (790 patients with AIS[5] and 2028 patients with AIS,[6] respectively) and performed an individual-patient data meta-analysis using original data from available studies.

Cerebral microbleeds are not only highly prevalent in patients with cerebrovascular disease but also constitute an independent risk factor for stroke.[29] Moreover, there seems to be a common link between cerebral ischemia/hemorrhage, Alzheimer disease, cerebral amyloid angiopathy, and vascular dementia.[30] Results from the Framingham Heart Study Offspring and Cohort study suggest that the overall prevalence of CMBs in the community is low (4.7%). However, significantly higher prevalence rates are observed with advanced age and male sex.[31] In another cohort study, a nearly 7-fold difference in the prevalence rate of CMB was observed among middle-aged persons aged 45 to 50 years (6.5%) and persons 80 years or older (35.7%).[32] The increased incidence of CMBs with age presumably reflects the cumulative effect of both hypertension and cerebral amyloid angiopathy on cerebral vasculature during age progression.[33] The occurrence of these microbleeds may manifest as either the result of a hemorrhagic infarction/microinfarction or an isolated interruption of vascular integrity.[30] Postmortem anatomical findings indicate that CMBs found in elderly patients occur at the capillary level, independently of both amyloid deposition at the CMB site and the history of hypertension.[34] In terms of pathophysiology, cortical CMBs in elderly individuals with no cognitive deficits were found to be associated with widespread chronic hypoperfusion and increased risk of neuronal injury and neurodegeneration.[35]

Extensive cerebral small-vessel disease may constitute the intermediate link between CMB burden and excessive risk of sICH following systemic thrombolysis for AIS. This is supported by the fact that increasing leukoaraiosis, another neuroimaging marker of cerebral small-vessel disease, has also been associated with a higher risk of sICH in patients with AIS treated with IVT.[36] In addition, higher rates of spontaneous ICH have been observed in cardiovascular patients with CMBs treated with aspirin.[37] Consequently, it may be postulated that small-vessel disease (including cerebral amyloid angiopathy and hypertensive arteriopathy) can cause weakening and fragility of blood vessel walls and subsequently lower the threshold for postthrombolysis sICH in patients with AIS.[7]

Cross-sectional study data from cognitively normal individuals suggest that cortical CMBs could be related to chronic hypoperfusion and increased risk for neuronal injury.[35] However, no significant differences were found in the rates of anatomical CMB distribution (cortical vs subcortical) in a cohort study of patients with primary ICH.[38] In addition, our individual-patient data meta-analysis indicated that the risk of sICH in patients with AIS treated with IVT did not differ on the basis of CMB location (cortical vs subcortical). Nevertheless, this specific research question deservers further investigation in larger, prospective registries.

Several limitations of this study need to be acknowledged. First, only 5 studies (comprising 1808 patients) of the 9 total included studies (comprising 2479 patients) reported data on the risk of symptomatic intracranial hemorrhage following IVT in patients with AIS according to CMB count stratification (Figure 2). Moreover, from the 9 study protocols that were included in the pairwise analysis, only 3 provided individual-patient data on our request for further analyses.[10,20,23] The aforementioned 3 study protocols included in the individual-patient analysis comprised 21% of the total patients that were included in the pairwise analysis. However, we should underline that the findings of the individual-patient analysis were practically identical to those of the pairwise analysis, suggesting true representativeness of the total population and a low risk of selection bias. Second, in the individual-patient data meta-analysis only, 8 patients had high CMB burden (>10 CMBs). Even though the number is relatively small, the finding of the excessively high sICH risk in this subgroup was also present in the pairwise meta-analysis (including 5 studies and 15 patients with >10 CMBs) with no evidence of heterogeneity among studies (Figure 2), indicating that the aforementioned association is not owing to a play of chance.

Third, as evident from eTable 2 in the Supplement, some of the baseline characteristics were not available in 3 of 9 study protocols.[21,22,27] However, nearly all studies provided data on age, sex, National Institutes of Health Stroke Scale score on admission, and onset-to-treatment time. Moreover, we should acknowledge that data on blood pressure control following intravenous tissue plasminogen activator infusion were not available in most study protocols. This could be another important limitation because it may be safer to treat patients with CMB on pre-IVT MRI scan when exquisite blood pressure control is provided.[35,39] Another potential limitation is that data concerning antithrombotic medication taken before admission are lacking; thus, the possible interaction between daily intake of aspirin and CMBs regarding the risk of post-IVT sICH cannot be evaluated. In addition, our analysis did not investigate the association between the anatomical distribution or size of CMBs and risk of sICH.[40,41] Another important limitation of our study protocol is that we cannot exclude the hemorrhagic transformation of cerebral infarction as the cause of a new hematoma causing clinical deterioration, and this needs to be taken into account when interpreting our findings. More specifically, ECASS-II criteria that were used for the definition of sICH include intra-infarct parenchymal hematoma type 2 owing to hemorrhagic transformation.[28] Even though the tissue plasminogen activator–mediated bleed into the infarct is not a CMB, our data still indicate that high CMB burden (CMB count >10) is associated with an increased risk for intracranial bleeding, even at sites remote to any CMB and only into the infarct. Therefore, it cannot be ruled out that the reported sICH are the concurrence of 3 varying kinds of bleeding, ie, parenchymal hematoma type 2 in the infarct but outside the CMB, parenchymal hematoma type 2 remote in the CMB but outside the infarct, or parenchymal hematoma type

2 remote both outside the infarct and outside the CMB. Fourth, we should emphasize that our findings apply to a limited number of patients with AIS who undergo MRI prior to treatment with intravenous tissue plasminogen activator. Patients undergoing MRI (in contrast to computed tomography) are less severely ill, less often disorientated or agitated, and do not have cardiac pacemakers.[42]

Regarding the imaging method used for the detection of CMBs on MRI scan, SWI is considered to be more sensitive for CMB detection compared with GRE T2*.[43,44] However, the higher sensitivity of SWI was not related to higher clinical relevance in terms of vascular risk factors and/or radiologic markers of small-vessel disease.[44] Of the 9 included studies in our meta-analysis, only 2 used SWI for CMB detection prior to the administration of IVT.[23,27] In the subgroup analyses that we performed according to the imaging protocol used for the detection of CMBs, no significant differences were found among the studies that used SWI and those that screened patients with GRE.

Furthermore, in the subgroup analysis according to the strength of the magnetic field used in the study protocols, only the 3-T MRI studies showed consistently significant increased risk of sICH with high CMB count (eFigures 9 and 10 in the Supplement), while the former association was significant in 1 (eFigure 9 in the Supplement) of 2 subgroup analyses including only 1.5-T MRI studies. However, the threshold of statistical significance was barely missed (P = .09) in the remaining subgroup analysis, including only 1.5-T MRI (eFigure 10 in the Supplement), and this may be because of the limited sample size and small number of included studies (n = 2), resulting in the wide 95% CI of reported associations. Moreover, susceptibility artifacts increase with the main magnetic field strength, but are only slightly larger at 3-T compared with standard 1.5-T MRI. This may be helpful in visualization but most likely does not change the number of visualized CMBs.[45,46] On the other hand, detection bias cannot be reliably excluded in the present analyses. Because higher-field MRIs and the use of SWI are known to increase CMB detection, some patients with CMB absence could be shifted to the low/moderate or high CMB burden categories if SWI and/or higher-field protocols were used. Because of this specific limitation and the small number of available studies, we consider that our analyses have a very limited power to detect a possible modifying effect according to the MRI protocol used.

Conclusions

Our findings suggest that CMB burden is an independent risk factor that may augment the risk of sICH in patients with AIS treated exclusively with systemic thrombolysis. These observations imply that CMB burden may be included in individual risk stratification predicting the risk of sICH following IVT for AIS. The challenge remains in identifying CMB burden without MRI in the setting of AIS management where only a noncontrast computed tomography is standard of care.

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