

Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy

A meta-analysis

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Abstract

Objective

To assess the association of cortical superficial siderosis (cSS) presence and extent with future bleeding risk in cerebral amyloid angiopathy (CAA).

Methods

This was a meta-analysis of clinical cohorts of symptomatic patients with CAA who had T2*-MRI at baseline and clinical follow-up for future intracerebral hemorrhage (ICH). We pooled data in a 2-stage meta-analysis using random effects models. Covariate-adjusted hazard ratios (adjHR) from multivariable Cox proportional hazard models were used.

Results

We included data from 6 eligible studies ($n = 1,239$). cSS pooled prevalence was 34% (95% confidence interval [CI] 26%–41%; I^2 87.94%; $p < 0.001$): focal cSS prevalence was 14% (95% CI 12%–16%; I^2 6.75%; $p = 0.37$), and disseminated cSS prevalence was 20% (95% CI 13%–26%; I^2 90.39%; $p < 0.001$). During a mean follow-up of 3.1 years (range 1–4 years), 162/1,239 patients experienced a symptomatic ICH-pooled incidence rate 6.9% per year (95% CI 3.9%–9.8% per year; I^2 83%; $p < 0.001$). ICH incidence rates per year according to cSS status were 3.9% (95% CI 1.7%–6.1%; I^2 70%; $p = 0.018$) for patients without cSS, 11.1% (95% CI 7%–15.2%; I^2 56.8%; $p = 0.074$) for cSS presence, 9.1% (95% CI 5.5%–12.8%; I^2 0%; $p = 0.994$) for focal cSS, and 12.5% (95% CI 5.3%–19.7%; I^2 73.2%; $p = 0.011$) for disseminated cSS. In adjusted pooled analysis, any cSS presence was independently associated with increased future ICH risk (adjHR 2.14; 95% CI 1.19–3.85; $p < 0.0001$). Focal cSS was linked with ICH risk (adjHR 2.11; 95% CI 1.31–2.41; $p = 0.002$), while disseminated cSS conferred the strongest bleeding risk (adjHR 4.28; 95% CI 2.91–6.30; $p < 0.0001$).

Conclusion

In patients with CAA, cSS presence and extent are the most important MRI prognostic risk factors for future ICH, likely useful in treatment planning.

Classification of evidence

This study provides Class III evidence that in symptomatic CAA survivors with baseline T2*-MRI, cSS (particularly if disseminated, i.e., affecting >3 sulci) increases the risk of future ICH.

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→ Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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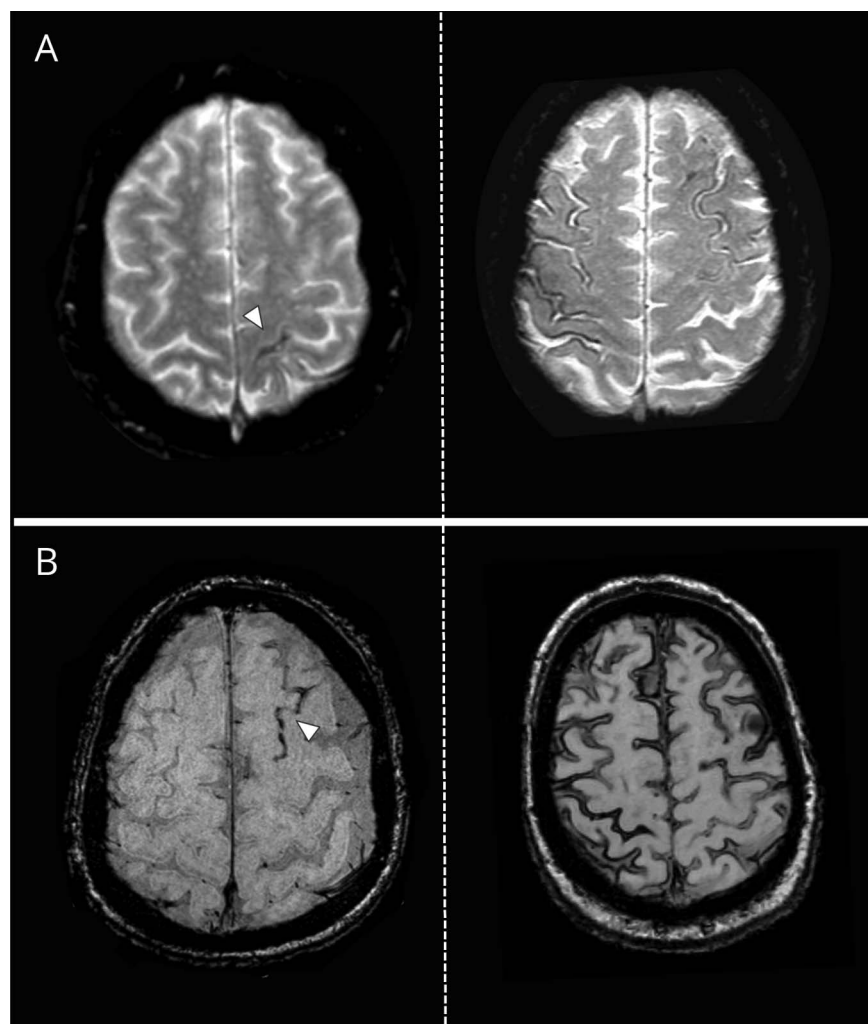
Glossary

A β = β -amyloid; adjHR = adjusted hazard ratio; CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; cSS = cortical superficial siderosis; GRE = gradient-recalled echo; HR = hazard ratio; ICH = intracerebral hemorrhage; MOOSE = Meta-analysis of Observational Studies in Epidemiology; SWI = susceptibility-weighted imaging; TFNE = transient focal neurologic episode.

Advanced cerebrovascular deposition of β -amyloid (A β), defined neuropathologically as cerebral amyloid angiopathy (CAA), is a prevalent small-vessel disease and a leading cause of spontaneous lobar intracerebral hemorrhage (ICH).¹ The clinical management of symptomatic patients with CAA (presenting with or without ICH, in stroke or memory clinics) is thus centered around preventing future ICH, either first-ever or recurrent, since these are associated with substantial morbidity and mortality. Identifying strong risk factors of future CAA-related ICH, including hemorrhagic MRI biomarkers, is thus a crucial focus in the field.²

Putative hemorrhagic MRI biomarkers of small vessel damage in CAA include small, and typically silent, strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS). While more recently described in relationship to CMBs, cSS has been implicated as a specific MRI footprint of a more aggressive CAA phenotype. cSS quite characteristically follows the curvilinear shape of the surrounding cerebral gyri on T2*-weighted MRI, reflecting blood breakdown products deposition that line the outermost surface of the cortex or the subarachnoid space (figure 1).³ cSS is thought to result from superficial cortical hemorrhages (designated as

Figure 1 Representative examples of cortical superficial siderosis (cSS) on blood-sensitive MRI in patients with cerebral amyloid angiopathy (CAA)



(A) T2*-weighted gradient-recalled echo sequence shows focal cSS (i.e., affecting up to 3 sulci) on the left and disseminated cSS (i.e., affecting >3 sulci) on the right. (B) Susceptibility-weighted imaging sequences from 2 different patients with CAA with focal cSS (left) and disseminated cSS (right).

convexity subarachnoid hemorrhage, when acute), likely as a consequence of brittle superficial cortical penetrators or leptomeningeal vessels affected by advanced cerebrovascular A β deposition.^{3,4} cSS is rapidly gaining particular relevance to clinical practice as a marker for increased future CAA-related ICH risk in various different CAA patient populations and clinical settings.^{3,5,6}

The aim of this work is to bring together the totality of evidence and obtain precise estimates on the effect sizes of cSS as an independent predictor of future ICH risk in patients with CAA, across the spectrum of different clinical presentations and settings. We investigate this clinical question in a systematic review and meta-analysis of published studies on the topic.

Methods

The study was conducted with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),⁷ Meta-analysis of Observational Studies in Epidemiology (MOOSE)⁸ guidelines, and the Cochrane Handbook for Systematic Reviews of Interventions.

Standard protocol approvals, registrations, and patient consents

This study was performed in accordance with the guidelines at our institution and using a predefined summary protocol⁹ developed in September 2017 within our group (not published or registered as a stand-alone document). The protocol was reviewed by the authors' team and all details provided in the rest of the section reflect our prespecified decisions and strategy for the literature search, data extraction, outcome measures, and statistical approach. Of note, this protocol was identical to the one we developed in an earlier (preliminary) meta-analysis we have performed on the topic.⁹

Search strategy and study selection

We searched PubMed for potentially eligible studies published between January 1, 1990, and February 21, 2019, using a combination of keywords and Medical Subject Headings (“cortical superficial siderosis” or “convexity siderosis” or “convexal siderosis” or “cortical hemosiderosis”) and (“cerebral amyloid angiopathy” or “intracerebral hemorrhage” or “intracerebral haemorrhage”), without language restriction. We also used snowballing to screen the reference lists of all potentially eligible articles, relevant review articles, and author's own files (including regular weekly PubMed search updates on cSS for the last 6 years). Retrospective or prospective cohorts of symptomatic patients with CAA were eligible for inclusion if they characterized cSS presence and severity at baseline MRI with subsequent patient follow-up for the development of ICH. Specific inclusion criteria were (1) retrospective or prospective CAA patient cohorts (including ICH and non-ICH presentations, e.g., with cognitive impairment or transient focal neurologic episodes) defined

according to the original or modified Boston criteria^{10,11} and including >50 adult patients; (2) baseline MRI (within 3 months of clinical presentations) with blood-sensitive sequences (T2*-weighted), incorporating cSS ratings for presence and severity using standard established criteria^{3,12}; (3) clinical follow-up >6 months for new lobar ICH (either first-ever or recurrent) according to standardized criteria³; and (4) investigation of the association between cSS at baseline MRI and symptomatic ICH risk during clinical follow-up. We excluded case reports, cohorts selected by having isolated cSS at baseline, and cohorts on familial CAA or CAA-related inflammation. For studies with more than one publication describing results among overlapping cohorts and with the same outcome measure, we included the dataset with the longest follow-up, or the dataset with the largest number of participants if the follow-up period was identical.

The abstracts of all articles identified from online searches were reviewed by 2 authors, who also then reviewed the full text of all eligible studies independently. The final list of included studies was decided upon consensus among all coauthors.

Outcome measures

The primary outcome of interest was spontaneous symptomatic lobar ICH. This was defined as an acute onset focal neurologic deficit of presumed vascular cause lasting at least 24 hours or interrupted by death within 24 hours (definition of stroke), and diagnosed as spontaneous lobar ICH (presumed to be due to CAA-related small vessel disease) based on standardized criteria on brain imaging (either CT or MRI).¹³

Data extraction

We classified studies as being conducted in CAA-related lobar ICH, CAA presenting without lobar ICH at baseline (e.g., in memory clinics with cognitive symptoms or stroke clinics with transient focal neurologic episodes), a combination of the above, or spontaneous ICH including CAA-related lobar ICH patient populations. Where possible, in studies that included a combination of different CAA presentations (ICH, non-ICH), we extracted data for each subgroup separately.

For each study, we used a data collection pro-forma to extract information on study design, number and nature of patients (including mean age, sex, hypertension, antithrombotic drug use at baseline, history of ICH), inception point for inclusion in the study, MRI sequence measures and classification rules used for cSS rating, prevalence and severity of cSS and other MRI markers of CAA and small vessel disease (e.g., lobar CMBs, white matter hyperintensities), duration and methods of follow-up, and number of participants with the outcome of interest per cSS presence and severity category (focal: affecting up to 3 sulci and disseminated: affecting >3 sulci, figure 1).¹¹ Where available, adjusted estimates from multivariable models of the independent association between cSS presence and severity (as well as other covariates included in the models from

each individual) and the outcome of interest were extracted as hazard ratios (HRs) or odds ratios with corresponding 95% confidence intervals (CI). Two authors independently extracted data and disagreements were resolved by consensus.

Quality and risk of bias assessment

We assessed each study against a list of key quality criteria we devised based on study size, cohort recruitment method (prospective vs other), blinding between cSS ratings and outcome of interest, blood-sensitive MRI sequence type used, criteria of cSS assessment, and interrater agreement. These criteria were created using elements of the MOOSE⁸ recommendations and consensus standards for cSS assessment and rating.³ We assessed the risk of bias of each cohort according to the Newcastle–Ottawa Scale for assessing the quality of cohort (nonrandomized) studies.

Statistical analysis and data synthesis

We meta-analyzed data using a random effects model with DerSimonian-Laird weights.¹⁴ We quantified the strength of the association between cSS presence and severity and future ICH risk by pooling the covariate-adjusted HRs (adjHR). These HRs were extracted from relevant multivariable survival analysis models of all included studies (table 1, bottom row). Meta-analyses were first conducted across all eligible CAA cohorts (irrespective of clinical presentation with vs without ICH) and then stratified according to cohorts of patients with CAA-related ICH and patients presenting without ICH at baseline. We assessed statistical heterogeneity using I^2 statistics and visually through inspection of the forest plot. Values of $\leq 25\%$, $25\%–50\%$, and $\geq 50\%$ were defined as low, moderate, and high degrees of heterogeneity, respectively. We explored publication bias with funnel plots. To provide estimates of absolute risks, often useful in clinical practice, we pooled and synthesized annualized symptomatic ICH risk (%/year) and corresponding 95% CIs where possible, using a Poisson regression model and exact Poisson intervals. We calculated pooled rates using the inverse variance method. All meta-analyses were performed using Stata 13.0 (StataCorp LP, College Station, TX) and considered a p value of <0.05 as evidence of statistical significance.

Data availability policy

Data were deposited locally, but are not publicly available. All relevant data are included in the article.

Results

Characteristics, quality, and critical appraisal of included studies

Based on our search criteria, we identified 94 publications, of which we retained 6 for the present meta-analysis, including a total of 1,239 patients.^{6,9,15–18} Figure 2 presents the flow chart for study selection. Table 1 summarizes basic study design elements and patient characteristics of all included studies. Study patient populations comprised 3 cohorts of CAA-related lobar ICH survivors,^{6,9,15} 1 cohort of patients

with probable CAA without ICH history presenting with cognitive impairment or transient focal neurologic episodes,¹⁶ and 1 cohort of patients with CAA presenting with both lobar ICH and non-ICH CAA syndromes.¹⁸ This latter study¹⁸ also included patients with incidental CAA diagnosed in patients with ischemic stroke/TIA (14%) and dizziness, headache, or other nonspecific neurologic complaints (4%), syndromes not typically caused by CAA. One of the studies we have identified included unselected survivors of spontaneous ICH with T2*-MRI available at baseline (i.e., both CAA-related lobar ICH and deep ICH).¹⁷ Since this was a prospective consecutive cohort, specifically investigating cSS in relation to ICH recurrence,¹⁷ for comprehensiveness and to increase the sample size, we have post hoc included it in our meta-analysis, but have also performed separate sensitivity analyses and reported estimates after removing this study. Of note, this applies only for the meta-analyses on disseminated cSS, since the study did not report estimates on any cSS presence and focal cSS. The outcome in this study was thus any recurrent ICH,¹⁷ but the majority of recurrences were lobar ICH in patients with CAA-ICH, thus not affecting the pooled estimates.

Included studies were somewhat different in their design and inception points, sample size, use of the Boston criteria (original vs modified), and presenting clinical features of patients. The MRI sequences used to assess cSS were comparable, though some studies used a combination of T2*-gradient-recalled echo (GRE) and susceptibility-weighted imaging (SWI) sequences. The criteria and instruments for cSS assessment were uniform across studies. All details can be reviewed in table 1. None of the studies have investigated (or incorporated in their adjusted models) blood pressure control and anticoagulation/antithrombotic treatment (only one study¹⁵) during follow-up. Of note, in all studies patients were treated according to current guidelines for blood pressure control after an ICH and a strategy of avoiding anticoagulation treatment in the setting of CAA-related ICH was followed.

Table 2 summarizes the results of the assessment of each cohort study against key quality indicators relevant for the clinical question under investigation and the risk of bias based on the Newcastle–Ottawa Scale. Studies were medium to high quality based on the total number of quality indicators fulfilled and had low risk of bias in the Newcastle–Ottawa Scale categories.

Pooled prevalence and severity of cSS in included studies

At baseline MRI, the pooled prevalence of cSS presence across all studies was 34% (95% CI 26%–41%; I^2 87.94%; $p < 0.001$). Focal cSS (i.e., up to 3 affected sulci) prevalence was 14% (95% CI 12%–16%; I^2 6.75%; $p = 0.37$) and disseminated cSS (i.e., >3 affected sulci) prevalence was 20% (95% CI 13%–26%; I^2 90.39%; $p < 0.001$). When removing the single cohort that did not use the Boston criteria to report on cSS

Table 1 Basic elements of cohort design and patient population characteristics of included studies

Characteristics	Charidimou et al. ⁶	Koo et al. ¹⁵	Charidimou et al. ¹⁶	Wollenweber et al. ¹⁸	Charidimou et al. ⁹	Moulin et al. ¹⁷
Country/setting	European, retrospective, multicenter (4 hospitals)	Korea, retrospective, consecutive, single-center (2005–2013)	United States, prospective, consecutive, single-center (2000–2015)	Prospective, multicenter cohort (4 hospitals): SuSPect-CAA (2013–2016)	United States, prospective, consecutive, single-center	France, prospective, consecutive, single-center: PITCH (2004–2009)
Inception point	Hospital admission with lobar ICH at baseline	Hospital admission with lobar ICH at baseline	Patients with CAA without ICH admitted to stroke (TFNEs) or memory clinics (cognitive complains)	Patients presented at stroke services (n = 194) or memory clinics (n = 108)	Hospital admission with lobar ICH at baseline, survived 30 days after index event	Unselected survivors of spontaneous ICH with T2* MRI
T2* MRI measures (field strength/ET/ST)	T2*-GRE (1.5T/15–70 ms/5 mm)	T2*-GRE (3T/16 ms/5 mm)	T2*-GRE (SWI in 33%) (1.5T/50 ms/5 mm)	T2*-GRE/SWI (1.5 and 3T/?/? (varied)	T2*-GRE (some cases: SWI) (1.5T/50 ms/5 mm)	T2*-GRE (1.5T/22.8 ms/5 mm)
Patient number (% men)	118 (51.7)	85 (57)	236 (60)	302 (40)	240 (53)	258 (58)
Diagnostic criteria used (possible/probable CAA)	Original Boston criteria	Modified Boston criteria	Modified Boston criteria: all patients: probable CAA	Modified Boston criteria ^a (possible: 88; probable: 214)	Original Boston criteria (possible: 92; probable: 148)	Not applied or reported
Age, y, mean/median (SD/IQR)	71.3 (95% CI 69.6–73)	70 (8)	81.8 (95% CI 66.6–97)	~73 (SD~7)	75.2 (66.7–81.1)	~67
Hypertension (%)	66 (61.1)	46 (54)	154 (65)	229 (76)	152 (63.3)	165 (64)
Previous ICH (%)	30 (25.4)	—	0	109 (36)	29 (12.1)	13 (0.05) [69 (27) with MRI old ICH]
Advance WMH (grade 2–3) (%)	52 (44.8)	52 (61)	78 (33)	Not reported	140 (58.3)	157 (61)
CMBs prevalence (%)	80 (67.8)	57 (67)	227 (96)	252 (83)	116 (48.3)	108 (42)
Follow-up method	Clinical records review, recurrent lobar ICH outcome events confirmed on brain CT	Clinical records review, recurrent lobar ICH outcome events confirmed on brain CT	Phone calls at 3 months after enrollment and every 6 months, chart review	Clinical visits (at 6 and 12 months), telephone interview, medical record review	Telephone follow-up, supplemented by chart review, outcome events confirmed on brain CT	Clinical visits (at 6 and 12 months and annually thereafter), telephone
Follow-up time, y (IQR)	2 (0.4–1.8)	3 (range 0.08–10.1)	3.26 (1.42–5.50)	1	2.6 (0.9–5.1)	6.4 (2.9–8.4)
Variables included in survival analysis adjusted models and in our models	Age (per year increase) ^b Previous lobar ICH (other than index event) Total WMH volume, per milliliter increase >5 CMBs presence cSS presence, burden ^b	Post-ICH antithrombotics use ^b CMB burden CSO-PVS severity cSS presence, burden ^b	Age ^b >5 lobar CMBs presence; severe WMH cSS presence, burden ^b	Age Number of CMB mRS ^c cSS presence, disseminated cSS ^b	Age (per year increase) ^b Multiple (>2) CMBs cSS presence, burden ^b	Old ICH Lobar CMBs presence Disseminated cSS ^b

Abbreviations: CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; CSO-PVS = perivascular spaces in the centrum semiovale; cSS = cortical superficial siderosis; ET = echo time; GRE = gradient-recalled echo; ICH = intracerebral hemorrhage; IQR = interquartile range; mRS = modified Rankin Scale; PITCH = Prognosis of Intracerebral Haemorrhage; SuSPect-CAA = Superficial Siderosis in Patients with Suspected Cerebral Amyloid Angiopathy Study; ST = slice thickness; SWI = susceptibility-weighted imaging; TFNE = transient focal neurologic episode; WMH = white matter hyperintensities.

^a Patients meeting a probable or possible CAA diagnosis based on modified Boston criteria were included with the following additional modification: the authors did not exclude patients with a maximum of 2 deep cerebral CMBs on baseline MRI provided they had at least twice the number of lobar CMB or a history of lobar ICH or cSS, a deviation from the validated Boston criteria. Results and effect sizes were unchanged when these patients were excluded.

^b Statistically significant variables within each study.

^c Extended model corrected for age, sex, hypertension, atrial fibrillation, use of antiplatelet agents, use of oral anticoagulants, number of CMB at baseline, previous intracranial hemorrhage, previous ischemic stroke, and mRS score at baseline.

specifically in CAA-related ICH, the pooled prevalence for cSS presence was 37% (95% CI 34%–40%; I^2 0%; $p = 0.59$), for focal cSS 15% (95% CI 12%–17%; I^2 0%; $p = 0.54$), and for disseminated cSS 22% (95% CI 18%–26%; I^2 60.5%; $p = 0.04$).

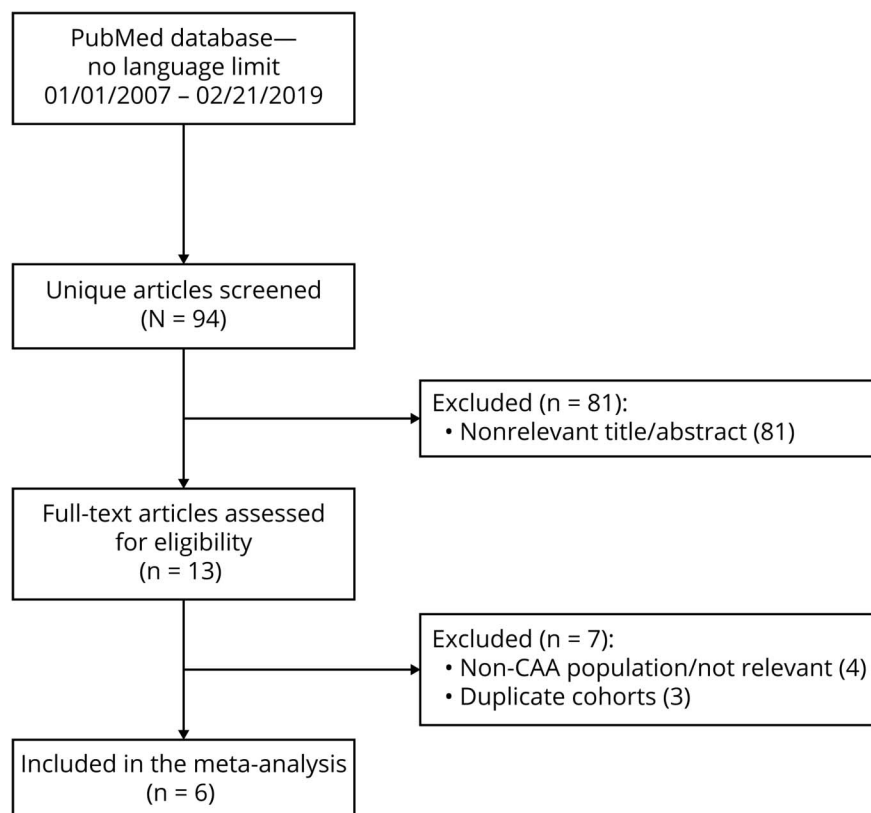
Meta-analyses: cSS and risk of future ICH

During a mean pooled follow-up time of 3.1 years (range 1–4 years), 162/1,239 patients overall experienced a symptomatic ICH, a pooled incidence rate of 6.9% per year (95% CI 3.9%–9.8% per year; I^2 83%; $p < 0.001$). Assuming a uniform follow-up time and stable estimates of risk across time, the pooled symptomatic ICH incidence rates per year according to cSS presence and severity were 3.9% per year (95% CI 1.7%–6.1%; I^2 70%; $p = 0.018$) for patients without cSS, 11.1% per year (95% CI 7%–15.2%; I^2 56.8%; $p = 0.074$) in the presence of cSS, 9.1% per year (95% CI 5.5%–12.8%; I^2 0%; $p = 0.994$) for focal cSS, and 12.5% (95% CI 5.3%–19.7%; I^2 73.2%; $p = 0.011$) for disseminated cSS.

All studies, except one,¹⁷ provided adjusted estimates from survival analysis on cSS presence and future ICH risk. In meta-analysis of adjusted estimates from multivariable models, any cSS presence was independently associated with increased future ICH risk during follow-up (adjHR 2.14;

95% CI 1.19–3.85; $p < 0.0001$), compared to patients without cSS (figure 3). The association with future ICH risk showed a dose relationship with increasing cSS severity: focal cSS was linked with ICH risk (adjHR 2.11; 95% CI: 1.31–2.41; $p = 0.002$), while disseminated cSS conferred the strongest independent future bleeding risk (adjHR 4.28; 95% CI: 2.91–6.30; $p < 0.0001$) in patients with CAA during follow-up (figure 4). The results on disseminated cSS were consistent and of similar effect sizes in a subanalysis excluding the single study¹⁷ that did not present estimates for patients with CAA-ICH separately (adjHR 4.39; 95% CI 2.72–7.09; $p < 0.0001$). Among other common clinical and MRI variables included into multivariable models, increasing age (adjHR 1.04; 95% CI 1.01–1.06; $p = 0.003$; I^2 0%; $p = 0.597$, per year increase), but not lobar CMBs (adjHR 1.05; 95% CI 0.76–1.44; $p = 0.771$; I^2 27.4%; $p = 0.229$), were associated with ICH risk in CAA. Only one study incorporated MRI-visible centrum semiovale perivascular spaces severity in the survival models—no association with risk of ICH was found (table 1). Two studies included white matter hyperintensities severity in the multivariable survival models—no association was identified with the risk of ICH (table 1). In the rest of the studies, white matter hyperintensities severity was not even a univariable predictor of ICH risk and was hence not investigated further in adjusted models.

Figure 2 Flowchart of studies identification and selection



CAA = cerebral amyloid angiopathy.

Table 2 Assessment of each of cohort study against key quality indicators of the risk of bias based on the Newcastle–Ottawa Scale^a

Key quality indicators	Charidimou et al. ⁶	Koo et al. ¹⁵	Charidimou et al. ¹⁶	Wollenweber et al. ¹⁸	Charidimou et al. ⁹	Moulin et al. ¹⁷
Prospective cohort	—	—	+	+	+	+
Clearly defined populations (and estimates separated per clinical setting/presentation)	+	+	+	+	—	—
Consecutive patients	+	+	+	—	+	+
Data on excluded patients presented among screened populations	—	—	+	—	+	+
Standardized and clearly defined MRI measures	+	+	+	—	+	+
Clear cSS definition, according to consensus guidelines	+	+	+	+	+	+
>1 year of mean/median follow-up	+	+	+	—	+	+
Completion of follow-up (>90%)	+	+	+	—	+	+
Fully adjusted survival models presented	+	—	+	? (OR vs HR)	+	—
No. of quality indicators fulfilled	7/9	6/9	9/9	3/9	8/9	7/9
Selection (Newcastle–Ottawa Scale)	****	***	****	***	****	***
Comparability (Newcastle–Ottawa Scale)	**	*	**	*	**	—
Outcome (Newcastle–Ottawa Scale)	***	***	***	**	***	***

Abbreviations: cSS = cortical superficial siderosis; HR = hazard ratio; OR = odds ratio.

^a Ratings for the Newcastle–Ottawa Scale: A study can be awarded a maximum of 1 star for each numbered item within the Selection (maximum 4 stars) and Outcome (maximum 3 stars) categories. A maximum of 2 stars can be given for Comparability. See the following for details: Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: ohri.ca/programs/clinical_epidemiology/oxford.asp.

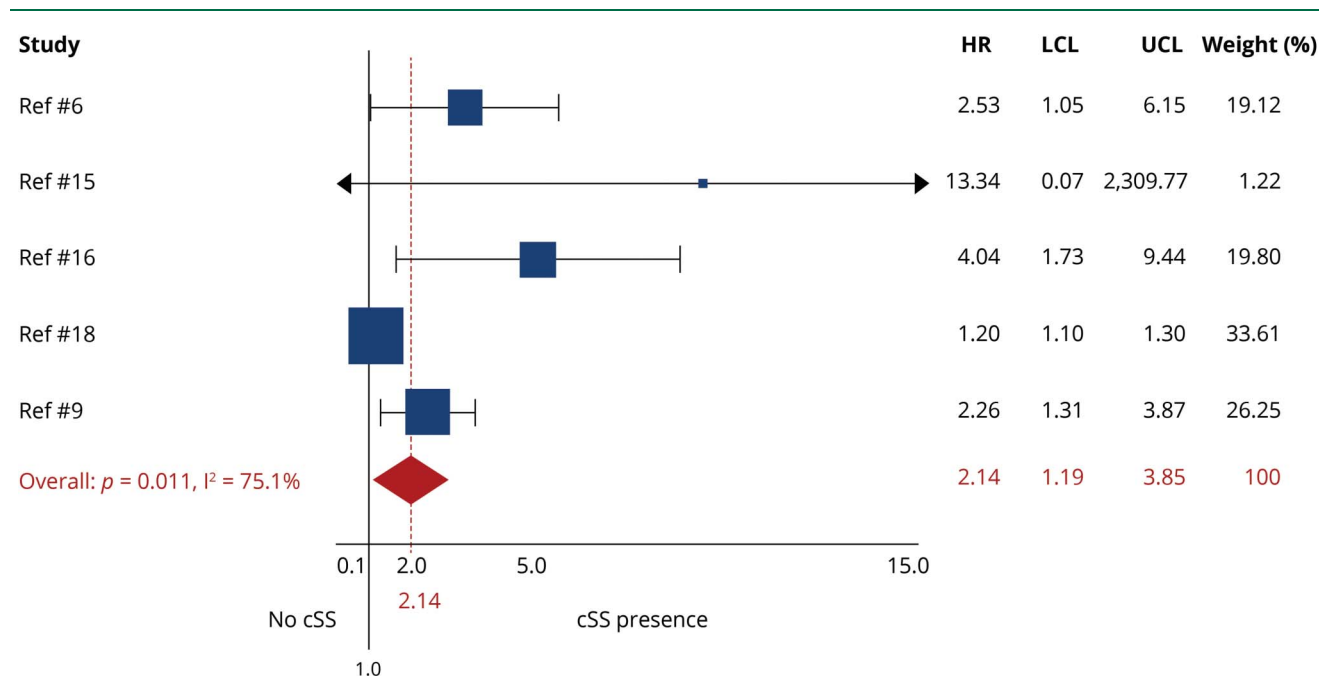
Discussion

In this systematic review and meta-analysis, we have examined all currently available group-level data to establish a precise estimate of future ICH risk in patients with cSS across the spectrum of CAA presentations. Using data from more than 1,200 patients (the largest combined patient group to date), our pooled analysis provides compelling evidence that cSS presence and extent is the single strongest independent risk factor for CAA-related bleeding overall. Patients with cSS on MRI appear to have approximately 2 times the HR for future hemorrhage, compared to those without cSS. While focal cSS was also associated with doubling the bleeding hazards, the major driver of the elevated bleeding risk seems to be disseminated cSS (affecting more than 3 sulci), with pooled HRs 4 times greater than in patients without cSS. These estimates were independent of previously identified risk factors for CAA-related hemorrhage, including increasing age and lobar CMBs, and were stable irrespective of whether patients with CAA presented with lobar ICH or other non-ICH syndromes at baseline.

An important finding of this work, which should not be overlooked, is that the quality and methodologic aspects of studies on the topic vary and are not optimal. This partly reflects cSS being a relatively new imaging biomarker among CAA and small vessel disease MRI markers.^{2,13} Hence, our

pooled estimates, while preliminary, do provide validity for earlier observations by synthesizing data from a larger number of patients from established CAA cohorts and more outcome events, conferring higher statistical power for multivariable survival models. These results add substantially to an increasing body of evidence supporting cSS (especially if disseminated) as a central and specific hemorrhagic footprint of advanced CAA.³ The major clinical relevance of current findings is that cSS should play a key part in the routine bleeding risk stratification in patients with symptomatic CAA, including decision-making around prognosis and treatment. This becomes particularly important for anticoagulation decisions in CAA—currently, one of the hotly debated topics in the field.^{19,20} Clinicians are often hesitant to prescribe oral anticoagulation in patients with suspected underlying CAA, who would otherwise have a strong indication for the medication (e.g., nonvalvular atrial fibrillation).²⁰ Our results demonstrate that hemorrhagic risk, and hence the balance between hemorrhagic and cardioembolic stroke, is not uniform in patients with CAA. Instead, different CAA phenotypes with varying propensities towards bleeding can be dissected out based on the MRI presence and extent of cSS. The exact tipping point for when oral anticoagulation treatment should be avoided in patients with CAA in light of ICH risk and anticoagulation-related complications is difficult to calculate. However, a future incident/recurrent ICH rate of 12.5% per

Figure 3 Forest plot of the association between the presence of cortical superficial siderosis (cSS) and risk of future intracerebral hemorrhage (ICH) during follow-up



Meta-analysis was performed using a random effects model, pooling adjusted hazard ratios (HRs). The squares represent study-specific HRs, with their size proportional to their statistical weight (WGHT). LCL = lower confidence limit; UCL = upper confidence limit.

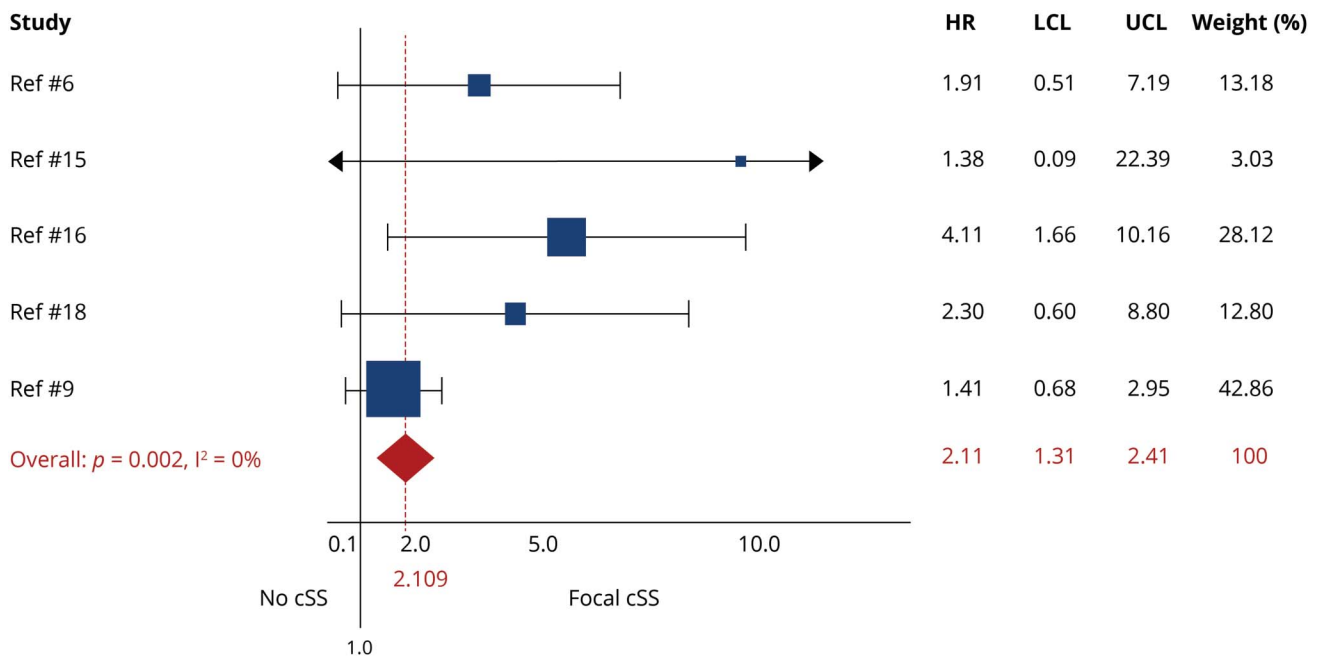
year (and HR of ~4) in the presence of disseminated cSS in the current meta-analysis identifies a specific CAA patient group in which the benefits of oral anticoagulation for preventing ischemic strokes should be carefully balanced in order to outweigh the risks.^{20,21} On the other hand, the presence of atrial fibrillation might confer enough risk for ischemic stroke to offset the presumed ICH risk in the subset of patients with CAA without cSS and a CHA₂DS₂ score >1–2. We note that data on the true risk vs benefit in this scenario are not available. Taken together, our data solidify the argument for using T2*-MRI sequences in patients with CAA to guide treatment planning. Direct analyses of cSS and outcomes in patients with suspected CAA and comorbid conditions requiring antithrombotic treatment, such as atrial fibrillation, are needed.

The potential pathophysiologic mechanisms linking cSS to elevated ICH risk in CAA remain largely undefined. The prevailing hypothesis is that cSS results from repeated episodes of superficial cortical hemorrhage into the subarachnoid (following the curvilinear shape of the surrounding cerebral gyri) from brittle CAA-laden leptomeningeal arterioles.³ It is possible that ICH results from the same mechanisms²² but further evidence is required. In the absence of direct neuropathologic support, indirect evidence for this hypothesis is provided by specific associations with *APOE* alleles. *APOE* genotype is an important genetic determinant of CAA pathophysiology^{23,24}: *APOE* ε4 seems to enhance vascular Aβ deposition in a dose-dependent fashion,²⁵ while *APOE* ε2 is linked to CAA-related vasculopathic degenerative

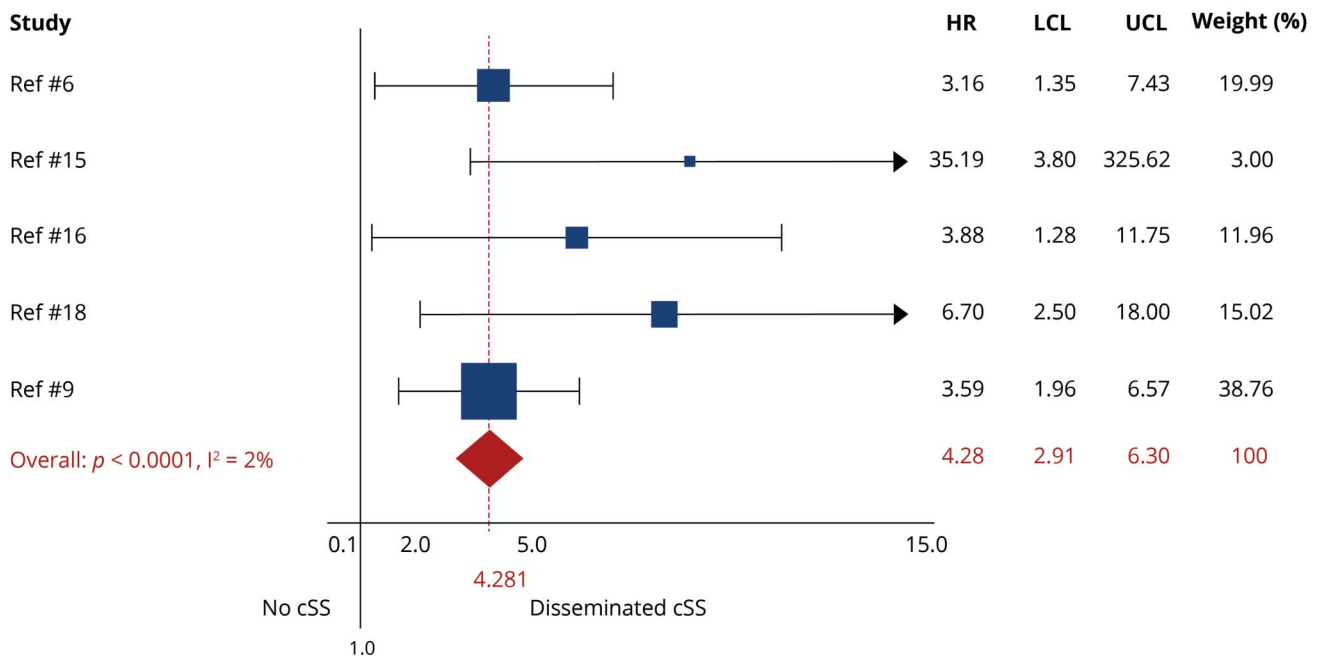
changes (vessel cracking, detachment and delamination of the outermost layer of the tunica media, and fibrinoid necrosis) that can lead to vessel rupture and ICH.²⁶ *APOE* ε2 is known to be associated with CAA-related ICH, perhaps causally,²⁷ and predisposes to larger volumes of CAA-related bleeding.²⁸ In recent studies, the *APOE* ε2 allele had a higher prevalence among patients with CAA with cSS, especially when disseminated.^{29–31} These observations create some prospects in that the presence of cSS, especially if disseminated, and *APOE* ε2 could in fact allow for a better stratification of bleeding risk in CAA (for example, in the case of anticoagulation decisions). The presence of cSS is also associated with positive PET amyloid imaging in the general elderly population³¹ and higher amyloid PET deposition among memory clinic patients.³² Whether lobar ICHs at follow-up are observed in the vicinity of previously detected cSS remains an open question in the field, but has promise in improving our understanding of the pathogenic mechanisms that bind these 2 hemorrhagic lesions. There are currently no good quality data regarding the spatial location of new symptomatic lobar ICH found in patients with CAA during follow-up in relation to cSS. This hypothesis remains difficult to test just by visually correlating the area of ICH with previous cSS. Often these patients have cSS occurring in multiple brain locations and hence a large hematoma is very likely to be close to a cSS region without a real statistical topographic correlation. Future studies will need to come up with more sophisticated approaches to specifically test this hypothesis rigorously.

Figure 4 Forest plots of the association between focal cortical superficial siderosis (cSS) (A) and disseminated cSS (B) with risk of future lobar intracerebral hemorrhage (ICH) during follow-up

A. Focal cSS and ICH risk



B. Disseminated cSS and ICH risk



Meta-analyses were performed using a random effects model, pooling adjusted hazard ratios (HRs). The squares represent study-specific HRs, with their size proportional to their statistical weight (WGHT). LCL = lower confidence limit; UCL = upper confidence limit.

In included studies, and similarly in our meta-analysis, lobar CMBs were not an independent predictor of future ICH risk. This finding might appear counterintuitive. Previous clinical-MRI cohorts in CAA have, often disproportionately, focused on the role of lobar CMBs as a risk factor for future bleeding risk, showing that their presence and burden are associated with

a higher risk of ICH recurrence.³³⁻³⁵ However, these older studies were performed prior to identification of cSS as an important CAA biomarker, and thus did not contain cSS in their analyses. When cSS is taken into account and included in adjusted survival models, lobar CMBs are no longer independently associated with the risk of future ICH,^{3,6} even in

CAA cases with lobar ICH at baseline. This has led to an evolution of thinking concerning CMBs in CAA. CMBs likely represent good MRI markers of the presence of advanced disease (for example, multiple strictly lobar CMBs indicate underlying CAA with good sensitivity and specificity³⁶), but are not necessarily strong predictors of the degenerative changes prone to ICH in amyloid-laden vessel wall segments. Corroborating this view, in a previous meta-analysis, strictly lobar microbleeds were related to *APOE* $\epsilon 4$ (OR 1.35, 95% CI 1.10–1.66; $p = 0.005$), but not *APOE* $\epsilon 2$.³⁷ There is also direct neuropathologic evidence that microbleeds and larger symptomatic hemorrhages (e.g., macrobleeds) might be pathophysiologically distinct, and not in a continuum.³⁸ These findings highlight the fact that cSS is more than just a cerebral sulcus equivalent of a microbleed—cSS is a distinct hemorrhagic signature of CAA and is strongly associated with risk of bleeding.

Strengths of our study include the increased sample size and number of outcome events by pooling all published data from retrospective and prospective MRI cohort studies investigating cSS. The combination of high statistical power and the homogeneity of effect sizes and direction across studies support the validity of the results. Some important limitations deserve careful consideration, and generally fall into 2 categories: (1) inherent limitations of CAA cohorts looking at baseline MRI markers and risk of future hemorrhage; and (2) limitations related to this type of aggregate data group-level meta-analysis. By definition, a potential limitation of any CAA clinical cohort is the selection bias due to the requirement for an MRI close to the baseline presentation, often as part of routine clinical care. Our results can thus only be generalized to symptomatic CAA survivors who get a brain MRI at baseline and fulfil the Boston criteria for CAA. This is often the clinical CAA population in which future ICH prevention is most relevant. Studies had varied follow-up times, ranging from 1 to 3 years, which are relatively short and might affect the reported future ICH estimates. In combination with the small sample sizes within individual cohorts, this led to wide CIs around risk estimates. Therefore, some of our meta-analyses were dominated in terms of statistical weighting by certain cohorts. The MRI protocols for cSS detection were not harmonized across, and often within studies, including the use of both T2*-GRE and SWI sequences at 1.5T or 3T, which might affect the sensitivity for grading cSS severity. This is an important limitation in synthesizing evidence for an MRI biomarker, in this case cSS, which might affect the rating for cSS presence and extent and affect our estimates. Of note, different MRI sequence measures and specifically SWI and T2*-GRE sequences have different sensitivities for blood product detection, as demonstrated in the CMB literature. However, there are no studies quantifying the difference in sensitivity of the 2 techniques for cSS classification. Given that cSS represents a much higher volume of blood breakdown products compared to CMBs, the differences in sensitivity might be less pronounced.

Despite using adjHR from multivariable survival models, a potential limitation of this study-level data approach is residual

confounding of the estimates by other baseline variables related to future ICH. Our approach for this initial meta-analysis on cSS and risk of future ICH was to look at the clinical relevance of the biomarker across all symptomatic CAA presentations (ICH and non-ICH) in order to draw more definite conclusions. We also hypothesized based on prior studies that the effect of cSS in elevating future bleeding risk is independent of whether patients had a history of ICH.^{16,39} However, careful phenotyping of CAA based on MRI signatures in combination with the clinical setting would still be of interest to further stratify future ICH risk. Based on the meta-analysis design, it remains uncertain whether cSS is a “stronger” predictor than clinical presentation with ICH and ICH history (single or multiple). Only 2 studies^{16,18} in our meta-analysis have provided data on patients with CAA without lobar hemorrhage presenting with transient focal neurologic episodes (TFNEs) or cognitive impairment, a largely understudied group in the field. In one of these studies¹⁸ the authors have not presented estimates separately for patients with CAA with vs without ICH in relation to the outcomes of interest. Hence, a secondary analysis according to patient presentations was not possible based on available data. We acknowledge that different CAA clinical presentations (i.e., with ICH vs TFNEs or cognitive impairment) might have different baseline absolute risks for future ICH. However, we have hypothesized, and confirmed, that the effect of the marker—in this case cSS—has a consistent effect in increasing the relative risk for future ICH across the spectrum of CAA. In the absence of precise patient-years of follow-up, our pooled estimates on ICH incidence rate per year according to cSS status and severity are not stable, with moderate to severe statistical heterogeneity, and likely underestimate the true incidence rate, especially in patients with severe cSS.⁴⁰ Finally, none of the included studies have investigated blood pressure control and antithrombotics use during follow-up, and how they might interact with MRI markers of CAA and ICH recurrence—a point for future investigation. The contribution of chronic arterial hypertension to lobar ICH risk is well-documented^{41–43} and blood pressure control in particular is a key target for reducing future ICH occurrence in CAA. The only way to circumvent the limitations discussed and further increase the sample size and generalizability of the findings, investigate the full range of interactions between different variables, and build more sophisticated multivariable models would be an individual patient data meta-analysis systematically exploring MRI and other predictors of CAA-related ICH recurrence. This analysis is currently planned under the umbrella of the International CAA Association (caforum.org/).

Altogether, data reported here solidify cSS as a biomarker of increased cortical and leptomeningeal small-vessel fragility and high CAA disease activity, heralding a high risk for future ICH. Our findings therefore provide a strong argument for using blood-sensitive T2*-weighted MRI sequences to identify specific subgroups of patients with CAA at high risk for ICH. This could be helpful to inform and tailor treatment planning. Large international efforts in the field are underway to validate and expand these findings.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
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G. Boulouis	Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston	Author	Project design, data collection critical revisions
S. M. Greenberg	Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston	Author	Funding, study concept, critical revisions
Anand Viswanathan	Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston	Author	Project supervision, data collection, funding, critical revisions

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