

# Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy

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## Abstract

### Objective

To investigate the prognostic relevance of cortical superficial siderosis (cSS) in patients with cerebral amyloid angiopathy (CAA).

### Methods

A total of 302 patients fulfilling clinical and imaging criteria for probable or possible CAA were enrolled into a prospective, multicenter cohort study and followed for 12 months. cSS was assessed on T2\*/susceptibility-weighted imaging MRI. The predefined primary composite endpoint was incident stroke or death in patients with cSS compared to those without. Secondary analyses included cerebrovascular events and functional outcome measured by the modified Rankin Scale (mRS). Multiple regression analysis was performed to adjust for possible confounders.

### Results

cSS prevalence was 40%. The primary endpoint occurred more frequently in patients with cSS (22%, 27/121) compared to those without (8%, 15/181,  $p = 0.001$ ). Rates of CAA-related incident intracranial hemorrhage were 17% (cSS) and 4% (no cSS,  $p = 0.0003$ ). The proportion of patients being functionally independent (mRS 0–2) 12 months from baseline were 59% (cSS) and 82% (no cSS,  $p = 0.00002$ ). Presence of cSS was associated with the primary endpoint (adjusted odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.3,  $p = 0.0005$ ), incident intracranial hemorrhage (adjusted OR 1.2, 95% CI 1.1–1.3,  $p = 0.0003$ ), and less favorable outcome as assessed by the mRS (common OR 1.9, 95% CI 1.2–3.1,  $p = 0.009$ ). Similar results were obtained in analyses restricted to patients with probable CAA and to patients with disseminated cSS (all  $p < 0.005$ ).

### Conclusions

Patients with cSS and suspected CAA are at high risk for CAA-related incident intracranial hemorrhage and poor functional outcome. Both the presence and extent of cSS have prognostic relevance and may influence clinical decision-making.

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## Glossary

CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleeds; cSS = cortical superficial siderosis; ICH = intracerebral hemorrhage; MMSE = Mini-Mental State Examination; mRS = modified Rankin Scale; OR = odds ratio; PVS = perivascular spaces; QC = quality control; SAH = subarachnoid hemorrhage; SVD = small vessel disease; SWI = susceptibility-weighted imaging; WMH = white matter hyperintensities.

Cerebral amyloid angiopathy (CAA), caused by deposition of  $\beta$ -amyloid in the walls of leptomeningeal arteries,<sup>1</sup> is remarkably common in the elderly.<sup>2</sup> Its major clinical consequences include intracerebral hemorrhages (ICH), typically in lobar location,<sup>3</sup> and cognitive impairment.<sup>4</sup> CAA is the underlying etiology in up to 74% of nontraumatic lobar ICH,<sup>2</sup> with mortality rates ranging between 10% and 30%.<sup>5,6</sup> Moreover, CAA-related ICH has a high recurrence risk (~10% per year) even in the absence of oral anticoagulation.<sup>7</sup> Meanwhile, the number of elderly patients with CAA with concomitant atrial fibrillation is growing,<sup>8</sup> thus posing a challenge to balancing the benefits and risks of antithrombotic treatment.

Recent single-center studies have suggested a prognostic relevance of cortical superficial siderosis (cSS) in predicting ICH risk in patients with probable or possible CAA.<sup>9–11</sup> However, data from prospective, multicenter studies are missing, as are data on functional outcome and on incident events other than ICH.

In this prospective, registered, multicenter cohort study, we set out to determine the prognostic value of cSS in patients with probable or possible CAA. Specifically, we aimed to compare the rate of incident stroke or death of any cause in patients with cSS compared to those without cSS.<sup>1</sup> Secondary endpoints included the rate of incident intracranial hemorrhage (including both ICH and sulcal subarachnoid hemorrhage [SAH]) and the proportion of patients being functionally independent 12 months from baseline.

## Methods

### Study setting

All data are derived from the Superficial Siderosis in Patients with Suspected Cerebral Amyloid Angiopathy Study (SuSPect-CAA), a prospective, hospital-based, multicenter, cohort study conducted at 4 university hospitals in Europe (Munich, Germany [coordinating center]; Reggio Emilia, Italy; Barcelona, Spain; and Porto, Portugal).

### Participants

A total of 302 patients were enrolled into the study between May 2013 and March 2016. Patients meeting a diagnosis of probable or possible CAA based on the modified Boston criteria<sup>12</sup> were included with the following additional modification: we did not exclude patients with a maximum of 2 deep cerebral microbleeds (CMB) on baseline MRI provided

they had at least twice the number of lobar CMB or a history of lobar ICH, or cSS as assessed by a central MRI read in consensus by 2 expert raters (F.A.W. and J.L.). This additional modification was made to avoid a potential selection bias towards CAA patients without hypertension. Major exclusion criteria were a history of ICH located in the deep gray matter (basal ganglia or thalami) or brainstem, history of head trauma resulting in loss of consciousness or radiologically visible brain injury in the last 5 years prior to inclusion, history of cerebral aneurysm or aneurysmal SAH, or infratentorial siderosis. For further details, see ClinicalTrials.gov: NCT01856699. Patients primarily presented at stroke services (n = 194) or memory clinics (n = 108). The main clinical symptoms that led to presentation to the hospital were as follows: intracranial hemorrhage (36%, 109/302), memory complaints (36%, 108/302), ischemic stroke or TIA (14%, 42/302), transient focal neurologic episodes or presumed focal seizure 11% (32/302), and dizziness, headache, or other nonspecific neurologic complaints (4%, 11/302). Patients with CAA-related inflammation were not included.

### Baseline assessments

Standardized assessments at baseline encompassed a medical history (including for vascular risk factors and medication use), a neurologic examination, MRI, genotyping for *APOE* carrier status, modified Rankin Scale (mRS), and Mini-Mental State Examination (MMSE).

MRI examinations were performed according to standardized imaging protocols on 3.0 or 1.5T MRI scanners at baseline and at follow-up including the following sequences: diffusion-weighted, fluid-attenuated inversion recovery, proton density-weighted, T1-weighted, T2\*-weighted gradient echo, susceptibility-weighted imaging (SWI), and time-of-flight magnetic resonance angiography. CMB and macrohemorrhages were defined according to the Standards for Reporting Vascular Changes on Neuroimaging criteria.<sup>13</sup> CMB were marked manually; lesion masks were normalized to Montreal Neurologic Institute standard space and rated automatically as described previously.<sup>14</sup>

### Exposure

cSS was identified on T2\*/SWI MRI by 2 independent expert raters (F.A.W. and J.L.) without disagreements. cSS was categorized into focal ( $\leq 3$  affected gyri) and disseminated ( $> 3$  affected gyri).<sup>3,12</sup> Disagreements on the extent of cSS were resolved by consensus reads, which were necessary in 4% of cases (5/121).

## Follow-up assessments

All patients were invited for personal visits at the local study site 6 and 12 months after baseline. Standardized assessments included a history of incident events, a neurologic examination, mRS, and neuroimaging. Stroke (ischemic and hemorrhagic) was defined by an acute focal neurologic deficit in combination with a corresponding new lesion detected by MRI or a CT scan. Patients unable or unwilling to undergo repeat MRI were offered CT imaging. Patients not returning to the study center were interviewed by telephone. Information on patients not reached by telephone was obtained by interview of relatives, private practitioners, and medical records (figure 1).

## Data management

Data were entered into machine readable case report files (Teleform; Electric Paper, Lüneburg, Germany),<sup>15</sup> which were processed by the coordinating center after centralized quality control (QC) by an independent data manager.

## Outcomes

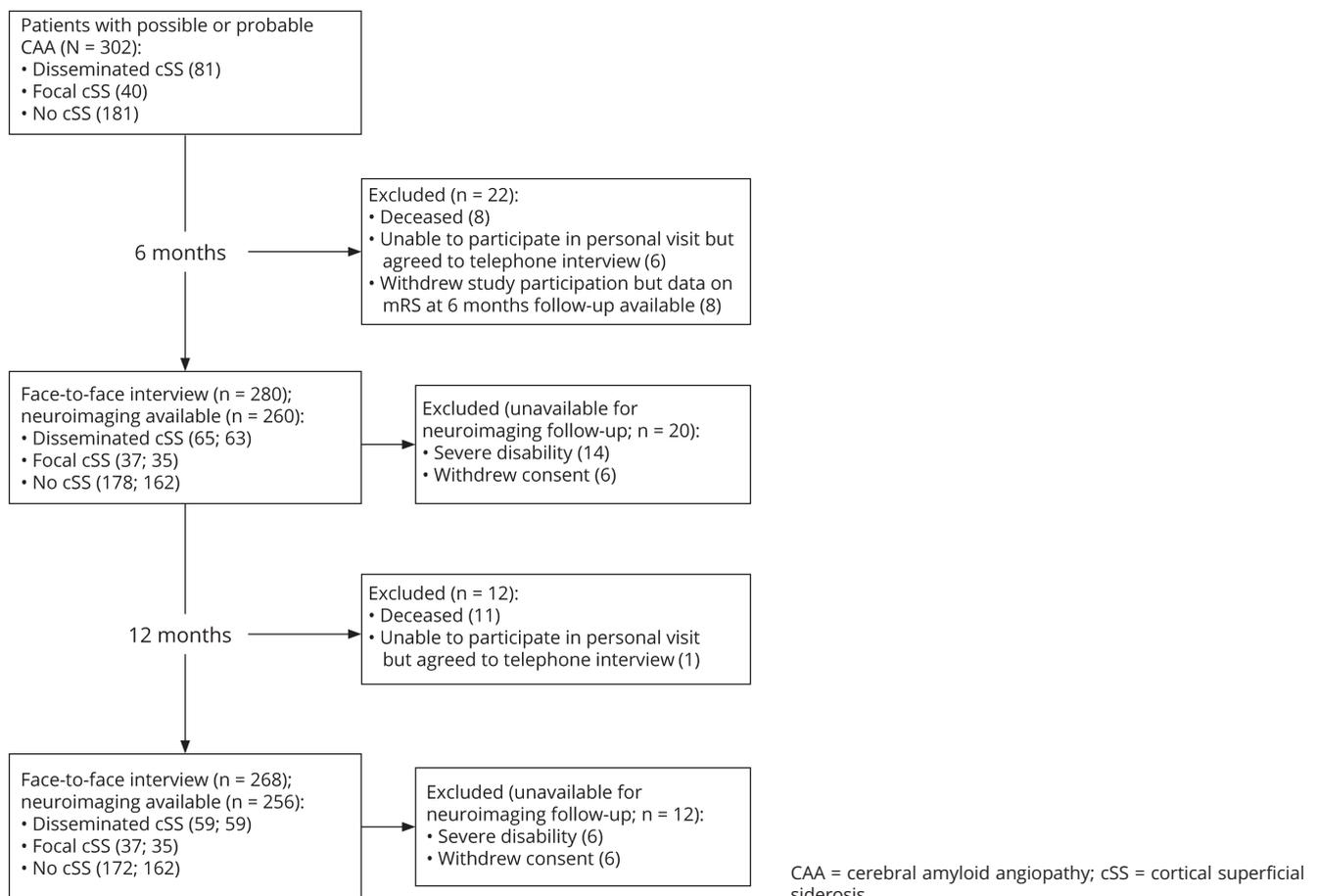
The predefined primary composite endpoint was the rate of stroke or death (defined as all-cause mortality) at follow-up. Secondary outcomes included (1) incident intracranial

hemorrhage (ICH or sulcal SAH) as confirmed by MRI or native CT and (2) functional outcome as assessed by the mRS (range, 0 [no symptoms]–6 [death]). All clinical and imaging endpoints were assessed by board-certified neurologists and neuroradiologists, respectively.

## Statistical analysis

All analyses were performed using R Core Team 2017, version 3.4.0 (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; R-project.org/). Baseline statistics were calculated using Student *t* tests or  $\chi^2$  tests where appropriate. Dichotomized analyses were carried out using logistic regression. Kaplan-Meier analysis and the log-rank test were carried out using the R package survival. Time to event was recorded in days. Ordinal logistic regression with ordered mRS as an outcome variable were carried out using the R package VGAM. Proportional odds were tested using a likelihood ratio test. The proportional odds assumption of equal slopes was met in all models. To adjust for possible confounders, we applied backward stepwise regression analysis optimizing on Akaike Information Criterion to select the optimal set of covariates for the main model. As a result, the following baseline measures were included into all ordinal

**Figure 1** Study flow chart



logistic regression models: age, number of CMB at baseline, and mRS at baseline. The number of CMB was coded in CMB groups. Grouping into 0, 1, 2–4, and >5 was carried out according to recent literature.<sup>16,17</sup> Interaction between subgroups was tested using the *rma* function from *metafor*. We further present results for an 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 (including both index events and a medical history of intracranial hemorrhage), previous ischemic stroke, and mRS at baseline.

### Data availability

Any data not published within this article are available in the supplemental tables (doi:10.5061/dryad.rb9665d). Patient-related data will be shared on request from any qualified investigator, maintaining anonymization of the individual patients.

### Standard protocol approvals, registrations, and patient consents

Study approval was obtained from the institutional review boards at each site with informed consent from all participants. The study is registered at clinicaltrials.gov (NCT01856699).

## Results

### Baseline characteristics

Patients with cSS (40%, 121/302) and without cSS (60%, 181/302) were balanced with respect to age, sex, *APOE* carrier status, and hypertension (table 1). Thirty-six percent (109/302) of patients had a history of previous intracranial hemorrhage, whereas 64% (193/302) had lobar CMB or cSS without previous intracranial hemorrhage. Compared to patients without cSS, patients with cSS more often had a history of intracranial hemorrhage, and their MMSE scores and median mRS scores were lower. In contrast, patients without cSS more often had a history of hyperlipidemia, diabetes, ischemic stroke, and use of antiplatelet agents.

### Incident events and functional outcome stratified for the presence of cSS

The primary composite endpoint of stroke or death of any cause occurred in 22% (27/121) of patients with cSS, as compared with 8% (15/181) of patients without cSS (table 2). In logistic regression analyses, the endpoint of stroke or death of any cause was reached significantly more frequently in patients with cSS compared to patients without cSS (adjusted odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.3,  $p = 0.0005$ , table 3). Incident intracranial hemorrhage occurred in 17% (20/121) of patients with cSS and 4% (7/181) of patients without cSS. In logistic regression analyses, cSS was significantly associated with incident intracranial hemorrhage (adjusted OR 1.2, 95% CI 1.1–1.3,  $p = 0.0003$ ). Death was significantly more frequent in patients with cSS (11%, 13/121) than in patients without cSS (3%, 6/181,  $p = 0.01$ ). In Kaplan-Meier analyses, the presence of cSS at baseline was a predictor of both faster time until the primary composite endpoint of stroke or death of any

cause (log-rank test  $p = 0.0001$ , figure 2A) and faster time until incident intracranial hemorrhage (log rank test:  $p = 0.00003$ , figure 2B). Of note, incident intracranial hemorrhage accounted for the majority of primary endpoints in patients with cSS (20/27; 74%) but not in patients without cSS (7/15; 47%).

Functional independence (mRS 0–2) at the 1-year follow-up was observed in 59% (71/121) of patients with cSS and in 82% (148/181) of patients without cSS (table 2 and figure 3). Corresponding rates for excellent outcome (mRS 0–1) were 45% (55/121) and 69% (125/181). In logistic regression analyses accounting for baseline variables including mRS, both functional independence and excellent outcome were significantly less frequent in patients with cSS than in patients without cSS (adjusted OR 0.3, 95% CI 0.1–0.8,  $p = 0.01$ ; and adjusted OR 0.3, 95% CI 0.1–0.7,  $p = 0.005$ , respectively, table 3). The results remained significant in shift analyses using ordinal logistic regression after adjustment for possible confounders identified by backward stepwise regression (common OR 1.9, 95% CI 1.2–3.1,  $p = 0.009$ ) and when forcing incident intracranial hemorrhage into the model (OR 1.8 [1.0–2.8],  $p = 0.03$ ). Results on the primary outcome, intracranial hemorrhage, and functional outcome further remained significant when extending the number of covariates in the logistic regression model to 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 at baseline (table e-1, doi.org/10.5061/dryad.rb9665d).

### Incident events and functional outcome stratified for the extent of cSS

cSS was disseminated in 67% (81/121) and focal in 33% (40/121). The primary composite endpoint occurred in 27% (22/81) of patients with disseminated cSS and in 12% (5/40) of patients with focal cSS ( $p = 0.1$ ; table e-2 [doi.org/10.5061/dryad.rb9665d]). Incident intracranial hemorrhage occurred in 20% (16/81) of patients with disseminated cSS and 10% (4/40) of patients with focal cSS ( $p = 0.2$ ; table e-2 [doi.org/10.5061/dryad.rb9665d]).

In logistic and ordinal logistic regression analyses, disseminated cSS was an independent predictor of reaching the primary composite endpoint (adjusted OR 5.0, 95% CI 2.3–10.9,  $p = 0.00005$ ), intracranial hemorrhage (adjusted OR 6.7, 95% CI 2.5–18.0,  $p = 0.0001$ ), and for unfavorable mRS scores at follow-up (common OR 2.6; 95% CI 1.5–4.5,  $p = 0.0007$ , table 3). In contrast, focal cSS was not a significant independent predictor of any of the outcomes in logistic and ordinal regression analyses.

### Incident events and functional outcome stratified for subgroups

We next repeated the logistic and ordinal logistic regression analyses for the presence of cSS in the subgroup of patients with probable CAA without exclusion of patients with 1 or 2 deep CMB (71%, 214/302). Results for the primary endpoint, intracranial hemorrhage, and functional outcome remained

**Table 1** Baseline characteristics in patients with suspected cerebral amyloid angiopathy stratified for presence of cortical superficial siderosis (cSS)

|  | cSS (n = 121) | No cSS (n = 181) | p Value |
|--|---------------|------------------|---------|
| Age, y, mean (SD)  | 73.80 (6.91)  | 73.15 (7.84)     | 0.5     |
| Female, n (%)  | 52 (43)       | 69 (38)          | 0.5     |
| APOE ε2 (≥1 copy), n (%) <sup>a</sup>                        | 20 (17)       | 23 (13)          | 0.4     |
| APOE ε4 (≥1 copy), n (%) <sup>a</sup>                        | 28 (23)       | 33 (18)          | 0.3     |
| Hypertension, n (%)  | 87 (72)       | 142 (78)         | 0.2     |
| Hyperlipidemia, n (%)  | 58 (48)       | 111 (61)         | 0.03    |
| Diabetes, n (%)  | 13 (11)       | 47 (26)          | 0.002   |
| Coronary artery disease, n (%)                               | 9 (7)         | 25 (14)          | 0.1     |
| Previous myocardial infarction, n (%)                        | 6 (5)         | 21 (12)          | 0.08    |
| Peripheral artery disease, n (%)                             | 12 (10)       | 34 (19)          | 0.05    |
| Atrial fibrillation, n (%)                                   | 17 (14)       | 36 (20)          | 0.3     |
| Inclusion from stroke service                                | 72 (60)       | 122 (67)         | 0.2     |
| Inclusion from memory clinic                                 | 49 (41)       | 59 (33)          | 0.2     |
| Previous TIA, n (%) <sup>b</sup>                             | 12 (10)       | 30 (17)          | 0.1     |
| Previous ischemic stroke, n (%) <sup>b</sup>                 | 25 (21)       | 92 (51)          | <0.0001 |
| Months since previous ischemic stroke median (Q3–Q1)         | 14 (1–34)     | 2 (1–30)         | 0.5     |
| Previous intracranial hemorrhage, n (%) <sup>b</sup>         | 71 (59)       | 38 (21)          | <0.0001 |
| Intracerebral hemorrhage, n (%)                              | 50 (41)       | 38 (21)          | 0.0002  |
| Sulcal subarachnoid hemorrhage, n (%)                        | 35 (29)       | 4 (2)            | <0.0001 |
| Months since previous intracranial hemorrhage (median Q3–Q1) | 4 (1–16)      | 7 (1–40)         | 0.4     |
| Cerebral microbleeds, n (%) <sup>c</sup>                     |               |                  | 0.007   |
| 0  | 28 (24)       | 22 (12)          |         |
| 1  | 15 (13)       | 29 (16)          |         |
| 2–4  | 27 (23)       | 67 (38)          |         |
| ≥5   | 49 (41)       | 60 (34)          |         |
| Antiplatelet agents, n (%)                                   | 34 (28)       | 104 (57)         | <0.0001 |
| Oral anticoagulation, n (%)                                  | 14 (12)       | 23 (13)          | 0.9     |
| Mini-Mental State Examination, mean (SD)                     | 24.2 (5.6)    | 25.8 (4.4)       | 0.009   |
| <b>Functional outcome</b>                                    |               |                  |         |
| mRS, median (Q3–Q1)  | 1 (2–0)       | 1 (2–0)          | 0.02    |
| mRS 0–1, n (%)   | 73 (60)       | 127 (70)         | 0.07    |
| mRS 0–2, n (%)   | 94 (78)       | 156 (86)         | 0.07    |

Abbreviation: mRS = modified Rankin Scale.

<sup>a</sup> Missing, n = 22 (no consent for molecular genetics).

<sup>b</sup> Definition, both index events and events determined by medical history.

<sup>c</sup> Missing, n = 5 (because of motion artefacts or other technical issues).

significant (figure 4). We further repeated the analysis in the subgroup of patients with probable CAA and strictly lobar CMB (i.e., with exclusion of all patients with any deep CMB, 59%, 179/302) thus fulfilling the modified Boston criteria.<sup>12</sup>

Again, the results for the primary endpoint, intracranial hemorrhage, and functional outcome all remained significant (table e-4, doi.org/10.5061/dryad.rb9665d), thus confirming the results of the overall cohort.

**Table 2** Incident events and functional outcome in patients with suspected cerebral amyloid angiopathy stratified for presence of cortical superficial siderosis (cSS)

|                                       | cSS<br>(n = 121)     | No cSS<br>(n = 181) | p Value |
|---------------------------------------|----------------------|---------------------|---------|
| <b>Stroke or death, n (%)</b>         | 27 (22)              | 15 (8)              | 0.001   |
| <b>Ischemic events, n (%)</b>         | 3 (2)                | 10 (6)              | 0.3     |
| Ischemic stroke                       | 1 (1)                | 7 (4)               | 0.2     |
| TIA                                   | 2 (2)                | 3 (2)               | 1       |
| <b>Intracranial hemorrhage, n (%)</b> | 20 (17)              | 7 (4)               | 0.0003  |
| Intracerebral hemorrhage              | 17 (14)              | 7 (4)               | 0.002   |
| Sulcal subarachnoid hemorrhage        | 3 (2)                | 0                   | 0.06    |
| <b>Death, n (%)</b>                   | 13 (11) <sup>a</sup> | 6 (3) <sup>b</sup>  | 0.01    |
| <b>Functional outcome</b>             |                      |                     |         |
| mRS 0–1, n (%)                        | 55 (45)              | 125 (69)            | 0.00005 |
| mRS 0–2, n (%)                        | 71 (59)              | 148 (82)            | 0.00002 |

Abbreviation: mRS = modified Rankin Scale.

<sup>a</sup> Causes of death: imaging confirmed intracranial hemorrhage (7 patients), sudden death of presumed vascular cause (n = 5), pulmonary embolism (1 patient).

<sup>b</sup> Causes of death: imaging confirmed intracranial hemorrhage (1 patient), ischemic stroke (1 patient), pneumonia (3 patients), pancreatic cancer (1 patient).

Next, we repeated the analysis for the subgroups of patients recruited through stroke services (64%, 194/302) and memory clinics (36%, 108/302). In logistic regression analyses, results for the primary endpoint, intracranial hemorrhage, and functional outcome reached statistical significance in patients recruited via stroke services but not in patients recruited through memory clinics (figure 4), although the test for interaction between group and cSS was not significant.

### Incident events and functional outcome stratified for small vessel disease (SVD) severity

We further examined the predictive ability of a recently proposed CAA-based SVD score<sup>17</sup> that includes cSS in addition to the presence and extent of other MRI features (white matter hyperintensities [WMH], perivascular spaces [PVS], and CMB). In logistic and ordinal logistic regression analyses the total score predicted the primary endpoint (adjusted OR 1.2, 95% CI 1.1–1.3,  $p = 0.001$ ), intracranial hemorrhage (adjusted OR 1.2, 95% CI 1.1–1.3,  $p = 0.0003$ ), and unfavorable mRS scores at follow-up (common OR 1.3, 95% CI 1.1–1.6,  $p = 0.0009$ ). Of note, however, cSS was the only MRI marker that predicted the primary outcome or intracranial hemorrhage when considered in isolation (table e-3, doi.org/10.5061/dryad.rb9665d).

## Discussion

The main findings from this prospective multicenter study on a large cohort of patients with probable or possible CAA can

**Table 3** Incident events and functional outcome in logistic and ordinal logistic regression analysis stratified for presence and extent of cortical superficial siderosis (cSS)

|                                  | Presence of<br>cSS (n = 121) | Disseminated<br>cSS (n = 81) | Focal cSS<br>(n = 40) |
|----------------------------------|------------------------------|------------------------------|-----------------------|
| <b>Stroke or death</b>           |                              |                              |                       |
| OR (95% CI)                      | 1.2 (1.1–1.3)                | 5.0 (2.3–10.9)               | 1.4 (0.4–4.5)         |
| p Value                          | 0.0005                       | 0.00005                      | 0.6                   |
| <b>Intracranial hemorrhage</b>   |                              |                              |                       |
| OR (95% CI)                      | 1.2 (1.1–1.3)                | 6.7 (2.5–18.0)               | 2.3 (0.6–8.8)         |
| p Value                          | 0.0003                       | 0.0001                       | 0.2                   |
| <b>Functional outcome</b>        |                              |                              |                       |
| mRS, shift analysis, OR (95% CI) | 1.9 (1.2–3.1)                | 2.6 (1.5–4.5)                | 1.1 (0.5–2.2)         |
| p Value                          | 0.009                        | 0.0007                       | 0.8                   |
| <b>mRS 0–1</b>                   |                              |                              |                       |
| OR (95% CI)                      | 0.3 (0.1–0.7)                | 0.2 (0.1–0.6)                | 1.1 (0.3–3.3)         |
| p Value                          | 0.005                        | 0.002                        | 0.9                   |
| <b>mRS 0–2</b>                   |                              |                              |                       |
| OR (95% CI)                      | 0.3 (0.1–0.8)                | 0.2 (0.1–0.6)                | 1.4 (0.4–5)           |
| p Value                          | 0.01                         | 0.001                        | 0.6                   |

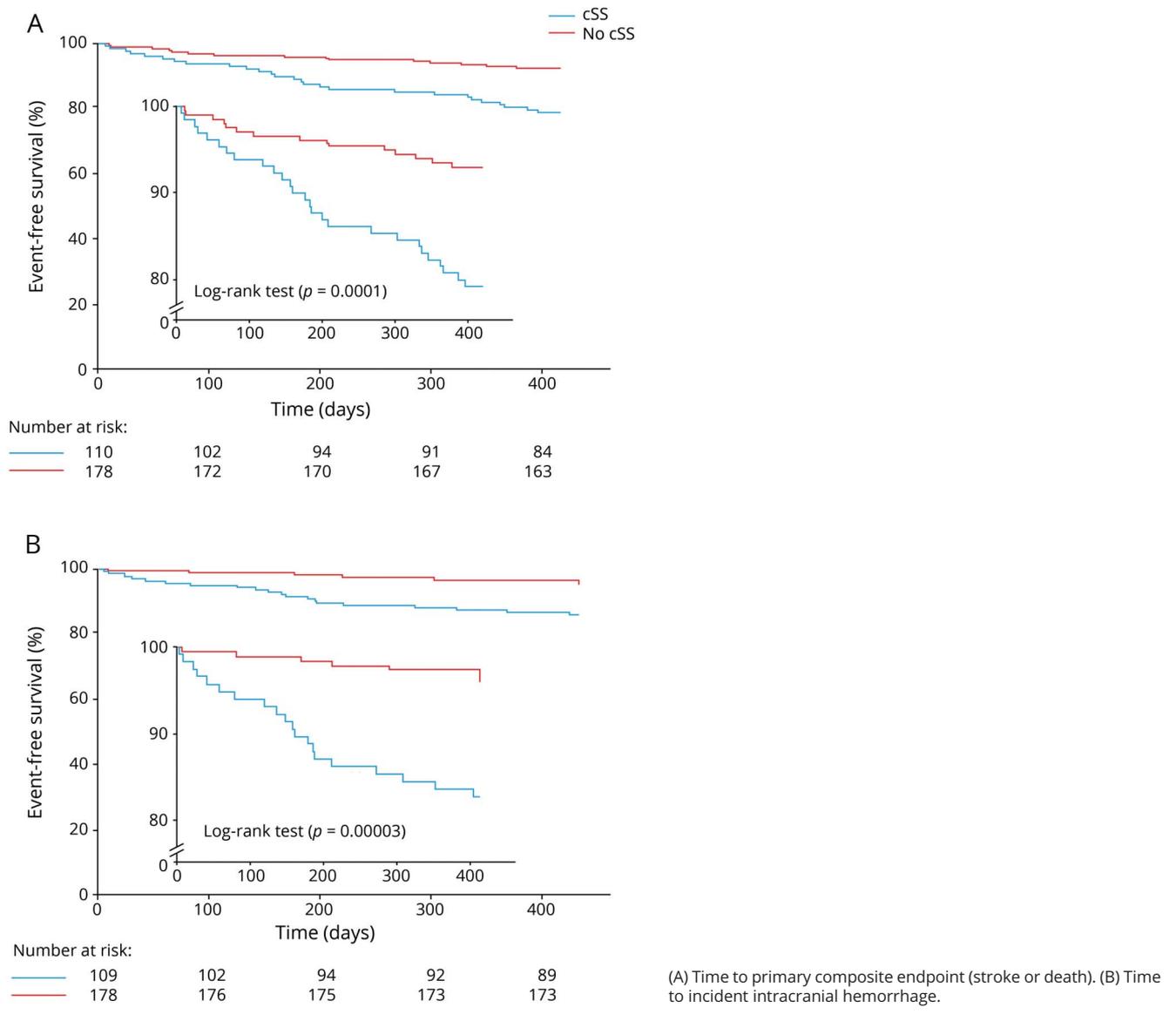
Abbreviations: CI = confidence interval; diss = disseminated (>3 gyri affected); mRS = modified Rankin Scale; OR = odds ratio.

Covariates selected by stepwise regression: age, number of cerebral microbleeds at baseline, and mRS at baseline. Models adjusted for age, sex, hypertension, atrial fibrillation, intake of platelet inhibitors, intake of oral anticoagulation, presence of cerebral microbleeds, history of intracranial hemorrhage and ischemic stroke, and mRS at baseline.

be summarized as follows: (1) both the presence and extent of cSS are strong predictors of the predefined composite endpoint of stroke or death within 12 months from baseline; (2) incidence rates for intracranial hemorrhage were remarkably high in CAA patients with cSS (17%) compared to those without cSS (4%); and (3) the presence and extent of cSS predict an unfavorable functional outcome.

The incidence rate for the primary composite endpoint of stroke or death within 12 months from baseline was high, reaching 22% in patients with cSS compared to 8% in patients without cSS. Importantly, all but 1 of incident strokes in patients with cSS were classified as CAA-related intracranial hemorrhage (defined as ICH or sulcal SAH), emphasizing the role of cSS as a predictor for intracranial hemorrhage risk. Mortality was significantly higher in patients with cSS compared with patients without cSS, and in 92% of the patients with cSS who died during follow-up, the underlying cause was intracranial hemorrhage or sudden death of presumed

**Figure 2** Kaplan-Meier analyses in patients with suspected cerebral amyloid angiopathy stratified for the presence of cortical superficial siderosis (cSS)



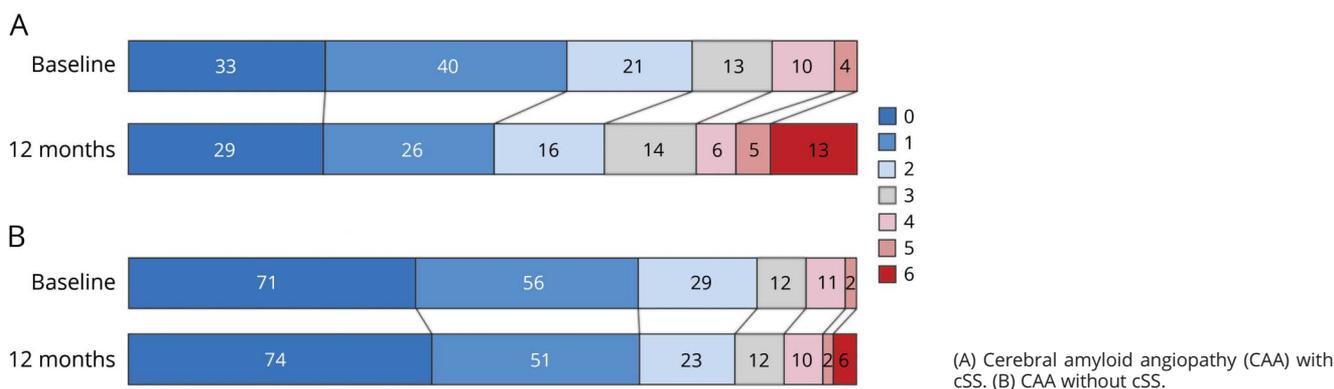
vascular cause. These observations highlight the prognostic relevance of cSS in patients with probable or possible CAA, particularly when viewed in conjunction with our data on functional outcome.

We found the presence of cSS to be associated with worse functional outcome 12 months from baseline both in binary analyses using different cutoffs and in shift analyses using ordinal logistic regression. While somewhat expected from the higher rate of intracranial hemorrhage, this finding emphasizes the clinical relevance of cSS, for which data on functional outcome have so far been missing. On average, patients with cSS were functionally more impaired at baseline than patients without cSS. Importantly, however, differences in outcomes remained significant both in the main logistic regression analyses controlling for functional status at baseline

among other factors and after forcing incident intracranial hemorrhage into the model. Hence, our study establishes cSS as an independent risk factor for poor functional outcome.

The proportion of patients who experienced an ICH within 12 months from baseline was 14% in patients with cSS and 4% in those without cSS. A recent study in survivors of spontaneous symptomatic probable or possible CAA-related lobar ICH found corresponding figures of 16% and 5% within a 6-month interval.<sup>18</sup> Differences in incidence rates for ICH likely reflect differences in case mix, study protocols, and possibly also medication use. For instance, only 29% of our patients had a previous ICH and the average age in our cohort was slightly lower than in the study on ICH survivors.<sup>18</sup> Regardless of these differences, the 2 studies underscore the clinical importance of cSS in predicting ICH risk in patients with probable or possible CAA.

**Figure 3** Distribution of modified Rankin Scale scores at baseline and at 12-month follow-up stratified for the presence of cortical superficial siderosis (cSS)



A previous study in ICH survivors found a higher recurrence rate of ICH in patients with disseminated cSS when compared to patients with focal cSS.<sup>18</sup> Another study in ICH survivors found disseminated cSS, but not the presence of cSS, to be associated with recurrent ICH.<sup>19</sup> We found both the presence of cSS and disseminated cSS to be independent predictors (table 3) for the primary composite endpoint, for intracranial hemorrhage, and for an unfavorable mRS, whereas the ORs for focal cSS did not reach statistical significance. However, the number of patients with focal cSS was relatively small (n = 40), leaving the possibility that we have missed a possible effect of focal cSS on the primary and secondary endpoints because of a lack in statistical power.

Thirty-six percent of our patients were recruited through memory clinics. Focusing on this subgroup, the presence of cSS was not a significant predictor of incident events. However, since the interaction test for group and cSS was not significant, the cSS-associated risk is probably similar between stroke service and memory clinic patients, but with lower confidence in the latter group due to smaller sample size. Additional studies are needed to determine the precise risk of incident events and functional outcome in CAA patients who present with cognitive complaints.

We found a recently proposed CAA-based SVD score<sup>17</sup> that includes cSS in addition to the presence and extent of WMH, PVS, and CMB to predict both the primary endpoint and the secondary endpoints of intracranial hemorrhage and functional outcome. We did not formally compare the predictive value of the composite score with cSS alone as this was outside the scope of our study. Of note, however, cSS was the only MRI marker that predicted outcome when considered in isolation (table e-3, doi.org/10.5061/dryad.rb9665d). More work is needed to determine whether the use of the composite score adds to prognostication in CAA when compared to the cSS alone.

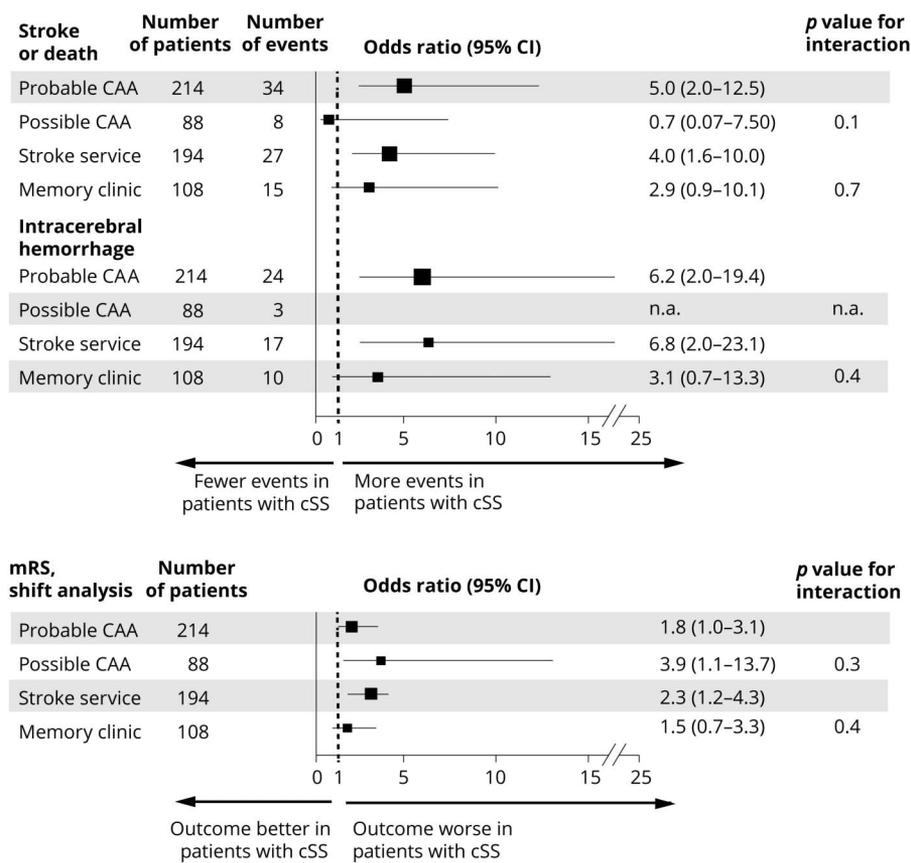
The proportion of patients taking antiplatelet agents was significantly higher among those without cSS than those with

cSS. Still, incidence rates for intracranial hemorrhage were substantially higher in the latter group. While the current study was not designed to test the effects of medication use on vascular risk, our findings highlight the need for studying the effects of antithrombotic use on incident cerebrovascular events in CAA patients while also stratifying for cSS.

Strengths of this study include the prospective setting with systematic follow-up by personal visits and neuroimaging. The retention rate was high with 93% and 89% of the patients returning for the face-to-face interviews at 6 and 12 months, respectively. Also, data on incident stroke and functional outcome were available for all 302 patients. Hence, information on the primary endpoint and on functional outcome was complete. Our study also has limitations. Despite a rather large sample size and a follow-up interval of 12 months, the total number of events for the primary endpoint was limited (n = 42). To restrict the analyses to a meaningful number of covariates, we applied a stepwise regression model. While we cannot rule out residual confounding with the selected covariates, the results remained significant in an extended model adjusting for 9 covariates selected on the basis of previous literature (table e-1, doi.org/10.5061/dryad.rb9665d). Finally, we did not exclude patients with a maximum of 2 deep CMB provided they had other typical CAA markers. Importantly, however, the results remained significant when excluding patients with any deep CMB (20% of our cohort, 59/302).

Follow-up MRI could not be obtained in 50% of patients. However, any imaging follow-up (MRI or CT) was available in 85% of the overall cohort and in all patients who experienced an incident stroke. Therefore, key secondary outcomes including intracranial hemorrhage were fully captured. The recruitment of patients from different centers may have resulted in slightly variable assessments. However, variations in assessments were minimized by a detailed study protocol, central data management, and rigorous QC. The use of 2 different field strengths (1.5 and 3.0T) might have influenced

**Figure 4** Subgroup analyses of incident events and functional outcome in logistic and ordinal logistic regression stratified for the presence of cortical superficial siderosis (cSS)



CAA = cerebral amyloid angiopathy; CI = confidence interval.

the accuracy of the detection and extent of cSS and CMB counts. However, MRI field strength as a variable showed no significant association with our endpoints in univariate analysis and was not selected by stepwise regression models, arguing against a strong effect. Also, the multicenter approach otherwise enhances the generalizability of our findings.

The current study shows that the presence of cSS strongly predicts the composite outcome of stroke or death of any cause with a high rate of incident intracranial hemorrhage over 12 months from baseline particularly in patients with disseminated cSS. We further found cSS to be associated with a higher mortality and with poor outcome. Our findings have clinical relevance. The exceedingly high rate of intracranial hemorrhage and associated mortality and risk of poor functional outcome in patients with cSS requires attention, particularly when balancing the risks and benefits of antithrombotic treatment in patients with probable or possible CAA. However, the optimal therapeutic strategy will eventually need to be determined in a controlled trial.

### Author contributions

Frank Arne Wollenweber: study concept and design, acquisition of data, manuscript writing. Christian Opherk: study

concept and design, analysis and interpretation of data. Marialuisa Zedde: acquisition of data, analysis and interpretation of data. Cihan Catak: acquisition of data, analysis and interpretation of data. Rainer Malik: analysis and interpretation of data. Marco Duering: acquisition of data, analysis and interpretation of data. Marek-Janusz Konieczny: acquisition of data, analysis and interpretation of data. Rosario Pascarella: analysis and interpretation of data. Raquel Samões: analysis and interpretation of data. Manuel Correia: analysis and interpretation of data. Joan Martí-Fàbregas: analysis and interpretation of data. Jennifer Linn: analysis and interpretation of data. Martin Dichgans: study concept and design, manuscript writing.

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### Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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## Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy

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