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CADMUS

A Novel MRI-Based Classification of Spontaneous Intracerebral Hemorrhage Associated With Cerebral Small Vessel Disease

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Abstract

Background and Objectives

Cerebral small vessel disease (SVD) is the major cause of intracerebral hemorrhage (ICH). There is no comprehensive, easily applicable classification of ICH subtypes according to the presumed underlying SVD using MRI. We developed an MRI-based classification for SVD-related ICH.

Methods

We performed a retrospective study in the prospectively collected Swiss Stroke Registry (SSR, 2013–2019) and the Stroke InvestiGation in North And central London (SIGNAL) cohort. Patients with nontraumatic, SVD-related ICH and available MRI within 3 months were classified as Cerebral Amyloid angiopathy (CAA), Deep perforator arteriopathy (DPA), Mixed CAA-DPA, or Undetermined SVD using hemorrhagic and nonhemorrhagic MRI markers (CADMUS classification). The primary outcome was inter-rater reliability using Gwet's AC1. Secondary outcomes were recurrent ICH/ischemic stroke at 3 months according to the CADMUS phenotype. We performed Firth penalized logistic regressions and competing risk analyses.

Results

The SSR cohort included 1,180 patients (median age [interquartile range] 73 [62–80] years, baseline NIH Stroke Scale 6 [2–12], 45.6% lobar hematoma, systolic blood pressure on

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Glossary

CAA = cerebral amyloid angiopathy; **CADMUS** = CAA, Arteriosclerosis/DPA, Mixed CAA-DPA SVD, Undetermined SVD; **CHARTS** = Cerebral Hemorrhage Anatomic Rating Scale; **DPA** = deep perforator arteriopathy; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **MARS** = Microbleed Anatomical Rating Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **SIGNAL** = Stroke InvestiGation in North And central London; **SSR** = Swiss Stroke Registry; **SVD** = small vessel disease; **UCLH** = University College London Hospitals; **WMH** = white matter hyperintensity.

admission 166 [145–185] mm Hg). The CADMUS phenotypes were as follows: mixed CAA-DPA (n = 751 patients, 63.6%), undetermined SVD (n = 203, 17.2%), CAA (n = 154, 13.1%), and DPA (n = 72, 6.3%), with a similar distribution in the SIGNAL cohort (n = 313). Inter-rater reliability was good (Gwet's AC1 for SSR/SIGNAL 0.69/0.74). During follow-up, 56 patients had 57 events (28 ICH, 29 ischemic strokes). Three-month event rates were comparable between the CADMUS phenotypes.

Discussion

CADMUS, a novel MRI-based classification for SVD-associated ICH, is feasible and reproducible and may improve the classification of ICH subtypes in clinical practice and research.

Introduction

Sporadic cerebral small vessel disease (SVD), including cerebral amyloid angiopathy (CAA) or deep perforator arteriosclerotic arteriopathy (DPA) is the most frequent cause of nontraumatic intracerebral hemorrhage (ICH) and accounts for approximately 80% of cases.[1-3] More than 50% of patients with ICH survive 1 year or longer[4] and face the risk of recurrent ICH and ischemic stroke. Individual risks of outcome events are believed to be related to the underlying SVD type, but data are scarce.[4,5] Recent studies used hematoma location as a surrogate for the underlying SVD type,[6-8] but both CAA and DPA can cause lobar ICH, and different SVD may often coexist in older people.[9-11]

ICH is a complex disease likely resulting from a combination of chronic arteriopathy (e.g., CAA/DPA) leading to higher vessel vulnerability and rupture in response to various forms of acute stress, for example, blood pressure variation.[12,13] Currently available classification systems are often based on single-center data, use a hierarchical approach (SMASH-U[14]), are rather complex for routine clinical use (CLAS-ICH,[15] H-ATOMIC[16,17]), and none require MRI—the reference standard for in vivo SVD diagnosis. Furthermore, these classifications include risk factors (which are not a reliable guide to the presence or type of SVD) and causes of ICH.[14,16] There is no widely accepted classification for ICH related to SVD. Studies using hematoma location as a surrogate for CAA or DPA have shown differences in long-term prognosis,[6,7] suggesting implications for secondary prevention. Although hematoma location is associated with the underlying SVD, conclusions are limited because lobar hemorrhage may be caused by CAA and DPA (or both)[18] while patients with deep ICH resulting from DPA may have concomitant CAA pathology[9] or macrovascular causes[19] on postmortem histopathology studies, with potential prognostic relevance.

MRI is the reference standard for noninvasive SVD detection and characterization[2,20] using various hemorrhagic and nonhemorrhagic lesions.[13] However, clearly defined neuroimaging criteria are only available for CAA (Boston criteria 2.0[21]) but not for other SVDs, including DPA or "mixed" CAA-DPA.

A comprehensive and easily applicable ICH classification system focusing on the likely underlying SVD pathology rather than vascular risk factors, using reference-standard MRI and well-defined criteria for the entire spectrum of SVD phenotypes, may be helpful for research and clinical practice. An MRI-based classification seems most suitable for survivors of ICH or patients enrolled in research projects where exact phenotyping and long-term outcome prognostication are warranted. Owing to the limited availability of MRI, such classification is not designed for unselected patients with ICH unlikely to undergo MRI, that is, patients with ICH in poor neurologic conditions likely to die of their index ICH. In these patients, long-term prognostication seems less relevant.

We therefore aimed to (1) develop a clinically useful, noninvasive classification for ICH subtypes according to their MRI SVD phenotype, (2) apply the classification in a broad sample of patients with ICH, and (3) determine the association of SVD phenotype with clinical outcome events. We sought a practical classification that accounts for the concomitant presence of the 2 main SVDs, CAA and DPA, including their combination.

Methods

Study Design

We derived a novel MRI-based classification system and applied it to 2 independent cohorts of patients: the prospective multicenter Swiss Stroke Registry (SSR) and the prospective

Stroke InvestiGation in North And central London (SIGNAL) cohort from University College London Hospitals (UCLH).

Derivation of the MRI SVD Phenotype Classification

We (M.B.G., D.W., D.J.W., D.J.S.) reviewed available literature on MRI markers of SVD in patients with ICH.[13] Based on this preexisting evidence, we derived a novel, 3-step classification system (Figure 1): First, we excluded ICH secondary to a macrovascular (e.g., arteriovenous malformation and aneurysm), structural (tumor), or other defined cause (e.g., endocarditis and hemorrhagic transformation, based on clinically appropriate investigations[3,22]) and cryptogenic ICH (defined as the absence of SVD markers apart from ≤20 basal ganglia or centrum semiovale perivascular spaces). Second, we determined the hematoma location (based on the Cerebral Hemorrhage Anatomic Rating Scale [CHARTS[23]]). Third, we determined the presence and severity of all known hemorrhagic and nonhemorrhagic MRI markers of SVD. Finally, we classified patients according to predefined criteria (Table 1) based on steps 2 (hematoma location) and 3 (MRI markers) into 1 of 4 mutually exclusive SVD phenotypes: CAA, Arteriosclerosis/DPA, Mixed CAA-DPA SVD, Undetermined SVD, resulting in the acronym CADMUS.

Cohorts

Swiss Stroke Registry Cohort

The first cohort comprised patients from the prospective, national SSR, a compulsory registry including all patients treated at one of the certified Swiss Stroke Units or Stroke Centers.[24,25] We included all consecutive adult patients with nontraumatic ICH between 2013 and 2019 who had undergone MRI within 3 months after the index ICH.

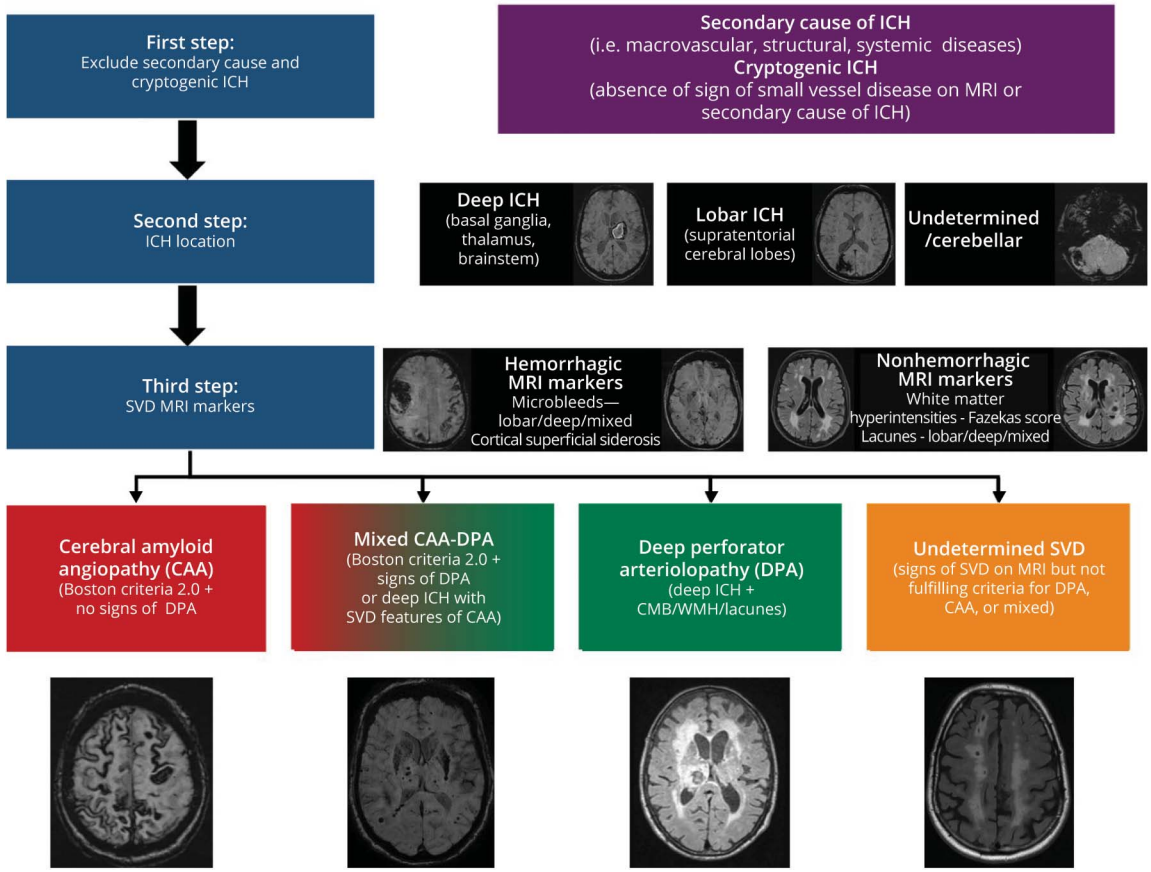
SIGNAL Cohort

As a second external cohort, we used data from the SIGNAL cohort, a prospective stroke registry of consecutive patients admitted to the UCLH Hyperacute Stroke Unit with spontaneous ICH from a defined North Central London population. We included all patients with nontraumatic ICH between January 2015 and October 2021 who had undergone MRI up to 3 months after the index ICH.

Clinical Registry Data

Local trained investigators collect clinical baseline data for all patients in both cohorts according to predefined variables. In the SSR, we extracted the following variables: age,

Figure 1 CADMUS SVD Classification



Steps to determine the SVD phenotype. CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; cSS = cortical superficial siderosis; DPA = deep perforator arteriopathy; SVD = small vessel disease; WMH = white matter hyperintensity.

Table 1 SVD CADMUS Phenotype Criteria

	Main classification
CAA	Boston criteria 2.0 Supratentorial lobar ICH or nonaneurysmatic, cSAH AND ≥1 of the following: • ≥1 additional, supratentorial lobar, cortical or subcortical hemorrhagic lesion (ICH, CMB, cSS/cSAH distant to the index ICH) • >20 CSO-PVSs per hemisphere • Multispot white matter hyperintensity pattern
Mixed CAA-DPA	Concomitant presence of characteristic features for CAA and DPA Deep supratentorial or brainstem ICH AND ≥1 of the following: • ≥1 additional, supratentorial lobar, cortical or subcortical hemorrhagic lesion (ICH, CMB, cSS/cSAH distant to the index ICH) • >20 CSO-PVSs per hemisphere • Multispot white matter hyperintensity pattern OR Lobar supratentorial or nonaneurysmatic, cSAH AND ≥1 of the following: • ≥1 additional, deep supratentorial or brainstem hemorrhagic lesion (ICH, CMB) • ≥1 deep supratentorial or brainstem lacune • Periventricular white matter lesions Fazekas grade ≥2 Additional SVD features can be present
DPA	Deep supratentorial or brainstem ICH AND ≥1 of the following: • ≥1 additional, deep supratentorial or brainstem hemorrhagic lesion (ICH, CMB) • ≥1 deep supratentorial or brainstem lacune • Periventricular white matter lesions Fazekas grade ≥2 Additional SVD features can be present
Undetermined SVD	ICH of any location AND Signs of SVD not fulfilling the criteria for CAA, DPA or mixed CAA-DPA, e.g. ≥1 of the following: • ≥1 lobar or cerebellar lacune • >20 BG-PVS per hemisphere • Periventricular white matter lesions Fazekas grade 1 or any isolated, deep white matter lesions • Recent, small infarcts OR Cerebellar or holohemispheric ICH or uncertain hematoma epicenter AND ≥1 of the following: • ≥1 additional, deep supratentorial or brainstem hemorrhagic lesion (ICH, CMB) • ≥1 deep supratentorial or brainstem lacune • Periventricular white matter lesions Fazekas grade ≥2 • ≥1 additional, supratentorial lobar, cortical or subcortical hemorrhagic lesion (ICH, CMB, cSS/cSAH distant to the index ICH) Additional SVD features can be present

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; CSO = centrum semiovale; cSAH = convexity subarachnoid hemorrhage; cSS = cortical superficial siderosis; DPA = deep perforator arteriopathy; ICH = intracerebral hemorrhage; PVS = perivascular space; SVD = small vessel disease.

sex, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, defined as previously known or diagnosed during hospitalization based on suggestive clinical findings, smoking, atrial fibrillation), history of previous cerebrovascular events, antithrombotic therapy on admission, clinical findings on admission (systolic and diastolic blood pressure, NIH Stroke Scale [NIHSS], Glasgow Coma Scale [GCS]), clinical outcomes (including ischemic stroke, intracerebral hemorrhage, or death). Etiology of ICH was classified according to a modified version of the SMASH-U classification by local raters.[24] In the SIGNAL cohort, we extracted demographic data (age and sex).

MRI Analysis

Pseudonymized DICOMs were stored on a local server at the respective central imaging core laboratory (Bern for SSR and London for SIGNAL). We included all MRI scans performed as part of routine clinical care within 90 days after the index ICH that fulfilled minimum imaging requirements (availability of SWI or GRE-T2* and T2-weighted or fluid-attenuated inversion recovery, see eTable 1, links.lww.com/WNL/D248 for an overview of protocols according to centers for the SSR).

MRI analysis was performed by trained raters (M.B.G. for SSR, W.Z. for SIGNAL) blinded to outcomes at the time assessing

MRI scans. The analysis was supervised by 2 independent raters at each center (A.H., D.J.S., D.J.W., R.J.) to resolve unclear cases by consensus. The analysis followed the neuroimaging standards for research into SVD.[20] We determined the hematoma epicenter using CHARTS.[23] Cerebral microbleed location and count were assessed using the Microbleed Anatomical Rating Scale (MARS).[26] We evaluated cortical superficial siderosis distribution (focal vs disseminated) and multifocality.[27,28] In the absence of a validated rating for lacunes and recent small infarcts, we used the MARS classification to assess their location and count as done in previous research.[26,29] White matter hyperintensity (WMH) severity was assessed using the Fazekas scale[30] and WMH pattern.[31] Enlarged perivascular spaces were assessed using a 5-point scale.[32]

A second rater (D.J.S. for SSR, M.B.G. for SIGNAL) determined inter-rater reliability in a subset of 50 patients from the SSR (4.2%) and 44 patients from the SIGNAL cohort (14.1%) by a blinded review of source MRI and independent application of the CADMUS classification.

Follow-up and Clinical Outcomes

All patients in the SSR receive standardized clinical 3-month follow-up by local investigators, including information on recurrent ICH, ischemic stroke, or death at 3 months after the index ICH.

Statistical Analysis

Statistical analysis was performed by M.B.G. using STATA/MP 16.0 (StataCorp., College Station, TX) based on a prespecified statistical analysis plan developed by M.B.G., M.B., and D.J.S. We performed descriptive statistics using the table1_mc package and reported the findings using absolute and relative counts for categorical variables, median and interquartile range (IQR) for non-normally distributed, continuous variables and mean and standard deviation for normally distributed, continuous variables.[33] The significance level was set at $\alpha < 0.05$.

Inter-rater reliabilities for the CADMUS phenotype were assessed using Gwet's AC1. Comparison between the SMASH-U classification (local rater) and the CADMUS classification (central rater) was displayed using a Sankey diagram. We compared demographic variables and prevalence of CADMUS phenotypes in the 2 cohorts.

Nonadjusted event rates were reported according to the CADMUS phenotype with corresponding 95% CIs. We assessed the association of CADMUS phenotypes with the coprimary outcomes using Firth penalized regression analysis to account for the small number of outcome events, using listwise deletion. Regression models were specified before the statistical analysis. We selected up to 4 covariables based on clinical plausibility and findings from previous studies (adhering to the 1:10 rule of thumb, ~40 expected events per outcome).[7,24] To determine the association of SVD phenotypes with ischemic stroke at 3 months, we corrected for age, arterial hypertension, and atrial fibrillation while we adjusted for age, arterial hypertension, and history of previous ICH in the model for recurrent ICH. We reported odds ratios (ORs) and 95% CIs in logistic regression analyses, using the largest subgroup as the reference, and subhazard ratios in cumulative incidence analysis according to Fine and Gray (competing outcomes for ICH: ischemic stroke and death, competing outcomes for ischemic stroke: ICH and death).

We performed 2 post hoc sensitivity analyses in the derivation cohort including only patients with first-ever ICH or who underwent MRI within 7 days after their ICH, respectively, using the same methods and regression models as in the primary analysis.

To further investigate the largest group of mixed CAA-DPA, we performed a post hoc sensitivity analysis according to whether these patients fulfill the Boston criteria 2.0.[21] This is of particular interest because the Boston criteria 2.0 consider deep hemorrhagic lesions as an exclusion criterion for the diagnosis of CAA, which is not the case for deep ischemic lesions (e.g., lacunes) or WMHs.[21]

Standard Protocol Approvals, Registrations, and Patient Consents

Enrollment in the SSR is compulsory for all patients with cerebrovascular events according to Swiss law on highly specialized medicine, and patients are informed accordingly. Patients who denied the use of their data for research were excluded from the analyses. The competent ethical boards in Bern and London, respectively, reviewed and approved the use of these data for this study (SSR Project ID: 2019-00689, SIGNAL: 5-201920-SE).

Results

Of 3,572 patients with ICH enrolled in the SSR, MRI was available in 1,439 patients (40.3%). In 212 patients (14.7%), ICH was due to a secondary cause. Forty-seven patients (3.3%) had cryptogenic ICH, resulting in 1,180 patients (82%) eligible for this study. In the SIGNAL cohort, MRI was available for 361 of 852 patients (42.4%), 39 (10.8%) had secondary ICH, and 9 (2.5%) had cryptogenic ICH (eFigure 1, links.lww.com/WNL/D248). Baseline characteristics of patients with vs without MRI in the SSR are presented in eTable 2.

Baseline Data and Demographics

Among the 1,180 patients from the SSR, the median age was 73 years (IQR 62–80) and 44.5% of patients were female. Patients from the SIGNAL cohort were younger (median 68 years, IQR 57–78) and with a similar gender distribution (44.1% female). Baseline characteristics are summarized in Table 2 and eTable 3 (links.lww.com/WNL/D248). Probable CAA according to the Boston criteria 2.0[21] was present in 338 of 1,180 patients from the SSR (28.6%) and 52 of 313 patients from the SIGNAL cohort (16.6%). 823 of 1,180 patients (69.7%) from the SSR and 247 of 313 (78.9%) from the SIGNAL cohort had neuroimaging markers of DPA.

CADMUS Phenotype Distribution and Inter-Rater Reliability

All patients were classified into one of the mutually exclusive groups. The most frequent CADMUS phenotype was mixed CAA-DPA (SSR: 751 patients, 63.3%; SIGNAL: 214 patients, 68.4%), followed by undetermined SVD (SSR: 203 patients, 17.2%; SIGNAL: 53 patients, 16.9%). DPA without SVD markers consistent with CAA was present in 72 patients (6.3%) from the SSR and 33 patients (10.5%) from the SIGNAL cohort; probable CAA without any evidence of (hemorrhagic or ischemic) lesions suggestive of DPA was present in 154 patients (13.1%) from the SSR and 13 (4.2%) from the SIGNAL cohort (eFigure 1, links.lww.com/WNL/D248). Baseline characteristics differed significantly between subgroups regarding age, hypertension, admission blood pressure, and admission NIHSS (Table 2 and eFigure 2). An overview of SVD markers according to the CADMUS phenotype is provided in eTable 4.

Findings in the subgroups restricted to patients with first-ever ICH and MRI within 7 days were comparable (eTable 5, links.lww.com/WNL/D248). The 2 raters agreed on the CADMUS phenotype in 38 of 50 evaluated cases from the SSR and in 35 of 44 evaluated cases from the SIGNAL cohort, resulting in a Gwet's AC1 inter-rater reliability of 0.69 (95% CI 0.53–0.85) for the SSR and 0.74 (95% CI 0.58–0.90) for the SIGNAL cohort.

Comparison With the SMASH-U Classification

Agreement between SMASH-U and CADMUS was achieved in 144 of 1,180 patients (12.2%). 32 of 154 patients (20.8%) with CAA as defined according to the Boston criteria 2.0[21] and without additional signs of DPA were classified as CAA using SMASH-U. Figure 2 compares the SMASH-U and CADMUS phenotypes.

Clinical Outcomes

Follow-up data were available for 1,113 of 1,180 patients from the SSR (follow-up rate 94.3%). Patients who were lost to follow-up were older (median age 76 years vs 73 years, $p = 0.046$), but otherwise similar to patients with available outcomes. Fifty-six patients (5.0%) suffered 57 events during follow-up. Ischemic strokes occurred in 29 patients (2.8%) and recurrent ICH in 28 patients (2.5%) (Table 2).

In the univariable, penalized logistic regression, female sex, CAA, and previous intracranial hemorrhage were independently associated with recurrent ICH at 3 months. Anticoagulation and higher GCS on admission were associated with ischemic strokes within 3 months (eTable 6, links.lww.com/WNL/D248). None of the CADMUS phenotypes were independently associated with 3-month outcomes.

Competing Risk Analysis

In the competing risk analysis over an observation period of 347.4 patient-years using the same models as for penalized logistic regression, we observed a trend toward a lower subhazard ratio of ischemic stroke in CAA (SHR 0.34; 95% CI 0.04–2.69). DPA was independently associated with a lower risk of recurrent ICH (SHR 7.06×10^{-7}; 95% CI 3.94×10^{-7} to 1.03×10^{-6}) as compared with mixed CAA-DPA. For Nelson-Aalen curves, see Figure 3, A and B.

Sensitivity Analyses

Baseline data in the populations restricted to patients with first-ever ICH and MRI within 7 days were comparable with the total population (eTable 5, links.lww.com/WNL/D248). In patients with first-ever ICH, CAA was independently associated with recurrent ICH (adjusted OR 4.47, 95% CI 1.54–12.97). Patients with mixed CAA-DPA who fulfilled the Boston criteria 2.0 (Boston-positive) were significantly older, more often had a history of ICH, and had a higher prevalence of antiplatelet therapy (eTable 7). On admission, blood pressure was significantly lower in Boston-positive mixed CAA-DPA. There were no significant differences in recurrence risks (eFigure 3).

Discussion

We present a novel MRI-based classification of SVD in ICH, which we applied to a large, multicenter cohort of patients treated at Swiss Stroke Units or Stroke Centers and the prospective SIGNAL cohort study in London, United Kingdom.

The CADMUS classification provides reproducible definitions for all observed CADMUS phenotypes, including the Boston criteria 2.0 for CAA[34] in addition to other validated neuroimaging markers associated with the respective SVD phenotypes.[13] Because there is no gold standard for in vivo diagnosis of different SVD subtypes, our classification applied the best available surrogate by using MRI as the most reliable imaging modality to detect markers of SVD. The validation in 2 ICH cohorts with MRI from clinical routine care including around 1,500 patients with MRI is a strong argument for clinical usability. It overcomes the limitations of previous studies with a hierarchical, single-cause approach[14] or a complex rating system accounting for several concomitant etiologies.[15,16] Inter-rater reliability in our study was comparable with the H-ATOMIC study ($\kappa = 0.76$) and slightly lower than the original study on the SMASH-U classification ($\kappa = 0.82$).[35]

The MRI-based CADMUS classification provides patient groups with distinct clinical characteristics, risk factor profiles, and diverging risks of recurrent ICH and ischemic stroke at 3 months. While neuroimaging features of CAA were present in 1,162 of 1,493 patients (77.8%), only 26.1% had probable CAA according to the revised Boston criteria 2.0,[21] underlining the potential limited sensitivity of these criteria. In 64.6% of ICH cases, neuroimaging features for CAA and DPA both were present, resulting in a mixed CAA-DPA phenotype. The proportion of patients with mixed CAA-DPA is higher than in studies evaluating only single SVD markers, for example, CMBs[36,37] or lacunes,[29] which we expected based on

Table 2 Baseline Table

	All ICH					
	Total (N = 1,180, 100%)	CAA (N = 154, 13.1%)	DPA (N = 72, 6.3%)	Mixed CAA-DPA (N = 751, 63.6%)	Undetermined (N = 203, 17.2%)	*p* Value
Demographics						
Age, y, median (IQR)	73 (62–80)	73 (65–79)	72 (61–79)	74 (64–80)	68 (56–78)	**<0.001**
Sex, female, n (%)	492 (44.5)	69 (49.6)	24 (35.3)	323 (45.4)	76 (40.9)	0.17
Cerebrovascular risk factors, n (%)						
Hypertension	797 (76.9)	80 (62.5)	54 (79.4)	529 (79.4)	134 (76.6)	**<0.001**
Diabetes mellitus	160 (16.4)	16 (13.8)	10 (15.9)	109 (17.0)	25 (15.7)	0.84
Hyperlipidemia (treatment or LDL >2.6 mmol/L)	500 (50.9)	55 (46.2)	35 (55.6)	336 (52.7)	74 (45.4)	0.22
Actively smoking (or stopped <2 y ago)	129 (14.6)	16 (15.0)	3 (5.6)	83 (14.6)	27 (17.9)	0.18
Atrial fibrillation (>1 documented episode)	148 (14.3)	18 (14.2)	13 (19.1)	96 (14.5)	21 (12.1)	0.57
History of intracranial hemorrhage	118 (11.4)	17 (13.4)	3 (4.4)	83 (12.5)	15 (8.6)	0.12
History of ischemic stroke or retinal infarction	110 (10.6)	10 (7.9)	8 (11.8)	69 (10.4)	23 (13.1)	0.52
Antiplatelets on admission	295 (27.8)	39 (29.3)	17 (25.4)	197 (28.6)	42 (24.0)	0.60
Anticoagulation on admission	184 (17.2)	22 (16.4)	11 (16.2)	118 (17.1)	33 (18.6)	0.95
Clinical presentation on admission						
Systolic blood pressure on admission, median (IQR)	166 (145–185)	153 (138–170.5)	177 (160–190)	168 (147–189)	165 (140–183)	**<0.001**
Diastolic blood pressure on admission, median (IQR)	89 (78–101)	83 (70–90)	92 (84–110)	90 (80–104)	90 (78–104)	**<0.001**
NIHSS on admission, median (IQR)	6 (2–12)	4 (1–11)	9 (5–14)	6 (3–12)	4.5 (1–11.5)	**<0.001**
GCS on admission, median (IQR)	15 (14–15)	15 (14–15)	15 (14–15)	15 (14–15)	15 (13–15)	0.57
Hematoma epicenter, n (%)						**<0.001**
Deep	439 (37.2)	0 (0.0)	65 (90.3)	347 (46.2)	27 (13.3)	
Lobar	538 (45.6)	139 (90.3)	0 (0.0)	362 (48.2)	37 (18.2)	
Brainstem	40 (3.4)	0 (0.0)	7 (9.7)	28 (3.7)	5 (2.5)	
Cerebellum	73 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	73 (36.0)	
Isolated IVH	11 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.4)	
Isolated cSAH	33 (2.8)	15 (9.7)	0 (0.0)	14 (1.9)	4 (2.0)	
Undetermined	46 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	46 (22.7)	
SMASH-U, n (%)						**<0.001**
Hypertension	538 (45.6)	23 (14.9)	54 (75.0)	365 (48.6)	96 (47.3)	
Antithrombotic	68 (5.8)	12 (7.8)	1 (1.4)	47 (6.3)	8 (3.9)	
CAA	152 (12.9)	32 (20.8)	0 (0.0)	105 (14.0)	15 (7.4)	
Unknown	290 (24.6)	63 (40.9)	14 (19.4)	155 (20.6)	58 (28.6)	
Missing information	132 (11.2)	24 (15.6)	3 (4.2)	79 (10.5)	26 (12.8)	

Continued

Table 2 Baseline Table *(continued)*

	All ICH					
	Total (N = 1,180, 100%)	**CAA (N = 154, 13.1%)**	**DPA (N = 72, 6.3%)**	**Mixed CAA-DPA (N = 751, 63.6%)**	**Undetermined (N = 203, 17.2%)**	***p* Value**
Outcomes (per 100 patient-years), median (IQR)						
Any event	58.5 (50.0–68.6)	51.3 (32.3–81.3)	57.4 (29.9–110.3)	52.40 (42.6–64.5)	89.6 (65.2–123.1)	
Ischemic stroke	11.0 (7.7–15.9)	2.9 (0.4–20.2)	12.8 (3.2–51.0)	10.0 (6.2–16.1)	21.2 (11.0–40.8)	
ICH	10.6 (7.3–15.4)	17.1 (7.7–38.0)	0	8.8 (5.3–14.6)	16.5 (7.9–34.6)	
Death	43.71 (36.4–52.5)	39.9 (23.6–67.3)	44.6 (21.3–93.7)	39.4 (31.0–50.1)	63.6 (43.6–92.8)	

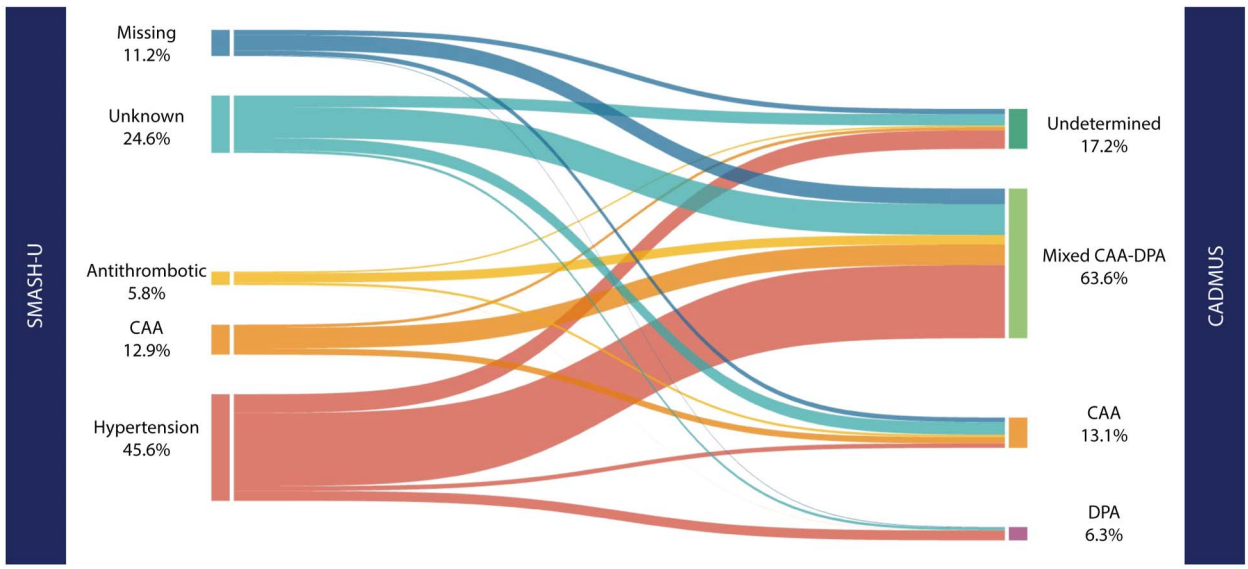
Abbreviations: CAA = cerebral amyloid angiopathy; cSAH = convexity subarachnoid hemorrhage; DPA = deep perforator arteriopathy; DOAC = direct oral anticoagulant; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; LDL = low-density lipoprotein; NIHSS = NIH Stroke Scale; SVD = small vessel disease.

the different methodology. The CADMUS phenotypes were similarly distributed in both cohorts with the exception of CAA. The cause of this difference is unknown, although there are several potential contributors including population differences (the SIGNAL cohort is a multiethnic metropolitan population cohort while SSR covers all types of stroke hospitals in Switzerland) with differences in baseline characteristics or risk factor management (e.g., antihypertensive treatment regimens). However, these additional aspects were beyond the scope of this study.

Agreement with the clinically determined SMASH-U classification[14] was found in 12.2% of participants. This low proportion is likely related to differences in categories and the use of neuroimaging biomarkers in our classification, rather than risk factors in SMASH-U. A substantial number of patients with mixed CAA-DPA were classified as CAA (according to the modified Boston criteria[34]) using SMASH-U, which might result from its hierarchical approach excluding potential concomitant diseases. Misclassification of this kind might lead to inappropriate therapies (e.g., reluctance toward antithrombotic therapy), with a risk of poorer patient outcomes. In particular, there is currently no evidence for withholding antithrombotic therapy in any patient group, if it was otherwise indicated.[38]

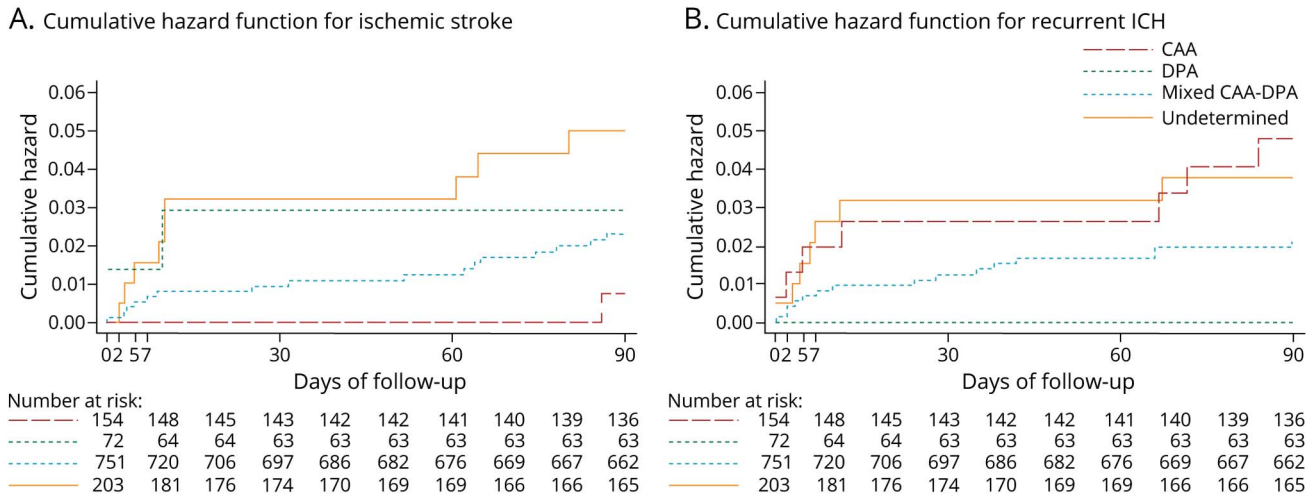
In a post hoc subanalysis splitting the mixed CAA-DPA group into Boston-positive and Boston-negative cases, we observed a numerically higher rate of ischemic events in patients with Boston-negative compared with Boston-positive mixed CAA-DPA while the rates of recurrent ICH were similar

Figure 2 Sankey Diagram Comparing SMASH-U and CADMUS Classification in the Swiss Stroke Registry



CAA = cerebral amyloid angiopathy; DPA = deep perforator arteriopathy; SVD = small vessel disease.

Figure 3 Cumulative Hazards for Cerebrovascular Events at 3 Months



(A) Nelson-Aalen curves displaying cumulative hazard ratio for ischemic stroke at 3 months. (B) Nelson-Aalen curves displaying cumulative hazard ratio for recurrent ICH within 3 months. CAA = cerebral amyloid angiopathy; DPA = deep perforator arteriopathy; ICH = intracerebral hemorrhage.

in both subgroups (eTable 3, eFigure 3, links.lww.com/WNL/D248). Future studies should elaborate whether histopathologic findings in patients with Boston-negative CAA-DPA differ from those with Boston-positive CAA-DPA (e.g., regarding presence of vascular amyloid, as suggested in previous research[9]) and assess the long-term risks and benefits of antithrombotic therapy in this particular patient group.

Clinical characteristics of the CADMUS phenotypes in our classification differed significantly, arguing for the value of this classification to differentiate underlying pathomechanisms associated with ICH[1] and for research investigating targeted treatments. The observed differences are consistent with the current pathophysiologic concepts, including the importance of arterial hypertension for all types of ICH[39] and the high risk of recurrent ICH in CAA.[40]

While CAA was associated with recurrent ICH at 3 months in patients with first-ever ICH, the observation period of 3 months is probably too short to detect all but a very large difference in outcome event rates between the other CADMUS phenotypes, which we could not expect based on previous literature.[6,7,24] Long-term studies using ICH location as a surrogate for the SVD etiology reported differences in the risk of recurrent ICH and ischemic strokes.[6,7] These findings are a strong argument to investigate the prognostic performance of this classification in a cohort with longer follow-up, which might help to identify risk profiles and potentially relevant subgroups for preventive strategies.

This study has the following strengths. The classification is based on well-defined SVD markers[20] on MRI, which is the reference standard for in vivo detection of SVD. It is the first classification mandating MRI use, overcoming imprecisions in prior classifications based on both CT imaging and MRI. All markers can be determined in a noncontrast MRI as part of the diagnostic routine workup in patients with ICH.[2] We provide detailed SVD neuroimaging criteria for all SVD phenotypes, resulting in a high reproducibility. Validation in an external cohort has revealed comparable distribution of phenotypes using clinically obtained MRI scans from different centers over several years with heterogeneous sequence parameters. Most of the SSR patients (62.2%) underwent MRI within 1 week after symptom onset. These are strong arguments for the generalizability and usability in clinical routine.

Our study has the following limitations: We only included patients who underwent MRI within 90 days after the index event. Patients with severe ICH were likely underrepresented. However, the CADMUS classification aims to provide the best possible classification of small vessel disease–related ICH. This information is of importance for survivors of ICH, where the risk of recurrence or subsequent treatment options is discussed. It is also of interest in research projects where MRI may be performed as part of the study to characterize patients with ICH . The information is of no relevance for patients in the hyperacute setting, in poor conditions, or likely to die of ICH who would not undergo MRI. All patients with ICH should undergo a basic comprehensive follow-up searching for macrovascular and non–SVD-related causes.[13] CADMUS was designed for the use in subacute/chronic patients with ICH where other causes—including suspicion of genetic SVD—have been eliminated.

CADMUS included only patients who underwent MRI within 3 months after the index ICH. All evaluated MRI scans were performed in clinical routine. Despite the different health care systems, both cohorts showed a similar prevalence of MRI,

suggesting that roughly 40% of all patients are deemed clinically suitable to undergo MRI within 3 months after an ICH. Owing to our stringent eligibility criteria, it is possible that we excluded patients who had undergone MRI recently before, but not after their ICH. Last but not the least, if CADMUS phenotyping proves to be prognostically relevant, this might prompt the use of MRI in the future.

The simplicity of this classification comes at the cost of omitting rare diseases that also lead to ICH (e.g., genetic SVD). However, it covers the great majority of ICH cases and may provide a foundation for further investigations. This classification is based on neuroimaging rather than clinical risk factors of SVD and ICH, but, nevertheless, allows us to determine the presumed CADMUS phenotype blinded to clinical information, making it potentially useful for clinical trials. Histopathologic validation of the type(s) of SVD present in our cohorts is lacking. This is a general problem in neurology because brain biopsy is potentially hazardous, and therefore, few data on this topic exist. However, for most markers, correlation with the underlying SVD has been shown in previous research.[13] As an exception, histopathology correlation for periventricular WMH is scarce, but periventricular venulopathy with concentric collagen deposition, resulting in vessel stenosis and occlusion, has been described.[41] We, therefore, included this marker based on clinical consensus as in previous classifications.[15] Information on treatment courses (e.g., secondary prevention after ICH) was not available, which might be an additional source of bias. Although this study was performed in a large, multicenter data set with 2 independent prospective cohorts, we urge caution in the interpretation of the results because our analysis was retrospective and thus prone to bias.

In conclusion, ICH can be classified into several CADMUS phenotypes, which are associated with different risk profiles and short-term outcomes. All patients with ICH have a considerable risk of recurrent cerebrovascular events. Therefore, targeted preventive strategies are paramount to improve the outcome for patients with ICH. Development of such therapies requires a clear understanding of the contribution of SVD pathologies leading to ICH.

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Continued

Appendix 1 *(continued)*

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Appendix 1 *(continued)*

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