CADMUS: A novel MRI-based classification of spontaneous intracerebral hemorrhage associated with cerebral small vessel disease

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INTRODUCTION

Unmet clinical need

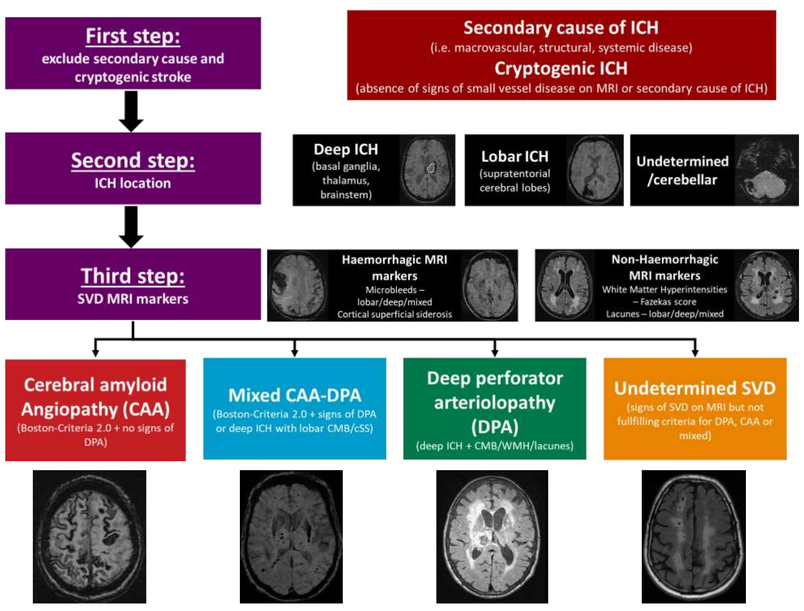
- Cerebral small vessel disease (SVD) is the major cause of intracerebral hemorrhage (ICH). There is no comprehensive classification of ICH subtypes according to the presumed underlying SVD defined by MRI, as previous classifications of ICH mixed risk factors and imaging findings, and did not account for concomitant diseases.

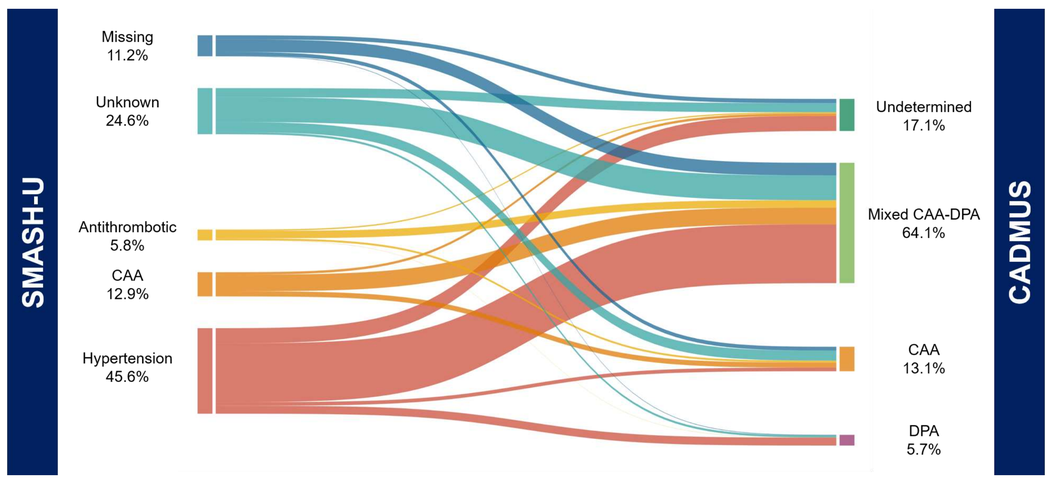
Aim

- We aimed to develop an MRI-based classification for SVD-related ICH and assess association with clinical outcomes (recurrent ICH or ischaemic stroke).

METHODS

- The CADMUS (Cerebral Amyloid angiopathy (CAA), Deep perforator arteriolopathy (DPA), Mixed CAA-DPA, Undetermined SVD) classification is a 3-step classification system based on currently available evidence on association of hemorrhagic (haematoma location, cerebral microbleeds, cortical superficial siderosis) and non-hemorrhagic (white matter hyperintensities, lacunes, basal ganglia and centrum semiovale perivascular spaces) MRI markers with the underlying SVD (Goeldlin, Stewart et al. 2022).
- We performed a retrospective validation study in patients with intracerebral hemorrhage associated with SVD enrolled in the prospectively collected Swiss Stroke Registry from 2013-2019 (Goeldlin, Mueller et al. 2022) with available MRI within 3 months after the index ICH.
- ICH was classified according to the SVD phenotype using the CADMUS classification and compared to the previously proposed SMASH-U classification (Meretoja, Strbian et al. 2012).
- The primary clinical outcomes were cumulative hazard for recurrent ICH or ischemic stroke at 3 months.





CADMUS
CA Cerebral Amyloid angiopathy
D Deep perforator arteriopathy
M Mixed CAA-DPA
U Undetermined SVD
S Small vessel disease

RESULTS

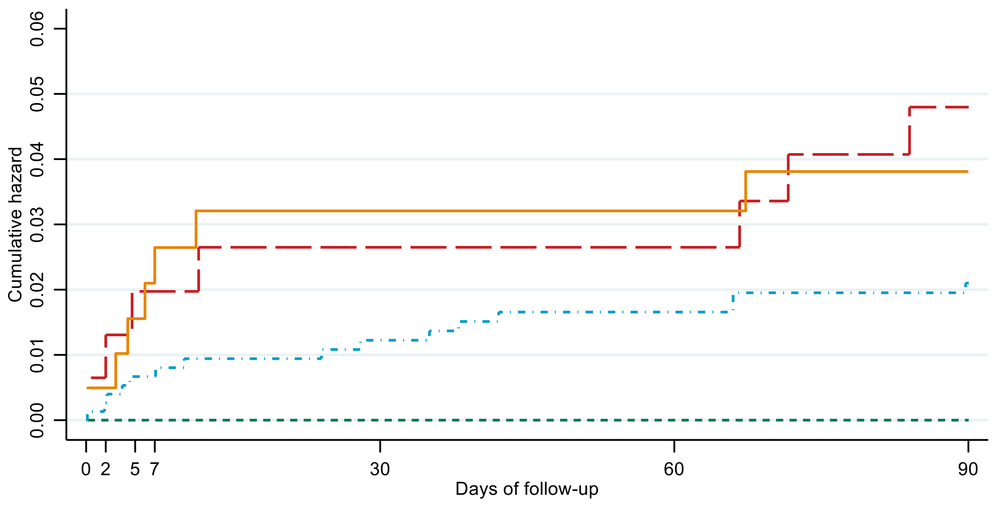
- CADMUS provides a feasible and reproducible classification system for ICH associated with SVD
- Baseline characteristics and clinical presentation on admission differed significantly between the different subgroups.
- We observed trends towards a higher cumulative hazard for ischemic stroke in DPA and undetermined SVD, but the observation period was too short to detect all but a very large difference between subgroups. CAA was independently associated with higher cumulative hazard for recurrent ICH at 3 months (subhazard ratio 2.9; 95%-CI 1.2-7.4; p=0.024)

	Total	CAA	DPA	Mixed CAA-DPA	Undetermined	p-value
	N=1,180	N=154	N=67	N=757	N=202	
Demographics						
Median age [years], (IQR)	73 (62-80)	73 (65-79)	72 (61-79)	74 (64-80)	68 (56-78)	0.001
Female sex	492 (44.5%)	69 (49.6%)	22 (34.9%)	325 (45.3%)	76 (41.1%)	0.18
Cerebrovascular risk factors						
Hypertension	797 (76.9%)	80 (62.5%)	50 (79.4%)	533 (79.3%)	134 (77.0%)	<0.001
Atrial fibrillation (>1 documented episode)	148 (14.3%)	18 (14.2%)	12 (19.0%)	97 (14.5%)	21 (12.1%)	0.61
History of intracranial hemorrhage	118 (11.4%)	17 (13.4%)	3 (4.8%)	83 (12.4%)	15 (8.7%)	0.16
History of ischemic stroke	110 (10.6%)	10 (7.9%)	6 (9.5%)	71 (10.6%)	23 (13.2%)	0.52
Antiplatelets on admission	295 (27.8%)	39 (29.3%)	16 (25.4%)	198 (28.6%)	42 (24.1%)	0.64
Anticoagulation on admission	184 (17.2%)	22 (16.4%)	10 (15.9%)	119 (17.1%)	33 (18.8%)	0.93
Clinical presentation on admission						
Systolic blood pressure on admission	166 (145-185)	153 (138-170.5)	177 (160-190)	168 (147-189)	165 (140-183)	<0.001
NIHSS on admission	6 (2-12)	4 (1-11)	9 (5-14)	6 (3-12)	4.5 (1-11.5)	<0.001

CONCLUSIONS

- CADMUS is an objective and reproducible classification system based on routinely available neuroimaging markers. It is therefore suitable for clinical routine and research.
- The MRI-based CADMUS classification provides patient groups with distinct clinical characteristics, risk factor profiles and diverging risks for recurrent ICH and ischemic stroke at 3 months.
- While features of CAA were present in 911/1180 patients (77.2%), only 13.1% had probable CAA as defined by the Boston criteria 2.0 (Charidimou, Boulouis et al. 2022) underlining the limitations of the Boston criteria in this population.
- Longer follow-up will be paramount to detect additional differences between subgroups, that might have implications for future acute treatment and secondary prevention strategies.

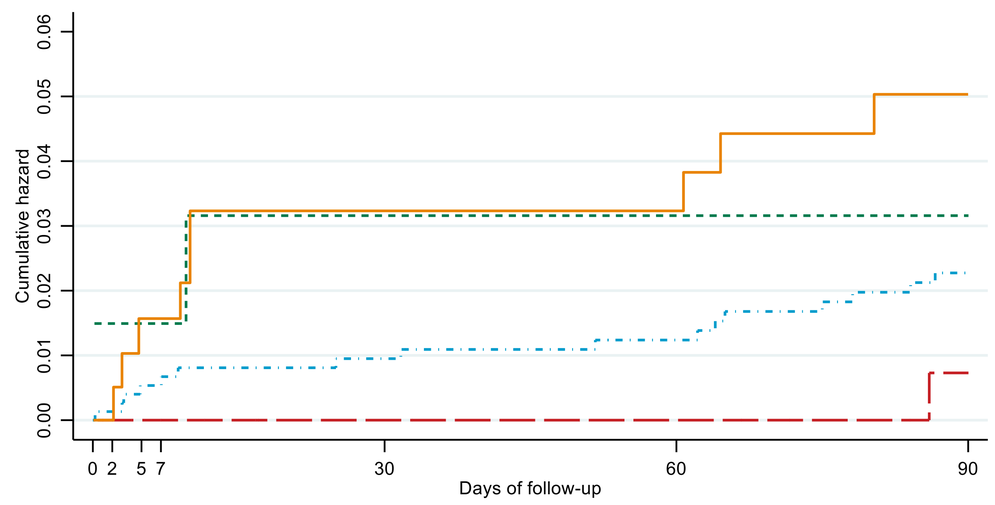
CUMULATIVE HAZARD FOR RECURRENT ICH



Number at risk

CAA	154	148	145	143	142	142	141	140	139	136
DPA	67	59	59	58	58	58	58	58	58	58
Mixed CAA-DPA	757	726	712	703	692	688	682	675	673	668
Undetermined	202	180	175	173	169	168	168	165	165	164

CUMULATIVE HAZARD FOR ISCHEMIC STROKE



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