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Highlights

- We examined the relationship between ischemic stroke and small vessel disease burden
- Cardioembolic causes of stroke are more frequent more severe small vessel disease
- This effect can be explained by the common risk factor of advanced age
- Stroke lesion location or size is not associated with small vessel disease burden

Cerebral small vessel disease and stroke: linked by stroke aetiology, but not stroke lesion location or size

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Abstract

Background: Cerebral small vessel disease (SVD) has previously been associated with worse stroke outcome, vascular dementia, and specific cognitive deficits. The underlying causal mechanisms of these associations are not yet fully understood. We investigated whether a relationship between SVD and certain stroke aetiologies or a specific stroke lesion anatomy provides a potential explanation.

Methods: In a retrospective observational study, we examined 859 patients with first-ever, non-SVD anterior circulation ischemic stroke (age = 69.0±15.2). We evaluated MRI imaging markers to assess an SVD burden score and mapped stroke lesions on diffusion-weighted MRI. We investigated the association of SVD burden with i) stroke aetiology, and ii) lesion anatomy using topographical statistical mapping.

Results: With increasing SVD burden, stroke of cardioembolic aetiology was more frequent (ρ=0.175; 95%-CI=0.103;0.244), whereas cervical artery dissection (ρ=-0.143; 95%-CI=-0.198;-0.087) and a patent foramen ovale (ρ=-0.165; 95%-CI=-0.220;-0.104) were less frequent stroke etiologies. However, no significant associations between SVD burden and stroke aetiology remained after additionally controlling for age (all $p>0.125$). Lesion-symptom-mapping and Bayesian statistics showed that SVD burden was not associated with a specific stroke lesion anatomy or size.

Conclusions: In patients with a high burden of SVD, non-SVD stroke is more likely to be caused by cardioembolic aetiology. The common risk factor of advanced age may link both pathologies and explain some of the existing associations between SVD and stroke. The SVD burden is not related to a specific stroke lesion location.

1 Introduction

Cerebral small vessel disease (SVD) is a common, mostly progressive pathology of the small arterioles, venules, and capillaries of the brain. With the progress in brain imaging over the last decades, various types of SVD-related brain lesions were discovered.[1,2] The burden of SVD-related lesions was found to be linked to a plethora of neurological and cognitive pathologies,[3,4] including an association with ischemic and hemorrhagic stroke.

The burden of SVD lesions was found to be associated with worse stroke outcome.[5-7] White matter hyperintensities – one of the imaging features of SVD[1,8] – were found to be linked with post-stroke disability,[9,10] decreased independence,[11] worse global cognition,[12-14] and specific cognitive deficits[15-18] as well as treatment response and recovery from cognitive deficits.[19,20] SVD is associated with an increased risk of stroke,[21-23] risk of recurrent stroke,[24] and the type of stroke.[2] The burden of SVD lesions is associated with secondary post-stroke pathology such as poststroke depression[25] or sleep breathing disorders.[26] However, the underlying causal mechanisms of these associations are not yet fully understood.

Many of these findings could be explained if a secondary variable affects both SVD burden and stroke and thereby statistically associates both pathologies. Shared risk factors could take on such a role. The risk factor profile of SVD includes common vascular risk factors such as advanced age, hypertension, and diabetes[1,27,28] which are also known to be risk factors for stroke.[29] For example, hypertension could be causally linked to the burden of SVD and certain stroke aetiologies or a specific stroke lesion anatomy. In such a case, SVD would be associated with the clinical characteristics and lesion locations typical to the stroke aetiology, which, in turn, could explain some of the existing findings on the link between SVD and stroke outcome. Such an indirect link between SVD and lesion anatomy by common risk factors would also be in line with the increased risk of (recurrent) stroke associated with SVD.

In the current study, we retrospectively investigated the associations between SVD and stroke aetiology, stroke lesion location, and stroke lesion size. We utilised topographical statistical lesion mapping for an exhaustive, voxel-wise whole-brain analysis of potential associations between SVD and lesion anatomy. We focussed on cerebral stroke not directly caused by SVD, for which a typical location is known,[30] but on the remaining general stroke population.

2 Methods

2.1. Patients

In this retrospective study, we included patients admitted to the Bern Stroke Centre for treatment of acute ischemic stroke between January 2015 and October 2020. Patients with i) a first-ever anterior circulation stroke verified by MRI and ii) available MRI acquired about 24h after admission were eligible. Exclusion criteria

and recruitment stages are shown in Figure 1. Patients for which any relevant MRI (see methods section 2.2.) was missing or of poor quality were excluded." All data for the current study were obtained during clinical routine practice. Demographic and clinical data including those on stroke aetiology and risk factors were retrieved from digital clinical records and the Bernese Stroke Registry. Written informed consent (institutional general consent for research) was available from all participants or their guardians. Approval from the local ethical committee (Kantonale Ethikkommission Bern KEK 2020-02273) was received for this study.

[Figure 1 Flowchart near here, 1 column]

Stroke aetiology was determined by the attending physician with extended TOAST classification criteria based on the entirety of the diagnostic evaluation. Categories included 'Large-artery atherosclerosis', 'Cardioembolism', 'Small vessel occlusion', 'Patent foramen ovale', 'Cervical artery dissection', 'Unknown aetiology despite complete evaluation', 'Unknown aetiology with incomplete evaluation', 'Other determined aetiology', and 'More than one possible aetiology' according to the recent recommendations.[31] As noted above, patients with 'small vessel occlusion' stroke aetiology were excluded from our study. The data on baseline clinical variables including vascular risk factors were documented by the attending physician.

2.2. Brain imaging

We retrieved clinical routine MRI acquired about 24h after stroke onset to assess the burden of SVD lesions and the location and size of the stroke lesion . The routine imaging with a 1.5T or 3T scanner included diffusion-weighted imaging with apparent diffusion coefficient (4-5mm slice thickness), axial fluid-attenuated inversion recovery (4-5mm slice thickness), axial susceptibility-weighted imaging (1.5mm slice thickness) and axial T1-weighted imaging (4-5 mm slice thickness).

2.2.1. Evaluation of small vessel disease burden

The burden of SVD was evaluated by recording four different types of SVD-related lesions in MRI. i) Lacunes were recorded as round or ovoid cavities of >3 and <20 mm with cerebrospinal fluid intensity and surrounding gliosis on fluid-attenuated

inversion recovery imaging.[1,2] ii) Microbleeds were recorded as small homogeneous hypointensities (<5mm) in susceptibility-weighted imaging across the entire brain. They were differentiated from mineralisation or calcification of the globus pallidus, suspected cavernoma with popcorn pattern, and petechial haemorrhage within the infarct.[32] iii) Enlarged perivascular spaces were defined as small punctuate or linear lesions in the basal ganglia with cerebrospinal fluid equivalent signal and were assessed in the hemisphere with more visible pathology with an established semiquantitative scale ranging from 0 to 4.[33] Because a T2 sequence, which is typically used to evaluate perivascular spaces, was not included in the local clinical protocol, neuroradiologists made the assessment based on the B0 diffusion-weighted image and ADC map compared with the fluid-attenuated inversion recovery and T1 images. iv) White matter hyperintensities were recorded as hyperintense abnormalities in fluid-attenuated inversion recovery imaging adjacent to the ventricles or in deep white matter. They were rated with the semiquantitative Fazekas scale[34] separately for periventricular and deep white matter hyperintensities (range 0-3). All raters were blinded to further clinical information and study data. The rating was supervised and reviewed by a trained and board-certified neuroradiologist, and performed by a student assistant and two neuroradiologists. We focussed on atherosclerotic SVD as the likelihood of cerebral amyloid angiopathy in ischemic stroke is low. Hence, we did not examine SVD features of cerebral amyloid angiopathy, such as cortical superficial siderosis.

Based on these (semi-)quantitative scales, we computed a sum score for the total SVD lesion burden, following established rating criteria for the SVD burden score.[2,35] We assessed four different binary features, which were i) the presence of at least one lacune, ii) the presence of at least one microbleed, iii) at least moderate severity of enlarged perivascular spaces in the basal ganglia (rating ≥ 3), and iv) the presence of severe white matter hyperintensities, which were either beginning or already existing large confluent hyperintense loci in the deep white matter (deep white matter Fazekas score ≥ 2) or irregular hyperintensities in the periventricular white matter extending into the deep white matter (periventricular Fazekas score = 3). We used the sum of these binary ratings (range 0-4), a score of SVD burden, as the main variable in the current study.

2.2.2. Lesion mapping

We created stroke lesion maps, i.e. binary topographies of lesioned tissue by a semi-automatic algorithm as previously described.[36] The stroke lesion was delineated on the diffusion-weighted images acquired about 24h post-stroke using a region-of-interest tool in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). For each patient, an intensity threshold was chosen to best match the binary lesion map with diffusion-restricted brain tissue. Lesion maps were normalized into the standard Montreal Neurological Institute space using normalization parameters from the coregistered anatomical T1 scans. The lesion size was defined as the volumetric size of the normalised lesion map.

2.3. Statistical analyses

We investigated the relationship between SVD burden and stroke aetiology by repeated rank correlation analysis. For this analysis, we excluded patients for which an unknown aetiology with incomplete evaluation was noted. For each aetiology, we tested the association between the score of SVD burden and the binomial variable of having the specific aetiology versus not having it. We controlled the multiple tests by rigorous Bonferroni correction. Additionally, given our assumption that common risk factors might underlie any association, we investigated if the SVD burden was linked to certain stroke aetiologies independently of age, hypertension, and diabetes. To this aim, we re-computed the previous analysis as a partial correlation analysis controlling for the potential risk factors of age, hypertension, or diabetes.

We investigated the relationship between the score of SVD burden and lesion size by Pearson correlation analysis and Bayesian linear correlation analysis using the BayesFactor package[37] v0.9.12 in R.

We performed topographical statistical mapping of the association between lesion anatomy and SVD burden using a well-established approach to lesion-symptom mapping. Commonly, lesion-symptom mapping is used to map the neural correlates of cognitive deficits.[38] However, the approach can also be used to evaluate anatomo-clinical correlations of relevance to clinical practice or to understand the impact of secondary variables in stroke.[39,40]

We first used frequentist statistical mapping method with general linear models in NiiStat Software (https://www.nitrc.org/projects/niistat/) in MATLAB R2022b. We analysed the association between the score of SVD burden and the damage status (intact or lesioned) of each voxel. The statistics were performed one-

sided, i.e. we only tested if the presence of a lesion is linked to more severe SVD. Only voxels with a lesion in at least 5 patients were tested (Figure 3A). We then controlled the voxel-wise, repeated testing procedure for multiple comparisons by an approximately exact family-wise error correction using maximum statistic permutation with 5000 permutations. We complemented these statistical analyses with a recently introduced Bayesian approach, which provided further insights into null results of the frequentist analysis. Bayesian statistical tests evaluating the Bayes factor conceptually mirror popular frequentist statistical tests, such as t-tests, but can provide evidence for the absence of effects.[41] Hence, they can provide evidence that an association between SVD and lesions in specific regions does not exist. We used the Bayesian Lesion-Deficit Inference toolkit[42] with the BayesFactor package[37] in R and applied Bayesian general linear models in each voxel lesioned in at least 5 patients. We interpreted the strength of evidence suggested by Bayes factors in line with established standards[43], i.e. we interpreted Bayes factors >3 as evidence for h1 and Bayes factors <1/3 as evidence for h0.

All frequentist statistical tests were conducted at a corrected $\alpha = 0.05$. Note that we did not assume a direct causal relationship between the variables in the anatomic-clinical analysis and did not have a clear dependent and independent variable. We still used the common analysis design as provided by lesion mapping tools, for which the lesion status is the independent variable. As we only investigated bivariate relationships, the statistical results are conceptually equivalent to results from simple correlation analyses.

3 Results

The final sample consisted of 859 patients for which demographic and clinical data are shown in Table 1. The majority of patients (61.8%) presented imaging features of SVD with an SVD burden ≥1. The SVD burden correlated moderately with age (Kendall's $\tau = 0.34$; $p < 0.0001$), but only weakly with the presence of hypertension ($\tau = 0.27$; $p < 0.0001$) and the presence of diabetes (Kendall's $\tau = 0.11$; $p = 0.0005$). Stroke severity (NIHSS at 24h) was only weakly associated with SVD burden (Kendall's $\tau = 0.13$; $p < 0.0001$).

[Table 1 near here]

3.1. Association between stroke aetiology and SVD burden

After the exclusion of patients with incomplete evaluation of stroke aetiology, we analysed 756 patients. Demographics broken down by aetiology are reported in Table 2. Repeated rank correlation analysis with Bonferroni correction found that with increasing SVD burden, a stroke is more likely to be associated with a cardioembolic than a non-cardioembolic aetiology (Spearman's ρ=0.175; 95%-CI=0.103; 0.244). On the other hand, with an increasing SVD burden, stroke due to cervical artery dissection (Spearman's ρ=-0.143; 95%-CI=-0.198; -0.087) or patent foramen ovale (Spearman's ρ=-0.165; 95%-CI=-0.220; -0.104) was less common. Full data and statistics are reported in Figure 2 and Table 3.

Additionally, we investigated if SVD burden is associated with stroke aetiology independently of common risk factors of stroke. Control of hypertension or diabetes did not alter the previous results even after Bonferroni correction. However, after the consideration of age, SVD was not significantly associated with any aetiology anymore (all corrected $p \geq 0.125$). Hence, SVD burden was not linked to stroke aetiology independently of age. Detailed statistical results in the analyses with covariates are reported in Supplementary Table 1.

[Table 2 near here]

[Table 3 near here]

[Figure 2 SVD_aetiology near here, 1 column]

3.2. Anatomo-clinical correlations of lesion anatomy and size and SVD burden

Frequentist statistical mapping in all 859 patients did not identify any brain regions with an association between lesion status and SVD burden after family-wise error correction. Uncorrected results are shown in Figure 3B.

According to the Bayesian statistical mapping (Figure 3C), the association between lesion anatomy and SVD burden was absent in the majority of brain regions (Bayes factors <1/3 in over 90% of the tested area; turquoise area in Figure 3C). No larger clusters with evidence for an association between lesion location and SVD were found. Of note, the areas in the left basal ganglia with inconclusive evidence (Figure 3C) and even a few voxels with evidence for the alternative hypothesis highlighted a *negative* association, where a lesion was linked to a lower SVD burden. Hence, the

Bayesian analysis did not point to a region which might be more susceptible to stroke in patients with more severe SVD.

The size of the stroke lesion did not significantly correlate with the SVD burden (Pearsons's r = -0.0012; p = 0.97). The Bayesian correlation analysis extended this finding and provided strong evidence for the null hypothesis (Bayes factor = 0.080), indicating that a relationship between SVD burden and stroke lesion size does not exist.

[Figure 3 Lesion Mapping near here, 2 columns]

4 Discussion

With a higher SVD burden, stroke was more likely to be caused by cardioembolism and less likely to be caused by a cervical artery dissection or a patent foramen ovale. However, this association was not reflected in the lesion anatomy. Bayesian statistics showed that SVD burden was not associated with a specific stroke location or the size of a non-SVD stroke. Advanced age, a common risk factor both for SVD and stroke, could explain the association between stroke aetiologies and SVD burden.

In general, an association of SVD burden with certain aetiologies could be explained by common risk factors. We identified advanced age as a possible strong link between SVD burden and stroke aetiology. Age has previously been found to be related to the progression and emergence of SVD features[28,44,45] and to stroke, especially to stroke of cardioembolic aetiology.[46,47] In our study, patients with a stroke due to cardioembolic aetiology had the highest average age, while patients with a stroke caused by a patent foramen ovale and cervical artery dissection – which were less frequent in patients with a higher SVD burden – were younger. At the same time, the SVD burden was moderately correlated with age. In line with these findings, SVD burden was not independently associated with stroke aetiologies when considering age. Note that we accounted for the aetiology of a patent foramen ovale separately from the category of cardioembolism. Hence, our classification scheme might have been especially suited to identifying the association between SVD burden and stroke aetiologies. However, besides age, other risk factors might still come into play, and the interplay of several factors including multimorbidity is likely relevant. Future prospective studies devoted to the investigation of the commonality of risk factors are

needed.

The association of stroke aetiology and SVD could, in parts, explain the existing findings on the relationship between stroke and SVD. Hence, previous findings on stroke outcome, recurrent stroke, and secondary post-stroke pathologies might not be directly connected to SVD, but rather to features related to stroke aetiologies that are more common in patients with severe SVD. In particular, the risk factor age may be considered to explain associations between stroke and SVD. For studies investigating the association between stroke and SVD, consideration of chronological age as a covariate seems reasonable.

A main variable to be consulted to understand or predict stroke outcome or specific post-stroke deficits is the lesion anatomy, i.e. lesion location, lesion size or other lesion-derived variables (e.g.[48,49]). The independence of stroke lesion anatomy and SVD is relevant in our endeavour to understand the impact of stroke lesions and SVD on any clinical outcome measure. Any entanglement of both variables would undermine our ability to conclude possible causal mechanisms. Especially considering the high dimensionality of stroke imaging data, this would have meant a considerable additional effort to distinguish the independent effect of any of the variables.

Given the independence of stroke anatomy and SVD, the concept of brain reserve[50] seems to provide a theoretical framework to assess the influence of SVD on stroke outcome and post-stroke cognitive deficits. According to this concept, the totality of conditions and pathologies affecting the structure of the brain before stroke, including the structural micro-damage accumulated in SVD, represents a variable that moderates the cognitive and behavioural impact of a stroke lesion and affects an individual's recovery trajectory. Specifically, this concept frames lesion anatomy and brain reserve reduced by SVD as two different variables that explain stroke outcome. Still, an impact of stroke aetiologies typically associated with SVD remains as a parallel framework to explain the many connections between SVD and stroke.

4.1. Limitations

In patients with acute stroke, previously existing SVD features could be masked by the acute stroke lesion. However, such decreased visibility of SVD features should be rather minimal as features are often symmetric and visible in the contralesional brain hemisphere or other brain regions on MRI. Further, the sample included anterior circulation stroke only, which leaves the validity of our findings for cerebral stroke in

general uncertain. Our study focused on arteriosclerotic SVD (type 1) and, hence, we did not assess criteria of cerebral amyloid angiopathy explicitly. However, this pathology is rare and, therefore, it is unlikely that such omission has significantly biased the current findings.

4.2. Conclusions and perspective

In patients with stroke not caused by small vessel occlusion a more severe burden of SVD is more likely to be associated with cardioembolic aetiology. However, this association is not reflected in the stroke lesion anatomy. Therefore, the concept of brain reserve may allow us to conceptualize the negative impact of SVD on stroke outcome and cognitive deficits. Future studies should evaluate the impact of risk factors that are shared between SVD and non-SVD stroke to deepen our insights into causal mechanisms.

Data availability

Additional online materials including statistical maps are available at https://data.mendeley.com/datasets/z332cwrjk2/1. Qualified researchers may contact author R.U. to request access to anonymised patient data. Any proposals need to be approved by the local ethics commission.

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Declarations of interest

None.

CRediT author statement

Christoph Sperber: Conceptualization, Methodology, Formal Analysis; Writing – Original Draft; **Arsany Hakim**: Investigation, Resources, Review & Editing; **Laura Gallucci**: Investigation, Data Curation; **Marcel Arnold**: Investigation, Resources, Review & Editing; **Roza Umarova**: Conceptualization, Investigation, Data Curation**,** Writing – Review & Editing, Funding Acquisition

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Figure Legends

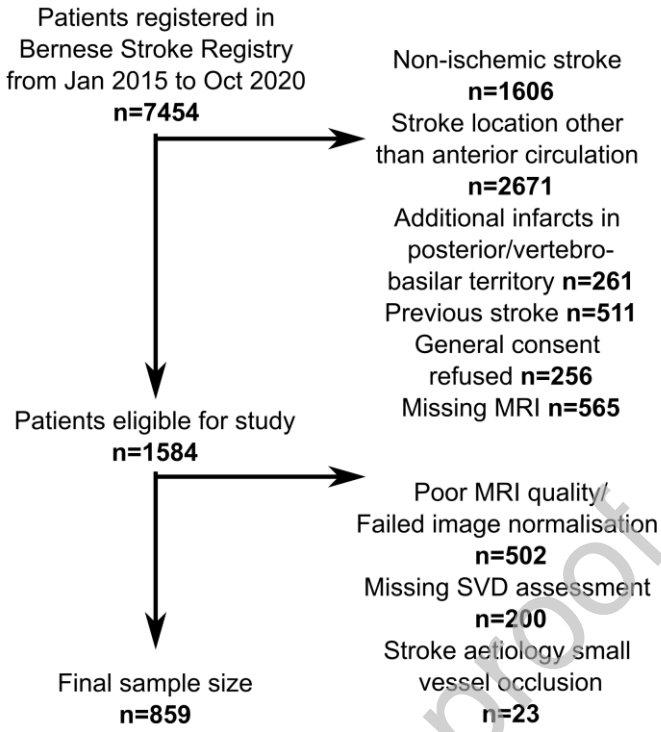

Figure 1: Recruitment flowchart

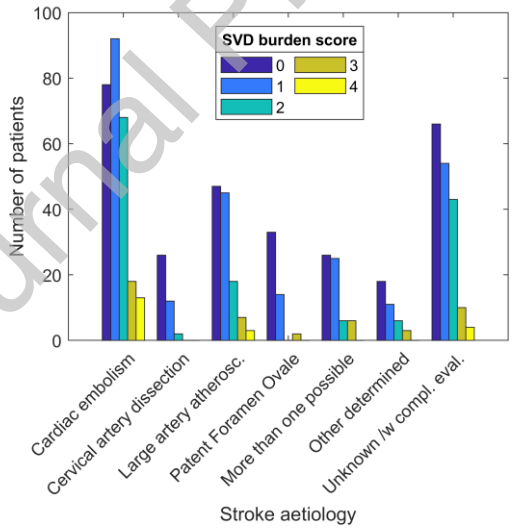

Figure 2: Relationship between small vessel disease burden and stroke aetiology

SVD burden scores across stroke aetiologies for 756 patients.

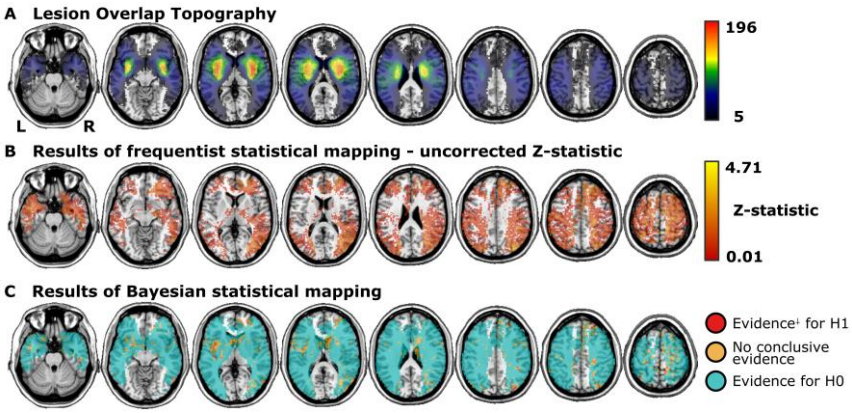

Figure 3: Results of the lesion mapping analysis

(A) Descriptive lesion overlap plot showing the location of stroke lesions in the full sample. **(B)** Uncorrected results of the frequentist statistical mapping investigating the association between SVD burden and lesion status. The map shows the voxel-wise Z-statistic resulting from the general linear models with a positive association between SVD and lesion status (i.e. Z statistics >0). Note that no significant results remained after correction for multiple comparisons. **(C)** Results of Bayesian statistical mapping with Bayesian general linear models. For better accessibility, we binned the Bayes factor map into evidence for h1, evidence for h0, and inconclusive evidence.
⸸ Evidence was categorised as in favour of h1 with Bayes factors >3, and in favour of the null hypothesis h0 with Bayes factors <1/3 (following established conventions[43]).

Tables

Table 1: Demographics and clinical data

Demographic or clinical variables marked with '⏚' contained missing values (not more than 13% of the total sample) which were omitted in the computation of characteristics. EPVS – enlarged perivascular spaces; NIHSS – National Institutes of Health Stroke Scale; SD – standard deviation; SVD – small vessel disease; WMH – white matter hyperintensities.

All participants, N = 859	
Age, years mean (SD; range)	69.0 (15.2; 16-98)
Sex, Male	56.1%
History of transient ischemic attack	5.3%⏚
Hypertension	68.9%⏚
Diabetes	16.8%⏚
Smoking	26.0%⏚
Hyperlipidemia	67.1%⏚
Atrial Fibrillation	29.1%⏚
Coronary Heart Disease	17.1%⏚
Body-Mass Index, mean(SD)	26.7 (4.7) ⏚
NIHSS 24h, mean(SD)	4.8 (5.7)
SVD Measures	
Lacunes present	20.8%
No. Lacunes when present, median[IQR]	1 [1,2]
Microbleeds present	25.3%
No. Microbl. when present, median[IQR]	2 [1,3]
EPVS, rating median[IQR]	2 [1,3]
Periventricular WMH, rating median[IQR]	1 [0,2]
Deep WMH, rating median[IQR]	1 [0,1]
SVD MRI burden, median[IQR]	1 [0,2]
SVD MRI burden = 0, N;%	328/38.2%
SVD MRI burden = 1, N;%	291/33.9%
SVD MRI burden = 2, N;%	159/18.5%
SVD MRI burden = 3, N;%	56/6.5%
SVD MRI burden = 4, N;%	25/2.9%

Table 2: Demographics across stroke aetiologies

Median and inter-quartile ranges are reported.

Stroke aetiology	N	Age	NIHSS 24h	Hypertension present	Diabetes present	SVD burden score
Cardioembolism	269	78.8 [68.9-84.9]	3 [2-7]	79.2%	18.2%	1 [0-2]
Cervical artery dissection	40	52.2 [43.0-60.5]	3 [0-9.75]	35.0%	2.5%	0 [0-1]
Large artery atherosclerosis	120	71.0 [60.7-78.8]	3 [1-8.75]	72.5%	20.8%	1 [0-1]
Patent Foramen Ovale	49	51.6 [36.6-60.7]	1 [0-3]	30.6%	2.0%	0 [0-1]
More than one possible aetiology	63	74.0 [62.6-82.6]	3 [1-6.25]	65.1%	22.2%	1 [0-1]
Other determined aetiology	38	62.5 [50.8-74.6]	2 [0-5]	47.4%	15.8%	1 [0-1]
Unknown despite complete evaluation	177	69.2 [56.6-78.1]	3 [1-6]	70.6%	15.8%	1 [0-2]

Table 3: Results of correlation analyses between SVD burden score and stroke aetiology

Results of the Spearman's rank correlation analyses of the score of SVD burden and stroke aetiology. We computed corrleations independently for each aetiology. The left columns report the simple rank correlations, the right columns the partial rank correlations controlled for age. p-values were corrected with Bonferroni correction for multiple testing. Asterisks indicate significance at $\alpha = 0.05$. CI = confidence interval

Stroke aetiology	Rank correlation ρ	95% CI	Corrected p-value	Rank correlation ρ corrected for age	95% CI	Corrected p-value
Cardioembolism	0.175	0.103; 0.244	**<0.0001***	0.006	-0.069;0.082	1
Cervical artery dissection	-0.143	-0.198; -0.087	**0.0005***	-0.033	-0.084; 0.028	1
Large artery atherosclerosis	-0.020	-0.088; 0.052	1	-0.019	-0.088; 0.051	1
Patent Foramen Ovale	-0.165	-0.220; -0.104	**<0.0001***	-0.042	-0.094; 0.015	1
More than one possible aetiology	-0.035	-0.101; 0.033	1	-0.062	-0.132; 0.007	0.627
Other determined aetiology	-0.036	-0.106; 0.037	1	0.010	-0.054; 0.082	1
Unknown despite complete evaluation	0.033	-0.039; 0.105	1	0.086	0.016; 0.158	0.125

Declarations of interest: None