



Phenotypes of Chronic Covert Brain Infarction in Patients With First-Ever Ischemic Stroke

A Cohort Study

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BACKGROUND AND PURPOSE: The aim of this study was to assess the rate of chronic covert brain infarctions (CBIs) in patients with acute ischemic stroke (AIS) and to describe their phenotypes and diagnostic value.

METHODS: This is a single-center cohort study including 1546 consecutive patients with first-ever AIS on magnetic resonance imaging from January 2015 to December 2017. The main study outcomes were CBI phenotypes, their relative frequencies, location, and association with vascular risk factors.

RESULTS: Any CBI was present in 574/1546 (37% [95% CI, 35%–40%]) of patients with a total of 950 CBI lesions. The most frequent locations of CBI were cerebellar in 295/950 (31%), subcortical supratentorial in 292/950 (31%), and cortical in 213/950 (24%). CBI phenotypes included lacunes (49%), combined gray and white matter lesions (30%), gray matter lesions (13%), and large subcortical infarcts (7%). Vascular risk profile and white matter hyperintensities severity (19% if no white matter hyperintensity, 63% in severe white matter hyperintensity, $P < 0.001$) were associated with presence of any CBI. Atrial fibrillation was associated with cortical lesions (adjusted odds ratio, 2.032 [95% CI, 1.041–3.967]). Median National Institutes of Health Stroke Scale scores on admission were higher in patients with an embolic CBI phenotype (median National Institutes of Health Stroke Scale, 5 [2–10], $P = 0.025$).

CONCLUSIONS: CBIs were present in more than a third of patients with first AIS. Their location and phenotypes as determined by MRI were different from previous studies using computed tomography imaging. Among patients suffering from AIS, those with additional CBI represent a vascular high-risk subgroup and the association of different phenotypes of CBIs with differing risk factor profiles potentially points toward discriminative AIS etiologies.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: atrial fibrillation ■ cohort study ■ ischemic stroke ■ risk factors ■ white matter

Chronic covert brain infarctions (CBIs) are focal, presumably postischemic lesions detected on brain imaging in patients without a history of an attributable obvious acute neurological dysfunction.^{1,2} Patients

with CBIs have a 2- to 3-fold increased risk of manifest acute ischemic stroke (AIS).^{2–4} Additionally, 1 in 3 patients with first-ever AIS has an additional chronic CBI on acute imaging.^{5–9}

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AIS	acute ischemic stroke
ARWMC	age-related white matter change
CBI	chronic covert brain infarction
CT	computed tomography
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
WMH	white matter hyperintensity

Previous studies addressing the role of CBI in patients with AIS are limited by use of computed tomography (CT) imaging, which is neither sensitive in detecting small CBIs nor specific in differentiating CBI from other cerebral lesions.¹⁰ Some studies used magnetic resonance imaging (MRI), but reliable imaging criteria for CBI diagnosis have only recently been proposed.¹¹ Most available studies compared patients with any CBI to patients without CBI but did not consider the imaging phenotype of the CBI lesion. Potentially relevant phenotypes include subcortical lacunes (=cavitary lesions), large subcortical infarcts, isolated gray matter lesions, and combined gray and white matter lesions.¹¹ In patients with AIS, CBI might convey clues to underlying vascular risk factors and stroke etiology. As a consequence of the methodological weaknesses of the existing studies, guidelines for AIS work-up do not include information on concomitant CBI to guide the diagnostic work-up in patients with AIS.¹²

The aim of this study was to describe the frequency, imaging phenotypes, and distribution of CBI—defined according to established imaging criteria as evidence of any prior brain infarct in patients with first clinically evident ischemic stroke. CBI included cortical infarcts as well as lacunes (cavitary), large subcortical (noncavitary) infarcts and cerebellar and brain stem lesions. In addition, we sought to determine the vascular risk factor profile according to CBI phenotypes and disentangle the association of CBI and undifferentiated white matter hyperintensities (WMHs).

METHODS

For the conceptualization of this project, we adhered to the Strengthening the reporting of observational studies in epidemiology international collaborative initiative guidelines.

Data Availability

Anonymized data and statistical analyses will be shared upon motivated request from any qualified investigator after clearance from the ethics committee.

Patients

This is a single center cohort study with 90 days follow-up. All consecutive patients treated at our comprehensive stroke center were enrolled in a prospective stroke registry. Among these patients, we applied the following inclusion criteria: (1) first clinically evident ischemic stroke, (2) MR-imaging on admission (MRI is the preferred primary imaging modality for patients with suspected stroke in the absence of contraindications), (3) admission between January 1, 2015 and December 31, 2017.

We excluded patients with CT imaging as first imaging modality and diagnoses potentially leading to brain lesions that could mimic CBI. These included previous AIS and/or transient ischemic attack defined as any transient neurological event of presumably vascular etiology, previous intracranial hemorrhage, traumatic brain injury, cranial interventions/surgery, and neuro-inflammatory diseases. Additionally, patients with stroke types other than AIS and insufficient image quality were excluded (see Figure 1 for full exclusion criteria).

Neuroimaging by Brain MRI

Type of baseline MRI, used protocols, and review by 2 raters is described in detail in the [Data Supplement](#).

Location

The CBIs were mapped in the following anatomic locations: basal ganglia (defined as involvement of deep nuclei, including the thalamus), subcortical supratentorial (white matter involvement only), cortical supratentorial, cerebellar, and brain stem. In addition to CBIs, the presence of vascular subcortical MRI WMH was graded according to the age-related white matter change (ARWMC) Rating Scale.¹³

Phenotypes

The following imaging phenotypes were included according to established criteria,^{10,11,14} (see Figure 1 for examples):

Lacunes (Of Presumed Vascular Origin)

1. Lesions ≥ 3 mm in size with central cavity formation with imaging intensities compatible with cerebrospinal fluid. A fluid-attenuated inversion recovery/T2 hyperintensity reflecting adjacent gliosis, symmetry as well as anatomic location was used to differentiate them from perivascular spaces. In the cerebellum, parenchymal defects ≤ 15 mm were rated in this category, whereas larger defects were rated as combined gray and white matter lesions.

Focal, Irregularly Shaped Hyperintensities on Fluid-Attenuated Inversion Recovery and/or T2-Weighted Imaging With Corresponding Hypointensity on T1-Weighted Imaging

These were subdivided as follows:

2. Combined gray and white matter lesions: involvement of cortical and subcortical areas.

3. Isolated gray matter lesions: isolated involvement of gray matter either in the supratentorial cortex or basal ganglia.

4. Large subcortical (noncavitary) infarcts: for differentiation of this phenotype from unspecific lesions, the lesion had to match a clear vascular supply territory in the distribution of the medial or lateral lenticular striatal arteries, with a size

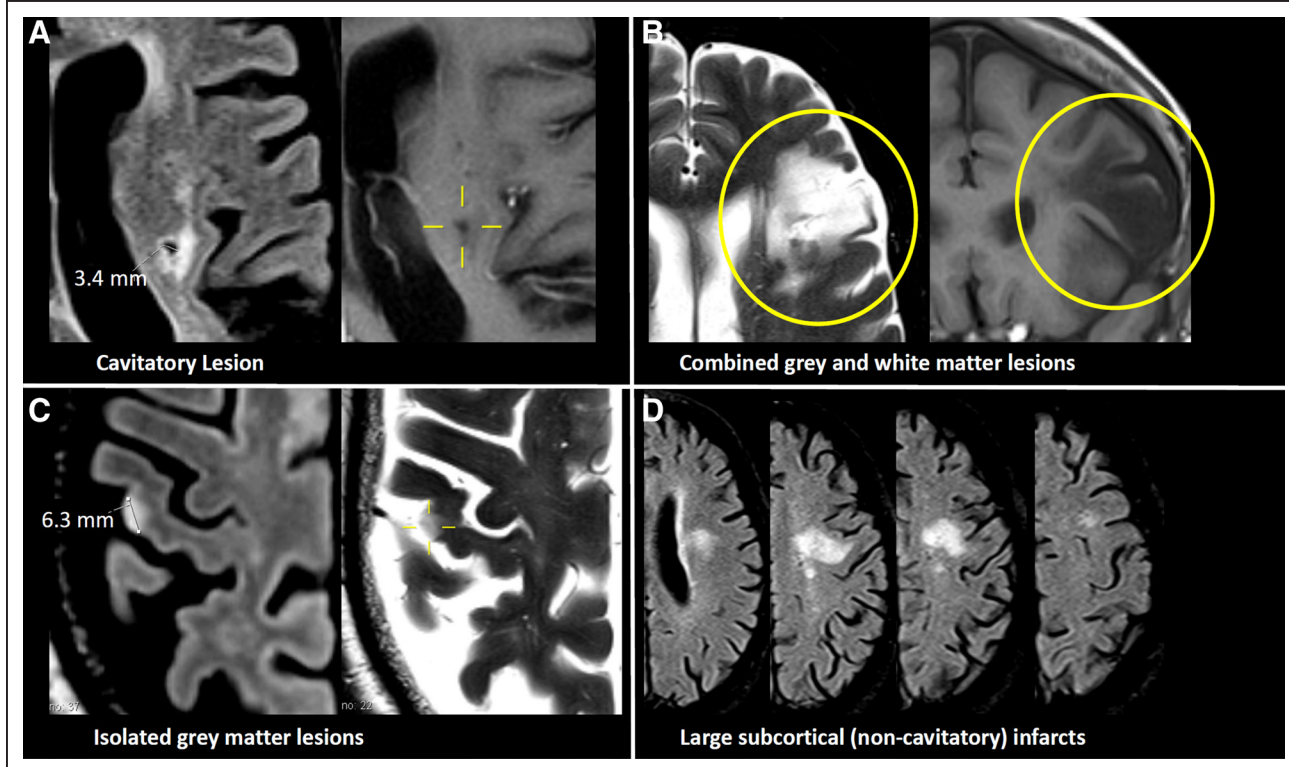


Figure 1. Examples of phenotypes of covert brain infarction.

A, Lacune. **B**, Combined grey and white matter lesions. **C**, Isolated grey matter lesions. **D**, Large subcortical (noncavitory) infarcts.

of 15 mm or more, and/or be new compared with a previous MRI performed within 3 months. Additionally, other diagnoses potentially explaining the lesion such as multiple sclerosis were excluded based on the medical history.¹¹

Clinical Baseline and Follow-Up Data Collection

Dedicated stroke research fellows collected standardized and prespecified variables including patient demographics (age, sex, body mass index), medical history (eg, history of prior AIS, prior intracerebral hemorrhage, hypertension, dyslipidemia, diabetes, smoking), medication at onset, clinical features (stroke severity, blood glucose, and blood pressure on admission), atrial fibrillation (AF: known before stroke or diagnosed up to 90 days after stroke with a work-up of ECG of 7 days duration starting 1 to 3 days after admission) as well as diagnostic tests performed (eg, imaging modality, presence of large vessel occlusion). Information on recanalization treatments included use of intravenous thrombolysis and/or mechanical thrombectomy.

Outcomes

The main outcomes for this analysis were (1) frequency of any CBI, (2) phenotypes of CBI, (3) anatomic distribution of CBIs, and (4) vascular risk profile according to CBI phenotype.

Statistical Analysis

We used medians (interquartile ranges or means [SD]), as appropriate, as well as percentages (95% CI by Clopper-Pearson method) to present the distribution of continuous, ordinal and categorical variables, respectively. We compared baseline characteristics between groups using the Pearson

χ^2 test for categorical variables and the Wilcoxon rank-sum or Kruskal-Wallis test for continuous and ordinal variables. We used Cohen's kappa statistics to report interrater agreement.

Backward elimination (significance level of 0.15) was used for selection of potentially causal covariates associated with CBI presence in logistic regression analysis. Those potentially causal vascular risk factors included age, sex, obesity, admission serum creatinine levels, hypertension, hyperlipidemia, AF, smoking, diabetes, and congestive heart failure. The analysis was done separately for each CBI phenotype as compared with patients without CBI and patients with isolated moderate or severe (ARWMC score ≥ 2) subcortical WMH without any CBI as compared with patients without subcortical WMH (with a sensitivity analysis considering only isolated CBIs). Logistic regression for the association of any cortical involvement and AF was done unadjusted and adjusted for the CHA₂DS₂-VASc score.

Stroke severity was analyzed using quantile regression analysis with CBI number as independent variable. All statistical analyses were performed using STATA (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). All *P* are 2-sided, with *P* < 0.05 considered statistically significant, and without adjustments for multiple testing. Because of limited information on CBI phenotypes, no study size calculation was possible.

Ethics

The local stroke database was approved by the ethics committee for quality control and research. ICF was waived by the ethics committee, and patients were informed about the registry and the potential use of their data for research. After information, patients may object the use of their data for research (but not for quality

control). In accordance to Swiss law, patients who refused the use of their data for research were excluded from this analysis.

RESULTS

Seventy-five percent (2992/4022) of patients underwent MRI on admission during the study timeframe. Overall, of 4022 patients considered, 1543 patients with first clinically evident ischemic stroke fulfilled the in- and exclusion criteria (Figure 2). The median age was 71 years (interquartile range, 60–81), 40% (95% CI, 38%–43%) were female, the median score on the National Institutes of Health Stroke Scale was 3 points (1–8).

Frequency, Agreement

In total, 574 patients (37% [95% CI, 35%–40%]) had a total of 950 CBIs. Seventeen percent of patients had multiple CBIs: 10% with 2 CBIs, 3% with 3 CBIs, and 4% with >3 CBIs. The interrater agreement was substantial for presence of any CBI (agreement 86%, $\kappa=0.72$, $P<0.0001$) and moderate to severe WMH (agreement 88%, $\kappa=0.75$, $P<0.0001$).

Location

Overall, 67% of CBIs were located supratentorially, 36% of which had cortical involvement, 46% extended purely

subcortically, and 18% involved the basal ganglia. Of the 33% infratentorial lesions, almost all (94%) were cerebellar lesions, making it the most common location overall (Figure 3). There was a trend for supratentorial lesions to be in the right rather than the left hemisphere (53% [95% CI, 49%–57%]), whereas for infratentorial lesions no such trend was observed (50% [95% CI, 44%–56%]).

Phenotypes

The distribution of CBI phenotypes is shown in Figure 4. In supratentorial location, the most frequent phenotypes of CBI included lacunes 298/637 (47%), combined gray and white matter lesions 145/637 (23%), and pure gray matter lesions 126/637 (20%, Figure 4). In infratentorial location, phenotype frequency of CBI were mostly lacunes 165/313 (53%), and combined gray and white matter lesions 145/313 (46%, Figure 4).

Risk Factors for Any CBI

Univariable analysis showed that the following potentially causal vascular risk factors were significantly associated with presence of any CBI (Table 1).

Age

Whereas in patients younger than 50 years only 13% had any CBI and 4% multiple CBIs, the numbers increased with age as follows: 51 to 60 years 32%/18%, 61 to 70

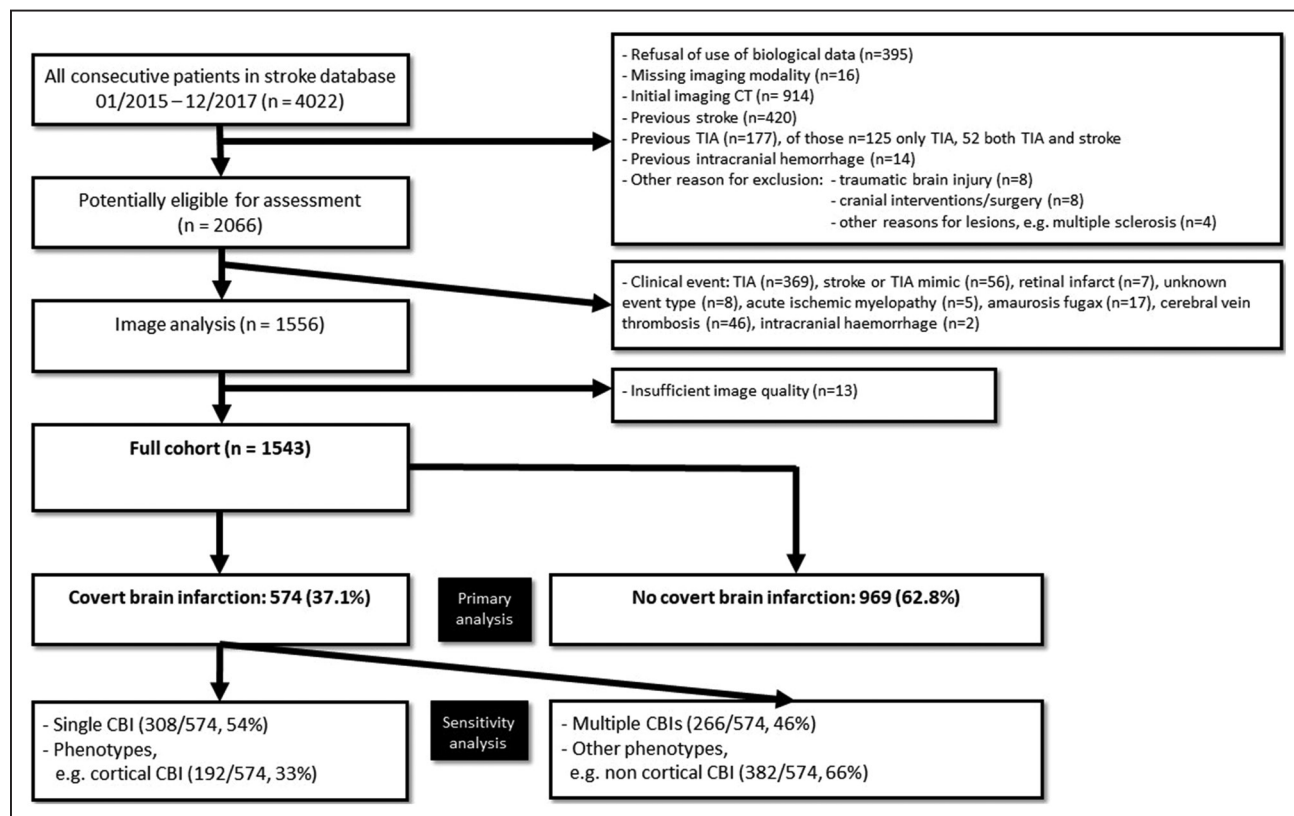


Figure 2. Study flow chart.

CBI indicates covert brain infarction; CT, computed tomography; and TIA, transient ischemic attack.

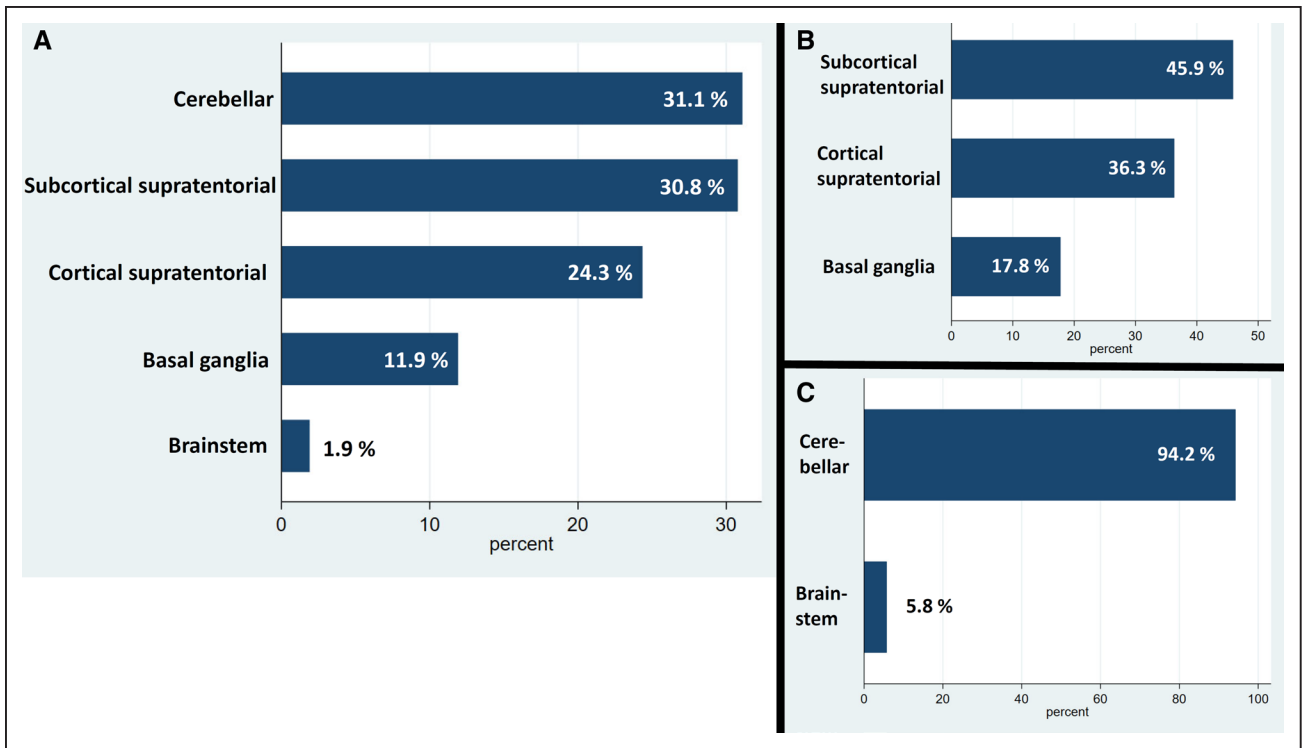


Figure 3. Location of covert brain infarction.
A, All lesions. **B,** Supratentorial lesions. **C,** Infratentorial lesions.

years 31%/14%, 71 to 80 years 43%/20%, 81 to 90 years 49%/22%, >90 years 57%/22%, $P < 0.001$.

Additionally, systolic blood pressure, hypertension, creatinine level, diabetes, AF, and congestive heart failure

were associated with any CBI. There was an inverse association of cholesterol levels and active smoking with CBI; however, the intake of lipid-lowering drugs, antiplatelets, oral anticoagulation, and antihypertensives was

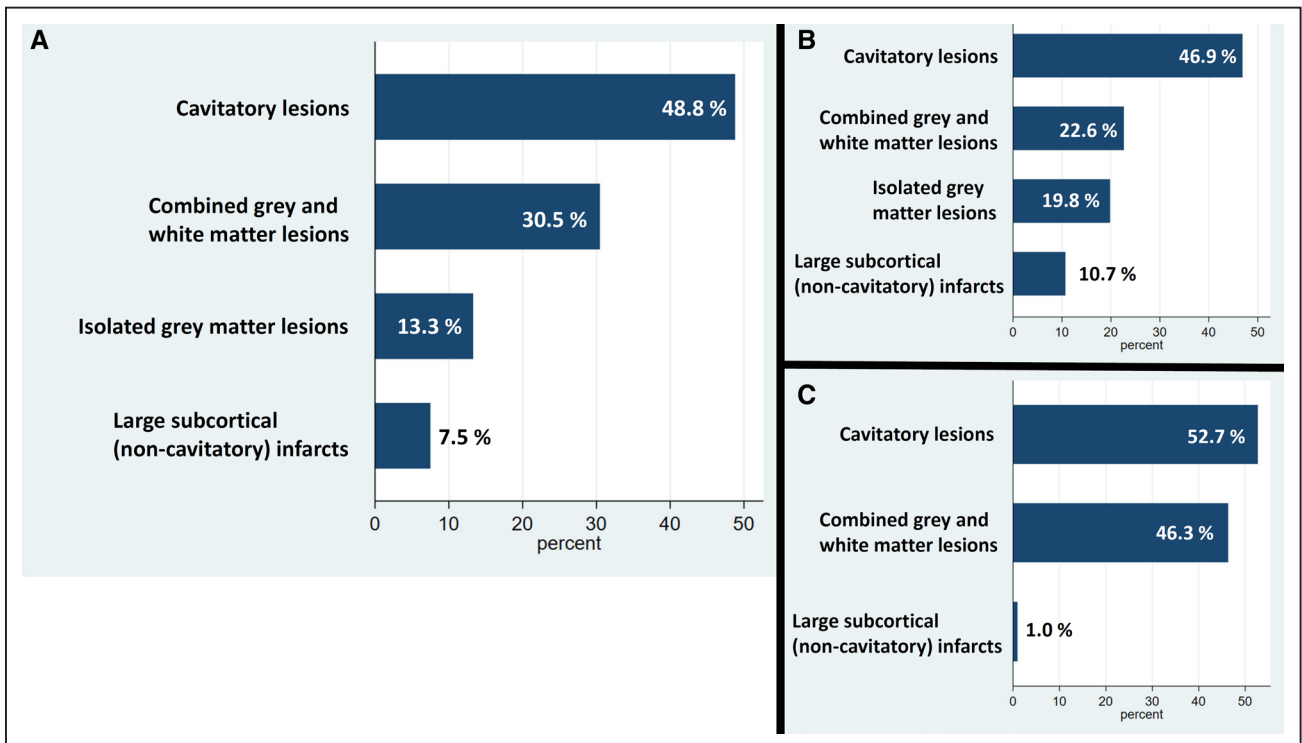


Figure 4. Frequency of phenotypes of covert brain infarction.
A, All lesions. **B,** Supratentorial lesions. **C,** Infratentorial lesions.

Table 1. Baseline Characteristics of Patients According to Presence and Number of Covert Brain Infarctions

	CBI absent (n=969)	CBI present (n=574)	Available of N=1543	P value
Clinical items				
Age, y	67.8 (56.4–77.9)	75.4 (66.1–82.7)	1543	<0.001
Sex (female)	393 (40.6%)	227 (39.5%)	1543	0.70
Living at home before stroke	704 (96.0%)	347 (94.8%)	1099	0.48
Pre-event modified Rankin Scale	0 (0–1)	0 (0–1)	839	0.017
Body mass index, kg/m ²	25.8 (23.2–28.7)	25.8 (23.5–29)	1277	0.95
Body mass index >30 kg/m ²	309 (31.9%)	197 (34.3%)	1277	0.33
Blood pressure systolic, mm Hg	159 (138–175)	165 (145–185)	1442	<0.001
Blood pressure diastolic, mm Hg	85 (73–95)	85 (74–98)	1442	0.16
Laboratory values (admission)				
Glucose, mmol/L	6.3 (5.6–7.4)	6.4 (5.7–7.6)	1400	0.16
Cholesterol, low density	2.91 (2.25–3.62)	2.69 (2.04–3.47)	1351	0.001
Cholesterol, total	4.99 (4.22–5.79)	4.8 (4.02–5.66)	1370	0.018
Creatinine	78.5 (66–91)	81 (67–100)	1500	0.005
Medication				
Antiplatelet			1094	<0.001
Mono	156 (21.5%)	118 (32.2%)		
Dual	14 (1.9%)	11 (3.0%)		
Antihypertensive drugs	340 (46.4%)	242 (65.9%)	1100	<0.001
Lipid-lowering drugs	131 (17.9%)	107 (29.0%)	1101	<0.001
Anticoagulation	64 (8.7%)	51 (13.7%)	1108	0.009
Risk factors				
Arterial hypertension	452 (61.2%)	311 (83.4%)	1111	<0.001
Hyperlipidemia	460 (63.7%)	252 (67.9%)	1093	0.17
Atrial fibrillation, known or newly diagnosed	159 (21.6%)	131 (34.7%)	1113	<0.001
Smoking	206 (30.2%)	68 (19.9%)	1022	<0.001
Diabetes	99 (13.5%)	87 (23.5%)	1102	<0.001
Congestive heart failure	90 (12.3%)	64 (17.3%)	1099	0.024
Peripheral artery disease	22 (3.0%)	18 (4.9%)	1093	0.13
CHA ₂ DS ₂ -VASc score	2 (1–3)	3 (2–4)	1083	<0.001

CBI indicates chronic covert brain infarction.

more frequent in patients with any CBI. Prestroke mRS was slightly higher in patients with any CBI.

There was a pronounced association of WMH and CBI: whereas in patients without signs of WMH (ARWMC score 0) only 19% had any CBI and 7% multiple CBIs, the numbers increased as follows: ARWMC score 1, 36%/15%; ARWMC score 2, 53%/26%, and ARWMC score 3, 63%/40%, $P < 0.001$.

Risk Factors According to CBI Phenotype

Distribution of risk factors differed among CBI phenotypes (Table 2): risk factors associated with lacunes as compared with patients without any CBI were age, hypertension, diabetes, and higher creatinine. Risk factors associated with cortical involvement of gray matter

were different: for isolated gray matter lesions, associations were significant for hypertension and AF. For combined gray and white matter lesions, increasing age, and hypertension were significant predictors whereas a borderline significance was found for AF. A similar trend for the association of any cortical involvement and AF was present. There was an association of any cortical involvement with AF in unadjusted (odds ratio, 2.4 [95% CI, 1.6–3.5]) and after adjustment for CHA₂DS₂-VASc score (adjusted odds ratio, 1.8 [95% CI, 1.2–2.8]).

Subcortical WMH

There was a linear association of WMH with AF: whereas in patients without signs of WMH (ARWMC score 0) only 16% had AF, the numbers increased as follows: ARWMC

Table 2. Vascular Risk Factor Analysis According to Phenotype of Covert Brain Infarction

	Phenotypes of CBI					Isolated subcortical WMH
	Lacunae (n=208)	Large subcortical (noncavitary) infarcts (n=36)	Isolated gray matter lesion (n=63)	Combined gray and white matter lesion (n=138)	Any cortical involvement (n=192)	ARWMC score 2–3 without any CBI (n=209)
Age	aOR, 1.018 (95% CI, 1.003–1.033)			aOR, 1.029 (95% CI, 1.009–1.051)	aOR, 1.036 (95% CI, 1.017–1.055)	aOR, 1.101 (95% CI, 1.076–1.126)
Hypertension	aOR, 2.302 (95% CI, 1.300–4.075)	aOR, 4.690 (95% CI, 1.039–21.167)	aOR, 2.442 (95% CI, 1.092–5.462)	aOR, 2.101 (95% CI, 1.046–4.222)	aOR, 1.614 (95% CI, 0.878–2.965)	aOR, 1.601 (95% CI, 0.864–2.967)
Obesity	aOR, 0.686 (95% CI, 0.433–1.086)	aOR, 2.430 (95% CI, 0.907–6.511)				
Diabetes	aOR, 1.858 (95% CI, 1.143–3.018)				aOR, 1.529 (95% CI, 0.898–2.605)	
Smoking	aOR, 0.671 (95% CI, 0.403–1.115)					
Creatinine	aOR, 1.006 (95% CI, 1.000–1.011)	aOR, 0.982 (95% CI, 0.907–6.511)			aOR, 1.006 (95% CI, 1.001–1.011)	
Atrial fibrillation			aOR, 2.032 (95% CI, 1.041–3.967)	aOR, 1.619 (95% CI, 0.948–2.763)	aOR, 1.535 (95% CI, 0.955–2.467)	
Female sex						aOR, 1.6136 (95% CI, 1.016–2.561)

aOR indicates adjusted odds ratio; and CBI, chronic covert brain infarction.

score 1, 28%; ARWMC score 2, 33%; and ARWMC score 3, 43%; $P < 0.001$. However, in patients with AF, CBI also was present more frequently with increasing subcortical WMH: in patients with AF with ARWMC score 0 already 30% had any CBI, the numbers increased as follows: ARWMC score 1, 41%; ARWMC score 2, 56%; and ARWMC score 3, 61%, $P = 0.004$. Therefore, AF was eliminated in the stepwise risk factor selection and risk factors associated with isolated moderate or severe subcortical WMH without presence of any CBI were age and female sex (Table 2). The association of WMH remained stable in a sensitivity analysis for isolated cortical CBIs (OR, 1.34 [1.05–1.73]).

Characteristics of AIS

The characteristics of the AIS according to number of CBI and their phenotypes is described in the [Data Supplement](#).

DISCUSSION

In this large dataset of patients with a first-ever AIS, we provide an MRI-based analysis of CBI frequency, phenotypes, and risk factor profiles. Various manifestations of cerebrovascular disease (CBI, white matter lesions, microbleeds, enlarged perivascular spaces) share common risk factors, but studies have not yet addressed different phenotypes of CBI in patients with AIS separately. This is the first study to apply harmonized radiological definitions for CBI to patients with AIS, in contrast with previously used heterogeneous diagnostic criteria.¹⁵

The main findings of this study are (1) 1 in 3 patients with first evident AIS had an additional chronic CBI. (2)

Several vascular risk factors and WMH severity were associated with presence of CBI, hence those with additional CBI represent a vascular high-risk subgroup. (3) Different phenotypes of CBIs were associated with differing risk factor profiles (eg, consistent association of cortical CBI with AF).

Frequency of CBI

The overall rate of 37% of patients with AIS with any CBI found in our study is similar to other contemporary studies using MRI.^{5–7} Only one study using MRI and a somewhat different definition of CBI reported a lower rate of CBI.¹⁶ Because of the lower sensitivity of CT imaging to detect CBI, most outdated studies using CT found a lower frequency of CBI in patients with AIS.^{17–21} However, in the more recent IST-3 study, which used CT in 98% of patients with AIS, a similar frequency of CBI (44%) was found.⁸ Also, in a substudy of the ENOS trial using CT in 92% of patients, 42% of patients showed any CBI.⁹ Because of the difficulties of CT imaging to differentiate Virchow-Robin spaces from lacunes, however, some of the CBIs might have been misclassified.¹⁰ We more frequently found multiple CBIs than in a previous study,⁷ probably because in that study, the frequency of cerebellar CBIs was very low. Our reported rate of CBI (13%) in patients with AIS <50 years is similar to published studies.^{22–24}

Location

In our study, the most frequent location of almost 1 in 3 CBIs was within the cerebellum. One in 4 CBIs involved supratentorial cortical structures with roughly 40%

isolated cortical lesions. This distribution is very different as compared with previous reports.⁷ Hence, one of the main findings of this study is that—taken together—CBIs within the basal ganglia and supratentorial subcortical white matter did not even account for half of the CBIs observed.

In population-based studies of asymptomatic patients, most CBIs had a subcortical supratentorial location. In contrast, in this AIS population, CBIs with cortical or infratentorial location were much more frequently found.^{25,26} This can be interpreted as a hint towards an increased risk of AIS in patients with such CBI locations. Another possible explanation is that selection bias in this population of hospital admitted patients with AIS accounts for the difference in distribution and prevalence of the lesions in our study as compared with population based studies. Hence, prospective studies need to confirm this finding. Lesions in the cerebellum can be very small and invisible on some sequences. Thus, they may be easily overlooked and future studies need to reliably take them into account.

The trend toward a right-sided location of supratentorial CBIs is in line with previous research¹⁹ and fits flawlessly the more frequent left-sided location of AIS.²⁷ Coherently to the presumed eloquence of the left supratentorial hemisphere, no such trend was seen for infratentorial lesions.

Phenotypes

The most common phenotype of CBI in our study was a lacune. This was true for both supra- and infratentorial location. Our finding that 20% of all patients with AIS have a lacunar CBI is within the reported range.²⁸ However, the reported frequency of lacunes accounting for only roughly half of the observed CBIs is much lower than previously reported.^{6,16,29} This probably has to do with the fact that most studies—especially studies using CT—were not able to detect or disregarded other phenotypes of CBI.

Most studies did not discern CBI location and phenotype, which hampers comparisons. Additionally, in infratentorial location, it is difficult to differentiate lacunes presumably caused by small-vessel disease and embolic lesions, since the STRIVE criteria were developed for supratentorial lesions and the hyperintense fluid-attenuated inversion recovery-rim was almost never present in our cohort.

The AHA/ASA guidelines on the prevention of stroke in patients with silent cerebrovascular disease recommend to use the STRIVE criteria to describe CBIs and other forms of cerebrovascular lesions. However, the authors acknowledge themselves that those criteria were not developed to classify cortical involvement, subcortical infarcts larger than 15 mm, subcortical infarcts involving gray matter and it is unclear, if the definitions for lacunes should be the same for infratentorial lesions.^{30–36}

Taken together, at least 25% of the CBIs found in this AIS population were not part of the small-vessel disease spectrum for which the STRIVE classification was developed. Furthermore, STRIVE was developed for supratentorial lesions, since at the time, there was not much info on cerebellar small-vessel disease lesions. Hence, an additional 30% of cerebellar CBIs present in this study was also not clear-cut classifiable. We think that the combination of STRIVE and other CBI phenotypes¹¹ to combine the concept of small-vessel disease^{2,28} as well as embolic causes of brain frailty, as performed in this study, is important to capture all information to optimally manage patients with AIS.

Risk Factors for Any CBI

Most importantly, the associations of many vascular risk factors with CBI shows that among patients suffering AIS, those with additional CBI represent a vascular high-risk subgroup. Previous studies using CT imaging found no association of AF with any CBI or number of CBIs.¹⁸ Our findings of increased rates of AF in patients with any CBI (35% versus 22%, $P < 0.001$) is consistent with other contemporary studies, that embolic sources including AF more frequently showed CBI (58% versus 34%, $P = 0.008$).⁵ This discrepancy probably has to do with the fact that CT imaging primarily detects lacunes in which AF is less important.^{18,20,37–39}

We also show that several other vascular risk factors are associated with presence of any CBI, of which the most important ones seem to be age and arterial hypertension. We explain the paradoxical association of lower cholesterol levels and nonsmoking with CBI by the fact that the intake of lipid lowering drugs was much more frequent in patients with CBI (reflecting the overall higher cerebrovascular risk profile of CBI-patients) and that active smokers were much younger. Since we found no associations of CBI with sex, and BMI, those risk factors might be less important for CBI occurrence.

Risk Factors According to CBI Phenotype

Because the risk factor profile differs according to CBI phenotype in a pathophysiologically plausible way, it suggests that the underlying etiology of AIS might differ.

An embolic cortical pattern of CBI was reported more often in patients with AF using CT imaging.^{18,40} Congruently, the stepwise selection model included AF for patients with isolated cortical CBI phenotype, combined cortical and subcortical CBI phenotype or the combination with any cortical involvement in our dataset with an overall consistent association of cortical lesions with AF. Importantly, when we accounted for covariates the apparent association of increasing WMH with AF disappeared. Hence, CBI phenotype seems more useful in identifying patients with AIS with covert AF than

mere CBI presence or number. Further research needs to determine whether addition of cortical CBIs refines strategies to optimize indications for long-term monitoring in patients with AIS.⁴¹

Relevance for Clinical Practice

As those patients with acute stroke and presence of CBI represent a vascular high-risk subgroup, it might well be considered that this might impact future trials on therapeutic strategies investigating the best secondary prevention strategies, stratifying patients accordingly (eg, more aggressive secondary prevention in patients with AIS with additional CBIs). Also, if the present results would be confirmed in patients with transient ischemic attack, it could be used as an adjunct to existing scales to guide hospitalization and need of acute diagnostics. The phenotype of CBI might also guide the clinician in tailoring the specific diagnostic workup to the presumed underlying etiology of not only the acute lesion, but also that of the CBIs (eg, prolonged monitoring to detect AF in patients with AIS with additional cortical CBIs). Prospective studies are needed, however, to test the hypothesis that such a tailored diagnostic work-up and precision treatment results in reduced rates of vascular events, disability, dementia, and death.

Strengths and Limitations

Our study has several strengths: (1) this is a large, prospectively collected sample giving sufficient power to identify associations of vascular risk factors with phenotypes of CBI. (2) MRI reading was performed according to harmonized recent definitions, was structured, and with blinded assessors skilled in stroke imaging. (3) We used data from consecutive patients in a prospective database with predefined variables, which limits selection bias. (4) Data completeness was good to excellent for most outcomes including imaging (100%) and National Institutes of Health Stroke Scale (91%).

Our study has several limitations: (1) although data were collected prospectively, the statistical analysis was retrospective and thus prone to bias. (2) The current study was underpowered to prove associations in multiple subgroups. However, we consider this study hypothesis generating. (3) Because of the low rate of 3T MRI use, we could not analyze cortical micro-infarcts. (4) Imaging acquisition parameters were heterogeneous throughout the study period, and some lesions might have been misclassified. However, the use of routine clinical MR imaging assures feasibility and generalizability in external cohorts. (5) Although Bern is a multiethnic city, racial and ethnic groups other than White participants are likely underrepresented and race and ethnicity are not available within the dataset. (6) The covert nature of the MRI lesion was retrospectively

adjudicated based on patient history and without a standardized questionnaire. Nevertheless, in clinical practice in our hospital, this information is thoroughly assessed in patients with AIS.

Conclusions

Using MRI, more than a third of patients with first-evident AIS had an additional chronic CBI. Several vascular risk factors and WMH severity were associated with presence of CBI. Thus, among patients suffering AIS, those with additional CBI represent a vascular high-risk subgroup. The location and phenotypes as determined by MRI definitions are different from previous studies using CT imaging with a frequent cerebellar location. Different phenotypes of CBIs with differing risk factor profiles (eg, consistent association of cortical CBI with AF) exist, potentially pointing toward discriminative AIS etiologies.

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Supplemental Material

Expanded Methods and Results
Online Tables I and II

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