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BRIEF COMMUNICATION

Association of Chronic Covert Cerebral Infarctions and White Matter Hyperintensities With Atrial Fibrillation Detection on Post-Stroke Cardiac Rhythm Monitoring: A Cohort Study

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BACKGROUND: This study was conducted to explore the association of different phenotypes, count, and location of chronic covert brain infarctions (CBIs) with detection of atrial fibrillation (AF) on prolonged post-stroke cardiac rhythm monitoring (PCM).

METHODS AND RESULTS: We conducted a cohort single-center study of consecutive first-ever ischemic stroke or transient ischemic attack patients undergoing PCM between January 2015 and December 2017. We blindly rated CBI phenotypes according to established definitions and white matter hyperintensities (WMHs) according to the age-related white matter changes rating scale. We used (multiple) regression models to assess the association of the imaging biomarkers and incident AF on PCM. A total of 795 patients (median [interquartile range]) aged 69 (57–78) years, 41% women, median National Institutes of Health Stroke Scale score 2 (0–5), median PCM duration 14 (7–14) days, and AF detection in 61 patients (7.7%) were included. On univariate analysis, WMHs (per point odds ratio, 1.35 [95% CI, 1.03–1.78]) but not CBIs (odds ratio, 0.90 [95% CI, 0.52–1.56]) were associated with AF detection. Neither CBI phenotype, count, nor location were associated with AF detection. After adjustment for age, hypertension, and stroke severity, neither increasing WMHs (per point adjusted odds ratio, 0.85 [95% CI, 0.60–1.20]) nor CBIs (adjusted odds ratio, 0.60 [95% CI, 0.33–1.09]) were independently associated with AF detection.

CONCLUSIONS: Although WMHs and CBIs represent surrogate biomarkers of vascular risk factors, neither WMHs nor CBIs, including their phenotypes, count, and location, were independently associated with AF detection on PCM. In patients with manifest ischemic stroke or transient ischemic attack, the presence of imaging biomarkers of chronic ischemic injury does not seem promising to further refine prediction tools for AF detection on PCM.

Key Words: atrial fibrillation ■ cardiac monitoring ■ covert brain infarction ■ ischemic stroke ■ transient ischemic attack

Post-stroke prolonged cardiac monitoring (PCM) is thought to be crucial to detect occult atrial fibrillation (AF)—a frequent cause of acute ischemic stroke.[1] PCM is limited by costs and availability and cannot be applied to all patients with ischemic stroke. Several predictors for AF detection on PCM have

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Nonstandard Abbreviations and Acronyms

ARWMC	age-related white matter changes
CBI	covert brain infarction
WMH	white matter hyperintensity

been identified, including older age, hypertension, heart failure, left atrial dilatation, frequent supraventricular extrasystoles, and laboratory biomarkers.[2,3] However, the algorithms currently available are insufficient to rule AF detection in or out with sufficient reliability.[3]

Favilla et al reported an independent association of prior cortical or cerebellar infarctions with incident AF on PCM in patients with cryptogenic stroke.[4] Recently, Kneihsl et al confirmed that prior cortical or cerebellar infarction was associated with AF detection on PCM in patients with cryptogenic stroke in univariate analysis.[5] In a recent study, we found a consistent association of chronic cortical covert brain infarctions (CBIs) with known or newly diagnosed AF.[6] There are insufficient data regarding potential differences according to phenotypes of CBI, including markers of small-vessel disease, such as lacunes and white matter hyperintensities (WMHs),[7] as opposed to non–small-vessel disease phenotypes such as cortical lesions.[6,8] Additionally, the associations between count or locations of CBIs and incident AF on PCM have not been analyzed.

Consequently, our study aimed to examine the association of different phenotypes, location, and count of CBIs and WMHs with AF detection on PCM in patients with ischemic stroke or transient ischemic attack (TIA). Our hypothesis was that CBI, especially embolic phenotypes such as cortical CBIs, are associated with AF detection on PCM.

METHODS

Deidentified data and methods will be made accessible upon submission of a reasonable request with a research plan to the corresponding author. Before its use, there needs to be a formal approval of the local ethics committee.

Details on ethics approval, methodology, and this cohort have been published previously.[6]

We retrospectively analyzed this prospective observational cohort, collected in the registry of our comprehensive stroke center. We included consecutive, first-ever manifest ischemic stroke and patients with TIA between January 1, 2015, and December 31, 2017. Patients had to have magnetic resonance imaging (MRI) either on admission or during the first week of hospitalization. Details on the MRI methodology are available elsewhere.[6] Patients had to have at least one 7-day ECG performed after the index event, initiated usually 1 to 3 days after the event. The institutional standard is to perform at least one 7-day ECG and preferably three 7-day ECGs in all patients, including those with TIA and ischemic stroke attributable to small-vessel disease and symptomatic carotid disease.

For this study, we excluded patients with known AF or AF diagnosed during hospitalization (emergency department, stroke unit, and ward) and patients receiving implantable cardiac monitors (<5 during the study time frame). We also excluded patients with computed tomography imaging only and patients actively refusing the use of their health-related data for clinical research. Finally, we excluded patients with diagnoses potentially leading to brain lesions that could mimic CBI (see the Figure for the full flow chart).

Standard Protocol Approvals, Registrations, and Patient Consents

The local institutional review committee (Ethics Committee of Bern, ID 2020-01696) approved this study, and individual informed consent was waived according to Swiss law.

Imaging

See our previous description for types of MRI scanners, used protocols, and interrater reliability.[6] Briefly, chronic phenotypes of CBI and WMH were blindly rated by 2 experienced vascular neurologists as described in more detail previously.[6] Acute or subacute ischemic lesions were not considered. Those CBI phenotypes included biomarkers of the small-vessel disease spectrum such as lacunes of presumed vascular origin, but likewise non–small-vessel disease phenotypes: isolated gray matter lesions, combined gray and white matter lesions, and large subcortical (noncavitatory) infarcts. We rated WMHs according to the age-related white matter changes (ARWMC) scale.[9] CBI location was mapped in the following anatomical sites: cortical supratentorial, cerebellar, brain stem, basal ganglia (deep nuclei, including thalamus), and subcortical supratentorial (white matter only). Furthermore, the absolute count of CBIs was rated (0, 1, 2, 3 or ≥4 CBIs).

We extracted the baseline data from our local registry including the laboratory values on admission. The primary outcome of this study was AF detection on PCM with a duration of at least 30 seconds. For PCM we used the Lifecard CF system (Spacelabs Healthcare, Issaquah, WA) for recording of 7-day continuous ECGs. Recordings were analyzed with the Pathfinder SL software (Spacelabs Healthcare) with additional manual confirmatory analysis by experienced operators. Only AF on PCM was rated as the

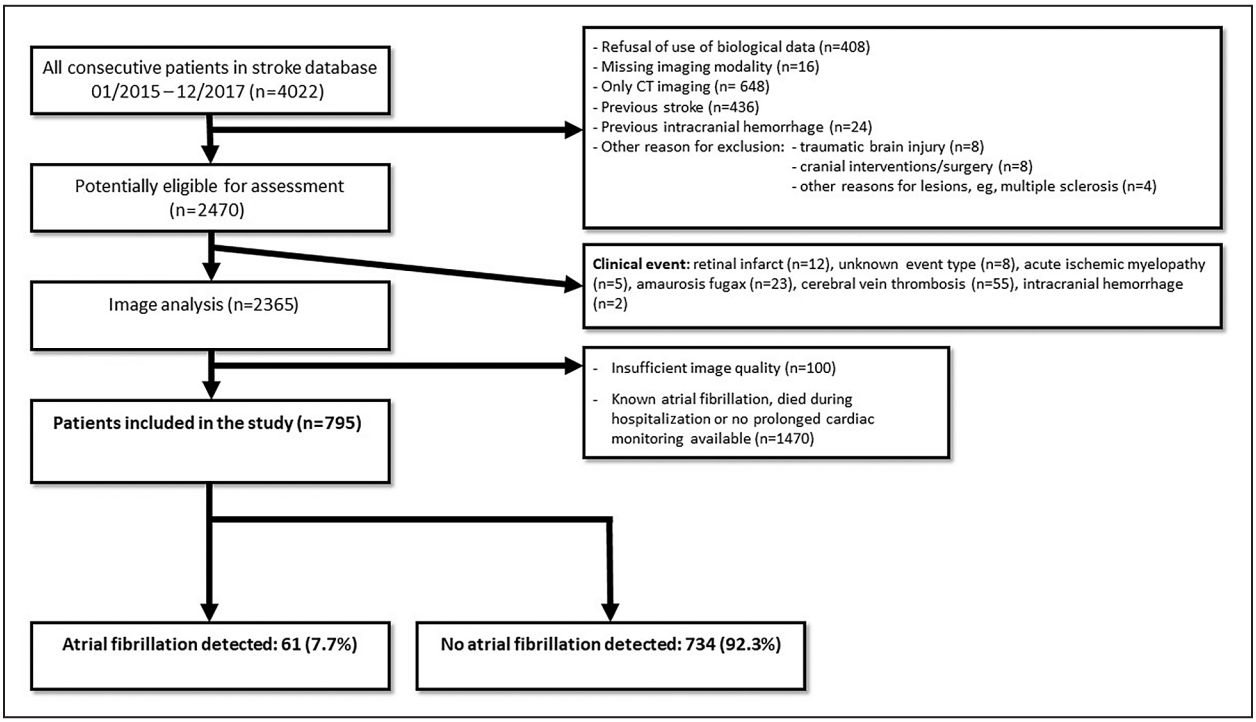

Figure. Study flowchart.
Study flowchart listing the reasons for exclusions at each stage. CT indicates computed tomography.

outcome and not if AF diagnosis was confirmed clinically outside the PCM windows.

We analyzed baseline differences between patients with and without AF detected during follow-up. Descriptive statistics (Fisher's exact test, Wilcoxon rank-sum) were used as appropriate and reported as number (%) for categorical variables and median (interquartile range) for continuous variables. We present odds ratios and adjusted odds ratios (aORs) as well as their 95% CIs for the association between the imaging biomarkers and incident AF detection. Logistic regression with adjustment for available baseline confounders known from the literature[2] was performed. Those included age on admission, sex, National Institutes of Health Stroke Scale score on admission, and hypertension. We did not categorize quantitative variables. We used Stata 16 for the analysis (StataCorp, College Station, TX) including the *table1_mc* and *idi* packages. Full case analysis without multiple imputation with a significance level of 0.05 was used with no adjustment for multiple testing. Because of unavailable data on CBI phenotypes and incident AF, no proper study size calculation was possible. Sensitivity analysis was done including only patients with ischemic stroke (tissue-based definition) and patients with cryptogenic stroke only (defined as absence of AF on at least 24-hour monitoring, absence of ≥50% ipsilateral vascular stenosis, not caused by small-vessel occlusion and without any other apparent cause).

RESULTS

Study Population

A total of 795 patients with first clinically evident ischemic stroke or TIA fulfilled the inclusion and exclusion criteria (Figure). Median age was 69 (interquartile range, 57–78) years, 41% were women, median National Institutes of Health Stroke Scale score was 2 (interquartile range, 0–5). Patients without available PCM had a slightly higher cardiovascular risk factor profile (see Table S1).

Median duration of PCM was days (interquartile range, 7–21). A total of 319 patients (40%) had one 7-day ECG, 147 (19%) two 7-day ECGs, and 325 patients (41%) three 7-day ECGs. Overall, AF was detected in 61 (7.7%) patients during follow-up, 46 (5.8%) in the first 7-day ECG, 13 (1.6%) in the second 7-day-ECG and 2 (<1%) in the third 7-day ECG. One patient was diagnosed outside the PCM window (assigned to the no AF on PCM group). Patients who had AF detected on PCM were older, had higher stroke severity, more frequently hypertension, and a higher blood plasma glucose level on admission (see Table 1 for full baseline differences).

Table 1. Baseline Characteristics According to AF Detection During Follow-Up

	No AF detected (N=734)	No. available	AF detected (N=61)	No. available	*P* value
Epidemiology					
Age at admission, median (IQR)	67.95 (56.75–77.25)	726	76.85 (69.2–82.9)	58	<0.001
Female sex, n (%)	269 (40.2)	726	28 (48.3)	58	0.23
National Institutes of Health Stroke Scale score on admission, median (IQR)	2 (0–5)	723	4.5 (2–8)	58	<0.001
Event type, n (%)					
TIA	144 (21.3)	734	8 (13.8)	58	0.18
Ischemic stroke	532 (78.7)		50 (86.2)		
Monitoring time, days, median (IQR)	14 (7–21)	734	7 (7–14)	61	<0.001
Admission systolic blood pressure, mm Hg, median (IQR)	161.5 (140–180)	664	165 (145–183)	58	0.36
Medical history of cardiovascular risk factors, n (%)					
Hypertension	414 (62.0)	668	47 (81.0)	58	0.004
Coronary heart disease	89 (13.3)	668	12 (20.7)	58	0.12
Diabetes	96 (14.4)	668	8 (13.8)	58	0.9
Hyperlipidemia	379 (56.7)	668	37 (63.8)	58	0.30
Smoking	161 (24.2)	665	11 (19.0)	58	0.37
Peripheral artery disease	23 (3.4)	668	3 (5.2)	58	0.50
Laboratory values, median (IQR)					
Admission glucose, mmol/L	6.2 (5.5–7.3)	430	6.9 (5.8–8.1)	34	0.037
Admission creatinine, μmol/L	77 (64.5–90)	668	79 (65–96)	58	0.37
Imaging biomarkers					
White matter hyperintensity score, median (IQR)	1 (0–2)	732	1 (1–2)	61	0.024
Any chronic covert brain infarction, n (%)	270 (36.8)	734	21 (34.4)	61	0.71

AF indicates atrial fibrillation; IQR, interquartile range; and TIA, transient ischemic attack.

The rates of AF detection increased with increasing WMHs: ARWMC 0 (3.9%), ARWMC 1 (9.1%), ARWMC 2 (8.6%), and ARWMC 3 (11.1%). This resulted in an unadjusted odds ratio for AF detection for 1-point increase in ARWMC rating scale of 1.35 (95% CI, 1.03–1.78). AF detection rate did not differ between patients with and without any CBIs (7.9% versus 7.2%; odds ratio 0.90 [95% CI, 0.52–1.56]).

After adjustment for confounders, neither WMH (aOR, 0.85 [95% CI, 0.60–1.20]) nor any CBI (aOR, 0.60 [95% CI, 0.33–1.09]) remained independently associated with increased risk of AF detection. Neither phenotype nor location or count was associated with AF detection (Table 2). Combining cortical and cerebellar phenotype was also not independently associated with AF detection.

When analyzing only patients with ischemic stroke, CBI was associated with lower odds of AF detection (aOR, 0.43 [95% CI, 0.22–0.85]). The point estimate was similar for patients with cryptogenic stroke only, although it did not reach significance (aOR, 0.37 [95% CI, 0.07–1.88]). No such association was found for WMHs, either for all patients with ischemic stroke (aOR, 0.84 [95% CI, 0.58–1.22]) or patients with cryptogenic stroke (aOR, 0.67 [95% CI, 0.25–1.79]).

DISCUSSION

This study exploring the association of CBIs and WMHs with AF detection on PCM has the following main findings:

1. In unadjusted analysis, WMHs, but not CBIs, were associated with AF detection on PCM.
2. After adjustment, neither WMHs nor CBIs remained significantly associated with AF detection, including CBI phenotypes, count, and locations.
3. In patients with manifest ischemic stroke or TIA, adding imaging biomarkers of chronic ischemic brain injury seems to have limited use for predicting AF detection on PCM.

AF detection on PCM is necessary to optimize secondary prevention after ischemic stroke.[2] Overall, AF detection rates on PCM are low, and the economic and

Table 2. Unadjusted and Adjusted Odds Ratios for Detection of Atrial Fibrillation on Prolonged Cardiac Monitoring Post-Stroke According to Imaging Biomarkers

	n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Any CBI	291 (36.6)	0.90 (0.52–1.56)	0.60 (0.33–1.09)
Phenotypes of CBI			
Lacunar	105 (13.2)	0.94 (0.40–2.21)	0.46 (0.18–1.13)
Large noncavitatory subcortical	13 (1.6)	2.39 (0.50–11.31)	2.42 (0.45–12.99)
Isolated cortical	28 (3.5)	1.01 (0.22–4.48)	0.69 (0.14–3.36)
Combined gray and white matter	41 (5.2)	1.04 (0.30–3.57)	0.49 (0.13–1.77)
Multiple CBI phenotypes	104 (13.1)	0.95 (0.40–2.24)	0.34 (0.12–0.95)
Pure severe WMH (ARWMC ≥2)	108 (13.6)	1.64 (0.81–3.35)	0.55 (0.25–1.24)
Location of CBI			
Subcortical	97 (12.2)	0.62 (0.24–1.59)	0.44 (0.15–1.27)
Cortical	81 (10.2)	1.36 (0.62–2.95)	1.04 (0.46–2.35)
Cerebellar	139 (17.5)	1.03 (0.52–2.03)	0.66 (0.31–1.42)
Brain stem	15 (1.9)	0.85 (0.11–6.60)	NA
Basal ganglia	37 (4.7)	1.48 (0.50–4.32)	1.32 (0.38–4.63)
Number of CBIs (reference: none)			
1	143 (18.5)	0.87 (0.42–1.77)	0.67 (0.32–1.41)
2	63 (8.1)	0.38 (0.09–1.61)	0.16 (0.02–1.24)
3	28 (3.6)	0.89 (0.20–3.89)	0.28 (0.04–2.19)
≥4	38 (4.9)	0.99 (0.29–3.37)	0.65 (0.18–2.29)
WMHs			
ARWMC 0 (reference)	230 (29.0)		
ARWMC 1	328 (41.4)	2.46, 1.14–5.28	1.21 (0.52–2.79)
ARWMC 2	163 (20.6)	2.31 (0.97–5.47)	0.61 (0.22–1.68)
ARWMC 3	72 (9.1)	3.07 (1.14–8.28)	0.90 (0.29–2.77)
ARWMC per point increase		1.35 (1.03–1.78)	0.85 (0.60–1.20)

ARWMC indicates age-related white matter changes scale; CBI, chronic covert brain infarction; NA, not possible to calculate because of low frequency; OR, odds ratio; and WMH, white matter hyperintensities.

logistic burden of PCM requires physicians to correctly identify patients who are at increased risk of incident AF. For this purpose, several prediction models mostly based on clinical, laboratory, ECG, and echocardiography biomarkers have been proposed.[3] Our hypothesis was that neuroimaging biomarkers and phenotypes of chronic ischemic injury could help to correctly predict AF detection on PCM and hence identify patients who would benefit from PCM. The appeal of those biomarkers is that brain imaging is performed in all patients with stroke and that those biomarkers are easily obtainable.

Contrary to our hypothesis, we could not show an independent association of CBIs and WMHs with AF detection on PCM. We could also not replicate the independent association of cortical and cerebellar CBIs with incident AF found by Favilla et al.[4] In fact, in the subgroup of patients with ischemic stroke, CBIs were inversely associated with a lower rate of AF detection. This might be attributable to the fact that we also adjusted for hypertension and stroke severity, potential confounders regarding this association. Another important difference is that in our cohort, we included only patients with first-ever TIA or ischemic stroke. Hence, bigger phenotypes in eloquent brain areas were probably included in the studies by Favilla et al[4] and Kneihsl et al[5] as compared with our cohort. Another possibility is that our results differ by chance.

We previously reported a consistent association of chronic cortical CBIs with known or newly diagnosed AF across all stroke etiologies.[6] It seems to be the case that patients with such lesions have a high burden of AF and hence are diagnosed with AF during the initial hospitalization. Therefore, they are not part of this study, which addressed only patients undergoing PCM after discharge. It is important to consider that all patients were hospitalized for ischemic stroke or TIA because this is a prerequisite for registry entry. Hence, the missing association might not be generalizable to patients not undergoing ECG monitoring during hospitalization or to patients not hospitalized because of ischemic stroke or TIA. The neutral association should be furthermore interpreted with caution because AF was detected in only 61 patients (8%), and the study size and follow-up period might have been too small to

exclude a potential association between CBIs/WMHs and incident AF.

Our data confirm several other independent predictors of AF detection on PCM, including age, stroke severity, and hypertension cardiovascular risk factors.

Strengths and Limitations

Our study has several strengths, including a large, prospectively collected sample with at least 7 days of ECG monitoring. Image analysis was harmonized, incorporating recent definitions,[6–8] and by blinded assessors skilled in stroke imaging. Obviously, our study also has limitations, including its retrospective analysis leading to a risk of bias. The number of 7-day continuous ECGs per patient was heterogeneous, and AF incidence would probably also be higher if all patients had undergone 3× 7-day continuous ECGs. The cohort is restricted to patients with obtainable and interpretable MRIs, so the findings should not be extrapolated to patients who cannot undergo MRI. Also, because of a low rate of high-field MRI (3T or 7T) use, we could not analyze cortical microinfarcts. We did not analyze the pattern or location of WMHs, which might differ between patients with and without paroxysmal AF. We analyzed only patients undergoing ECG monitoring (imperfect monitoring) but not implantable cardiac monitors because this approach was infrequently used during the study time frame and does not reflect global practice. Thus, our findings might not be applicable to those at the highest risk for AF.

CONCLUSIONS

When excluding patients with AF diagnosed during hospitalization, neither WMHs nor CBIs were independently associated with AF detected on PCM.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics according to PCM availability

	PCM available (N=795)	No PCM available (N=1410)	P
Epidemiology			
Age at admission	68.9 (57.3-77.8)	72.1 (59.7-81.1)	<0.001
Female sex	297 (40.9%)	556 (42.9%)	0.36
National Institutes of Health Stroke Scale on admission	2 (0-5)	3 (1-7)	<0.001
Event type - TIA - Ischemic stroke	 151 (20.7%) 579 (79.3%)	 252 (19.2%) 1,061 (80.8%)	0.42
Admission systolic blood pressure, mmHg	162 (140-180)	158 (139-178)	0.043
Medical History of cardiovascular risk factors			
Hypertension	457 (63.3%)	873 (67.5%)	0.058
Coronary heart disease	100 (13.9%)	208 (16.1%)	0.19
Diabetes mellitus	103 (14.3%)	235 (18.2%)	0.025
Hyperlipidemia	413 (57.2%)	690 (53.3%)	0.093
Smoking	172 (23.9%)	308 (24.3%)	0.87
Peripheral artery disease	26 (3.6%)	58 (4.5%)	0.34
Laboratory values			
Admission glucose, mmol/L	6.2 (5.5-7.3)	6.4 (5.7-7.7)	0.005
Admission creatinine, µmol/L	77.5 (65-90)	81 (67-95)	0.001
Imaging Biomarkers			
White matter hyperintensity score, median (IQR)	1 (0-2)	1 (0-2)	0.59
Any chronic covert brain infarction	289 (36.5%)	507 (36.0%)	0.79

Patients who died in-hospital or had atrial fibrillation known before admission or diagnosed during the stroke-unit stay were excluded from this analysis.
PCM: prolonged cardiac monitoring