Stroke

CLINICAL AND POPULATION SCIENCES

Covert Brain Infarction as a Risk Factor for Stroke Recurrence in Patients With Atrial Fibrillation

Do Yeon Kim, MD; Seok-Gil Han, MD; Han-Gil Jeong, MD; Keon-Joo Lee, MD; Beom Joon Kim, MD, PhD; Moon-Ku Han, MD, PhD; Kang-Ho Choi, MD, PhD; Joon-Tae Kim, MD, PhD; Dong-Ick Shin, MD, PhD; Jae-Kwan Cha, MD, PhD; Dae-Hyun Kim, MD, PhD; Dong-Eog Kim, MD, PhD; Wi-Sun Ryu, MD, PhD; Jong-Moo Park, MD, PhD; Kyusik Kang, MD, PhD; Jae Guk Kim, MD; Soo Joo Lee, MD, PhD; Mi-Sun Oh, MD; Kyung-Ho Yu, MD, PhD; Byung-Chul Lee, MD, PhD; Hong-Kyun Park, MD; Keun-Sik Hong, MD, PhD; Yong-Jin Cho, MD, PhD; Jay Chol Choi, MD, PhD; Sung Il Sohn, MD, PhD; Jeong-Ho Hong, MD, PhD; Tai Hwan Park, MD, PhD; Kyung Bok Lee, MD, PhD; Jee-Hyun Kwon, MD, PhD; Wook-Joo Kim, MD; Jun Lee, MD, PhD; Ji Sung Lee, PhD; Juneyoung Lee, PhD; Philip B. Gorelick, MD, MPH; Hee-Joon Bae, MD, PhD

BACKGROUND: We aimed to evaluate covert brain infarction (CBI), frequently encountered during the diagnostic work-up of acute ischemic stroke, as a risk factor for stroke recurrence in patients with atrial fibrillation (AF).

METHODS: For this prospective cohort study, from patients with acute ischemic stroke hospitalized at 14 centers between 2017 and 2019, we enrolled AF patients without history of stroke or transient ischemic attack and divided them into the CBI (+) and CBI (−) groups. The 2 groups were compared regarding the 1-year cumulative incidence of recurrent ischemic stroke and all-cause mortality using the Fine and Gray subdistribution hazard model with nonstroke death as a competing risk and the Cox frailty model, respectively. Each CBI lesion was also categorized into either embolic-appearing (EA) or non-EA pattern CBI. Adjusted hazard ratios and 95% CIs of any CBI, EA pattern CBI only, non-EA pattern CBI only, and both CBIs were estimated.

RESULTS: Among 1383 first-ever stroke patients with AF, 578 patients (41.8%) had CBI. Of these 578 with CBI, EA pattern CBI only, non-EA pattern CBI only, and both CBIs were 61.8% (n=357), 21.8% (n=126), and 16.4% (n=95), respectively. The estimated 1-year cumulative incidence of recurrent ischemic stroke was 5.2% and 1.9% in the CBI (+) and CBI (−) groups, respectively (P=0.001 by Gray test). CBI increased the risk of recurrent ischemic stroke (adjusted hazard ratio [95% CI], 2.91 [1.44–5.88]) but did not the risk of all-cause mortality (1.32 [0.97–1.80]). The EA pattern CBI only and both CBIs elevated the risk of recurrent ischemic stroke (2.76 [1.32–5.77] and 5.39 [2.25–12.91], respectively), while the non-EA pattern only did not (1.44 [0.40–5.16]).

CONCLUSIONS: Our study suggests that AF patients with CBI might have increased risk of recurrent stroke. CBI could be considered when estimating the stroke risk in patients with AF.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Risk stratification tools to predict stroke in patients with atrial fibrillation (AF) have been developed and are widely used in clinical practice.[1,2] However, these tools, which are based on usual clinical information, have limited applicability in identifying patients at high risk of recurrent ischemic stroke among patients

Correspondence to: Hee-Joon Bae, MD, PhD, Department of Neurology and Cerebrovascular Center, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi–ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea. Email braindoc@snu.ac.kr
This manuscript was sent to Theresa A. Jones, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.122.038600.
For Sources of Funding and Disclosures, see page 94.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AIS	acute ischemic stroke
CBI	covert brain infarction
CRCS-K-NIH	Clinical Research Collaboration for Stroke in Korea–National Institutes of Health
EA	embolic-appearing
EAFT	European Atrial Fibrillation Trial
EAST-AF	East Asian Ischemic Stroke Patients With Atrial Fibrillation Study
HR	hazard ratio
MRI	magnetic resonance imaging
NOACs	new oral anticoagulants
NT-proBNP	N-terminal pro-B-type natriuretic peptide
TIA	transient ischemic attack
WMH	white matter hyperintensity

with AF presenting with acute ischemic stroke (AIS).[3] Detailed stroke-related information, including neuroimaging, might help to build a more robust and precise risk prediction tool for AIS patients with AF.

Covert brain infarction (CBI), a chronic cerebral infarction detected by neuroimaging in patients without history of stroke or transient ischemic attack (TIA), increased the risk of stroke ≈2-fold in meta-analysis.[4] Although previously considered,[5] CBI in the AF patients has not been used as a component of a risk stratification tool. CBI is highly prevalent (15%–50%) among patients with AF.[6] Furthermore, the lesion patterns of CBIs vary among general population and patients with AF: an EA pattern CBI is more frequently observed in patients with AF,[7] whereas a lacunar CBI is more frequent in the general population.[8] Stroke guidelines recommend investigation of a cardioembolic source when the EA pattern of CBI is observed.[8]

However, data on the predictive value of CBI for stroke recurrence in patients with AF is scarce. A substudy of the EAFT (European Atrial Fibrillation Trial), the only study in literature regarding this topic, reported that CBI increased the risk of recurrence by 1.7×.[9] EAFT is a study conducted decades ago before the advent of the new oral anticoagulants (NOACs) and brain magnetic resonance imaging (MRI).

Under the hypothesis that AF patients with CBI might have increased risk of recurrent stroke, this study aimed to describe the frequency and features of CBI on brain MRI in patients with AF presenting with AIS and having no prior history of stroke or TIA and determine whether CBI increases the risk of recurrent stroke. This study also investigated whether this risk may differ according to the patterns of CBI, an embolic-appearing (EA) pattern or a non-EA pattern.

METHODS

Study Participants

The data analyzed in this study are available from the corresponding author upon reasonable request. This study included patients who were enrolled in the EAST-AF (East Asian Ischemic Stroke Patients with Atrial Fibrillation Study)-Part II. The EAST-AF-part II was a prospective multicenter cohort study consisting of patients with AIS hospitalized at 14 stroke centers in South Korea since October 2017. Patients who were registered into the Clinical Research Collaboration for Stroke in Korea–National Institutes of Health (CRCS-K-NIH) registry[10] and had nonvalvular AF, were enrolled in the EAST-AF-Part II. Patients with AF that was known before or diagnosed after stroke by routine electrocardiography (ECG), automated ECG monitoring in the stroke unit, or Holter monitoring during the admission were enrolled. Institutional review boards of the participating centers approved the study protocols.

Among 14832 patients with AIS, 2397 nonvalvular AF patients were admitted at EAST-AF centers between October 26, 2017, and October 31, 2019, and 2028 patients gave a written informed consent. Among these 2028, 1971 patients (97.2%) underwent an MRI scan as a routine clinical practice during hospitalization. After excluding patients whose MRI scan had poor quality (n=80), who had missing data on essential clinical information (n=6), who withdrew the study consent (n=1), and who had prior stroke or TIA (n=501), 1383 first-ever stroke patients were analyzed in this study (Figure 1).

Data Collection and Outcome Assessment

Information on age, sex, vascular risk factors (hypertension, diabetes, dyslipidemia, current smoking, coronary heart disease, and congestive heart failure), CHA_2DS_2-VASc score, stroke characteristics (initial National Institutes of Health Stroke Scale and symptomatic steno-occlusion of relevant major cerebral arteries [>50%]),[11] initial blood pressure, initial blood glucose, and treatments (intravenous thrombolysis, endovascular recanalization therapy, and antithrombotics and statins at discharge) were obtained from the registry database.

The primary outcome was recurrent ischemic stroke, and secondary outcome was all-cause mortality. Outcome events were collected at the clinical office visits and through structured telephone interviews and review of medical records at 3 months and 1 year after index stroke by trained study coordinators at the participating centers. The detailed protocols for outcome collection were previously described.[10] The events collected during the first year after the index stroke were analyzed.

Imaging Assessments

MRI scans were obtained using a 1.5T or 3T MRI scanner including diffusion-weighted imaging, T1, and T2 or T2 fluid-attenuated inversion recovery sequences. Chronic infarction was defined as a focal lesion with T1 hypointensity and T2/T2 fluid-attenuated inversion recovery hyperintensity representing tissue destruction or cavitation with negative diffusion-weighted

 Stroke. 2023;53:87–95. DOI: 10.1161/STROKEAHA.122.038600

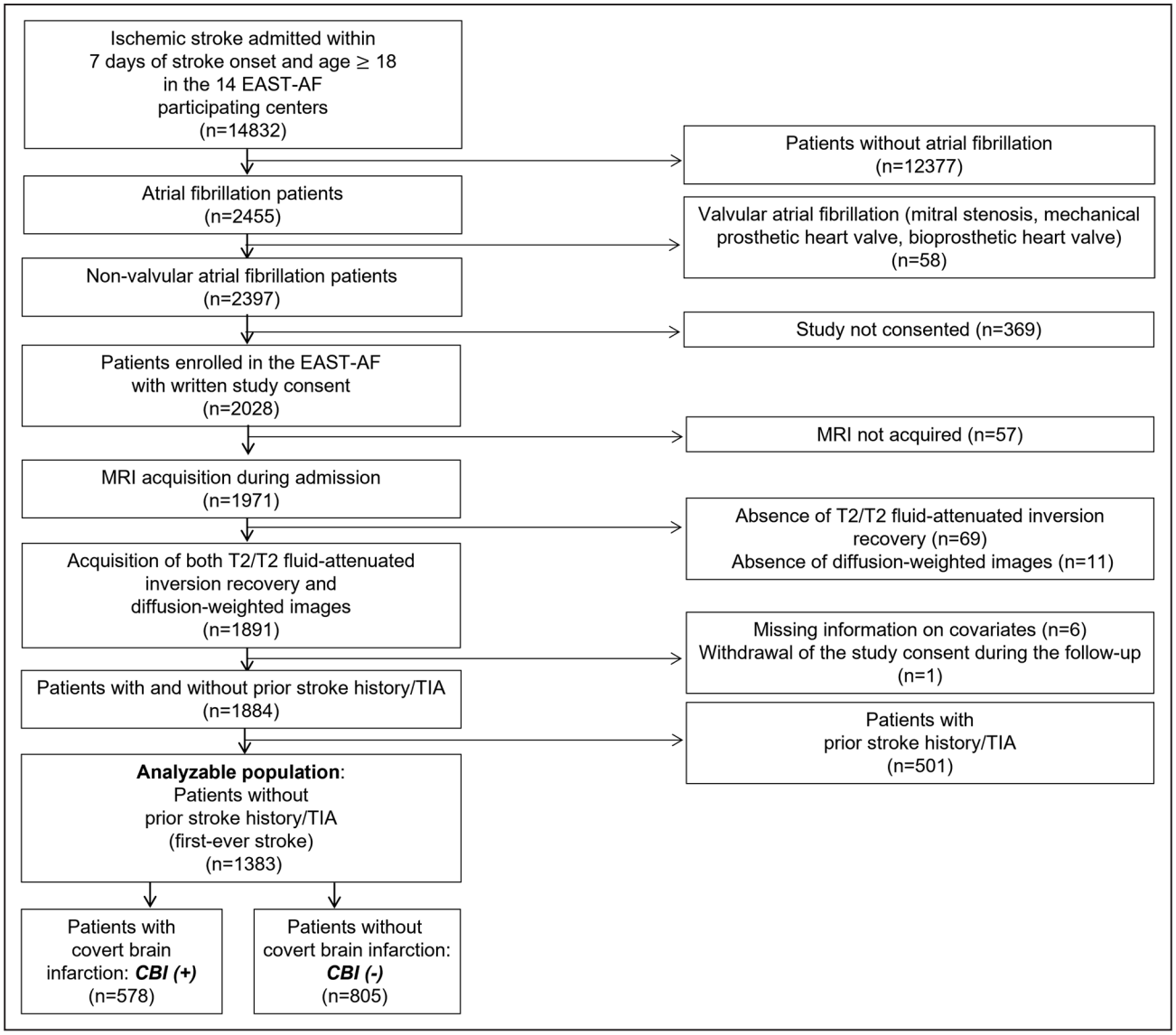

Figure 1. Flow chart of the study population.
CBI indicates covert brain infarction; EAST-AF, East Asian Ischemic Stroke Patients With Atrial Fibrillation Study; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

imaging.[12] Chronic infarction was differentiated from the perivascular space by a size larger than 3 mm and ovoid or irregular margins instead of a linear shape, and from white matter hyperintensities (WMHs) by the presence of tissue destruction or a cavitated tissue signal intensity consistent with cerebrospinal fluid on all of the sequences according to the previously published guidelines.[13] Individual chronic infarctions were mapped according to the anatomical location and categorized into either EA pattern or non-EA pattern: Supratentorial cortical, corticosubcortical, subcortical (out of penetrating artery territory), and cerebellar infarctions were classified as the EA pattern, and supratentorial deep lacunar, deep large subcortical (in penetrating artery territory), and brainstem infarctions as the non-EA pattern. A single patient could have the EA pattern, the non-EA pattern, or both. Chronic infarction observed in patients without prior stroke or TIA was defined as CBI.

Other features of chronic infarction including vascular territory (single territory versus multiple territories) and the number and size of lesions (largest diameter ≥20 mm versus <20 mm) for the EA pattern, and the number of lesions for the non-EA pattern, were also examined. An operational definition of each feature is elaborated in Figure S1.

Imaging analysis was performed by 2 vascular neurologists (D.Y.K. and H.-G.J.) blinded to the clinical data and the interobserver agreement for detection of chronic infarction and distinguishing the EA pattern from the non-EA pattern was 0.91 and 0.92 by Cohen Kappa coefficient, respectively.

Statistical Analysis

Complete case analysis without imputation was adopted in this study. Patients with missing information were excluded from the analysis when selecting the study subjects. Enrolled subjects were divided into those with CBI, CBI (+) group, and without CBI, CBI (–) group. Comparison of baseline characteristics between the CBI (+) and CBI (–) groups was made

using χ^2 test for categorical variables and Student t test or Wilcoxon rank sum test for continuous variables as appropriate. According to the presence of the EA and non-EA pattern CBIs in an individual patient, the CBI (+) group was divided into the 3 subgroups: EA pattern CBI only, non-EA pattern CBI only, and both CBIs.

Thirty-day and 1-year cumulative incidence functions for recurrent ischemic stroke were estimated with nonstroke death as a competing event and compared between the 2 groups using Gray test, while Kaplan-Meier survival curves for all-cause mortality were compared using the log-rank test. In multivariable analysis, the Fine and Gray subdistribution hazard model was used for recurrent ischemic stroke to account for competing nonstroke death, while the Cox frailty model with random intercepts was used for all-cause mortality to adjust for clustering within centers. Center effect was not considered in the Fine and Gray model since an appropriate statistical approach is unavailable. Instead, to account for center effect, we applied the Cox frailty model with random intercepts for recurrent ischemic stroke as a sensitivity analysis. The proportionality assumption was examined by including interaction terms between CBI and time. Two models were constructed: in model 1, hazard ratios (HRs) and 95% CIs of CBI (+) were estimated with CBI (–) as a reference. In model 2, HRs with 95% CIs of the 3 subgroups of the CBI (+) were estimated, respectively, with CBI (–) as a reference.

To avoid model overfitting, variables for adjustment were selected according to the predetermined following criteria: (1) for recurrent ischemic stroke, among established risk factors of stroke recurrence,[3,11,14–17] variables with a $P<0.15$ in bivariate analysis were chosen; (2) for the all-cause mortality, initial National Institutes of Health Stroke Scale score,[3] and initial systolic blood pressure[3] were chosen additionally; (3) discharge antithrombotics were predetermined as covariates for both of recurrent ischemic stroke and all-cause death; (4) CHA_2DS_2-VASc score was selected to adjust possible imbalances by risk factors not included in the models. Multicollinearity among covariates was examined by variance inflation factor.

Individual model performance was measured by the concordance index. Whether the addition of CBI to the CHA_2DS_2-VASc score could improve the performance of predicting recurrent ischemic stroke was examined by comparing the concordance index of the 2 models: CHA_2DS_2-VASc score only versus CHA_2DS_2-VASc score plus CBI. CIs were estimated based on the percentile bootstrap method with 1000 replications and its P value was obtained by testing the difference between 2 correlated overall C-indices.

Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC) and a $P<0.05$ was considered statistically significant. This article follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.[18]

RESULTS

Among 1383 first-ever stroke patients (male, 54%; mean age, 74.4 years), CBI was found in 41.8% (n=578). Compared with the CBI (–) group, the CBI (+) group were more likely to be older, be on antiplatelets at discharge, have moderate to severe WMHs, and higher CHA_2DS_2-VASc score, systolic blood pressure and initial National Institutes of Health Stroke Scale score (Table 1). NOAC was the predominant anticoagulant at discharge; 95.7%, 1101 of 1150 patients with anticoagulants at discharge.

Covert Brain Infarctions

A total of 1020 CBIs including 696 EA pattern CBIs and 324 non-EA pattern CBIs were observed in 578 patients. Among this CBI (+) group, 357 patients (61.8%) had EA pattern CBI only, 126 (21.8%) had non-EA pattern CBI only, and 95 (16.4%) had both CBIs (Table 2). Among those with EA pattern CBIs, 116 (25.7%) had CBIs in multiple vascular territory and 155 (34.3%) had multiple CBIs; whereas, among those with non-EA pattern CBIs, 207 (93.7%) had supratentorial lacunes and 65 (29.4%) had multiple CBIs. Other details on the constituents of CBIs are presented in Table 2.

Outcomes

During the median follow-up of 366 days (interquartile range, 348–377), 44 ischemic strokes and 173 deaths were observed. The 30-day and 1-year cumulative incidence was 2.0% and 3.2% for recurrent ischemic stroke and 3.5% and 12.5% for all-cause mortality, respectively.

CBI and Outcomes

The estimated 1-year cumulative incidence of ischemic stroke and all-cause mortality differed between the CBI (+) and CBI (–) groups (5.2% versus 1.9%, $P=0.001$ by Gray test; 16.8% versus 10.3%, $P<0.001$ by log-rank test, respectively; Figure 2, Table 3). CBI increased the risk of recurrent ischemic stroke in the subdistribution model (adjusted HR [95% CI], 2.91 [1.44–5.88]) and tended to increase the risk of all-cause mortality in the Cox frailty model (1.32 [0.97–1.80]; model 1 of Table 4; Table S1). The sensitivity analysis with the Cox frailty model for recurrent ischemic stroke showed the similar results. The concordance index was about 0.67 for recurrent ischemic stroke and about 0.81 for all-cause mortality.

The patients with EA pattern CBI only had increased risk of recurrent ischemic stroke but had no significantly increased risk of all-cause mortality, whereas those with non-EA pattern only had increased risk of all-cause mortality but had no increased risk of recurrent ischemic stroke (model 2 of Table 4; Table S1). Those with both CBIs had increased risk of both recurrent ischemic stroke and all-cause mortality.

As post hoc analyses, we examined whether the effect of CBI on recurrent ischemic stroke differed according to discharge antithrombotics by including interaction terms between CBI and discharge antithrombotics (anticoagulant and antiplatelet, respectively) in the model. The increased risk by CBI seemed to be reduced numerically in patients with discharge antithrombotics compared to those without. However, the interactions were not significant ($P>0.05$; Table S2).

Stroke. 2023;53:87–95. DOI: 10.1161/STROKEAHA.122.038600

Table 1. Baseline Characteristics of Participants According to CBI

	CBI(+; n=578)	CBI(−; n=805)	*P* value*
Sex†			0.41
Male, n (%)	305 (52.8)	443 (55.0)	
Female, n (%)	273 (47.2)	362 (45.0)	
Age, mean±SD, y†	76.1±9.5	73.1±10.8	<0.001
Risk factors, n (%)			
Hypertension†	419 (72.5)	557 (69.2)	0.18
Diabetes†	173 (29.9)	209 (26.0)	0.10
Dyslipidemia†	135 (23.4)	195 (24.2)	0.71
Current smoking†	66 (11.4)	117 (14.5)	0.09
Coronary heart disease†	75 (13.0)	86 (10.7)	0.19
Heart failure†‡	47 (8.1)	74 (9.2)	0.49
AF diagnosis, n (%)†			0.50
Known AF	264 (45.7)	353 (43.9)	
AF diagnosed after stroke	314 (54.3)	452 (56.1)	
CHA_2DS_2-VASc score, median (IQR)†	5 (5-6)	5 (4-6)	<0.001
Stroke characteristics			
Initial systolic BP, mean±SD, mm Hg	148.0±27.9	144.8±25.8	0.03
Initial diastolic BP, mean±SD, mm Hg	83.1±17.4	83.1±16.3	0.97
Initial glucose level, mean±SD, mg/dL	143.6±58.8	141.5±56.1	0.51
Initial NIHSS score, median (IQR)	7 (3-15)	5 (2-14)	<0.001
Significant steno-occlusive lesion, n (%)†	345 (59.7)	474 (58.9)	0.76
White matter hyperintensities†			<0.001
None or mild	236 (40.8)	508 (63.1)	
Moderate to severe	342 (59.2)	297 (36.9)	
Acute reperfusion therapy, n (%)			
Intravenous thrombolysis	133 (23.0)	190 (23.6)	0.80
Endovascular treatment	136 (23.5)	203 (25.2)	0.47
Prior antithrombotics, n (%)			
Anticoagulant	105 (18.2)	134 (16.6)	0.46
Antiplatelet	164 (28.4)	216 (26.8)	0.53
Discharge antithrombotics, n (%)			
Anticoagulant	473 (81.8)	677 (84.1)	0.27
Antiplatelet	130 (22.5)	140 (17.4)	0.02
Discharge statin medication, n (%)†	494 (85.5)	688 (85.5)	1.00

A indicates atrial fibrillation; BP, blood pressure; CBI, covert brain infarction; IQR, interquartile range; and NIHSS, National Institutes for Health Stroke Scale.

*P value by Pearson χ^2 test, Student t test, or Wilcoxon rank sum test as appropriate.

†Potential confounders related to being associated with stroke recurrence.

‡Congestive heart failure or dilated cardiomyopathy with ejection fraction <40%.

The addition of CBI to the CHA_2DS_2-VASc score improved the concordance index from 0.49 (95% CI, 0.46–0.60) to 0.63 (0.56–0.71) but the difference was not statistically significant (P=0.09).

DISCUSSION

This prospective cohort study investigated the significance of CBI as a predictor of stroke recurrence in AIS patients with AF. Approximately 42% of the first-ever AIS patients with AF had CBI, and the presence of CBI increased the risk of recurrent ischemic stroke more than 2-fold. When classifying CBIs into the EA and non-EA pattern CBIs, the patients with the EA pattern CBI only and both CBIs had significantly increased risk of recurrence while those with the non-EA pattern CBI only did not.

According to a recent meta-analysis,[4] the stroke risk was increased 2-fold by CBI in stroke-free individuals recruited from the general population and patients with a history of stroke. However, the substudy of the PRoFESS trial (Prevention Regimen for Effectively Avoiding Second

Table 2. Constituents of EA and Non-EA Pattern CBIs

	EA pattern CBI			Non-EA pattern CBI	
	No. of patients (n=452)*†	No. of lesions (n=696)		No. of patients (n=221)*‡	No. of lesions (n=324)
Subtypes			Subtypes		
Supratentorial cortical	296	395	Supratentorial deep lacune	207	296
Supratentorial cortico-subcortical	77	79	Supratentorial deep large subcortical	13	13
Supratentorial subcortical	97	139	Brainstem	13	15
Cerebellar	78	83			
Characteristics§			Characteristics§		
Vascular territory			Number of infarction		
Single	336		1	156	
Multiple	116		2	46	
No. of infarction			≥3	19	
1	297				
2	99				
≥3	56				
Largest diameter					
<20 mm	224				
≥20 mm	228				

CBI indicates covert brain infarction; and EA, embolic-appearing.
*Patients with a presence of subtypes or characteristics amongst patients.
†Patients with EA pattern CBI (n=452) included those with EA pattern CBI only (n=357) and both CBIs (n=95).
‡Patients with non-EA pattern CBI (n=221) included those with non-EA pattern CBI only (n=126) and both CBIs (n=95).
§Characteristics of CBI were defined for each individual.

Strokes) reported that, in patients with noncardioembolic stroke, CBI did not increase the risk of stroke recurrence.[19] In this substudy, more than two-thirds of CBIs were not cortical (lacunar, subcortical, or brainstem infarction). These results are contradictory to our study results whereby the risk of stroke recurrence was increased by CBI in AIS patients with AF and the EA pattern CBI was predominant.

The EAFT substudy also analyzed AIS patients with AF.[9] Compared to it, our study had a higher detection rate of CBI (42% versus 14%), a higher proportion of the EA pattern CBI among those with CBI (78% versus 46%), and a lower recurrence rate (4% versus 14% per year). These differences might be attributable to the differences in neuroimaging modalities and types of antithrombotic agents used: the high rate of MRI acquisition (97%) was a strength of this study and 83% of our patients had oral anticoagulants (mostly NOAC) at discharge, whereas, in the EAFT study, brain computed tomography was used and ≈25% had oral anticoagulants and 40% had aspirin.[20] This justifies the current study, which was performed 25 years after the publication of the EAFT substudy.[9] In the current study, the patients

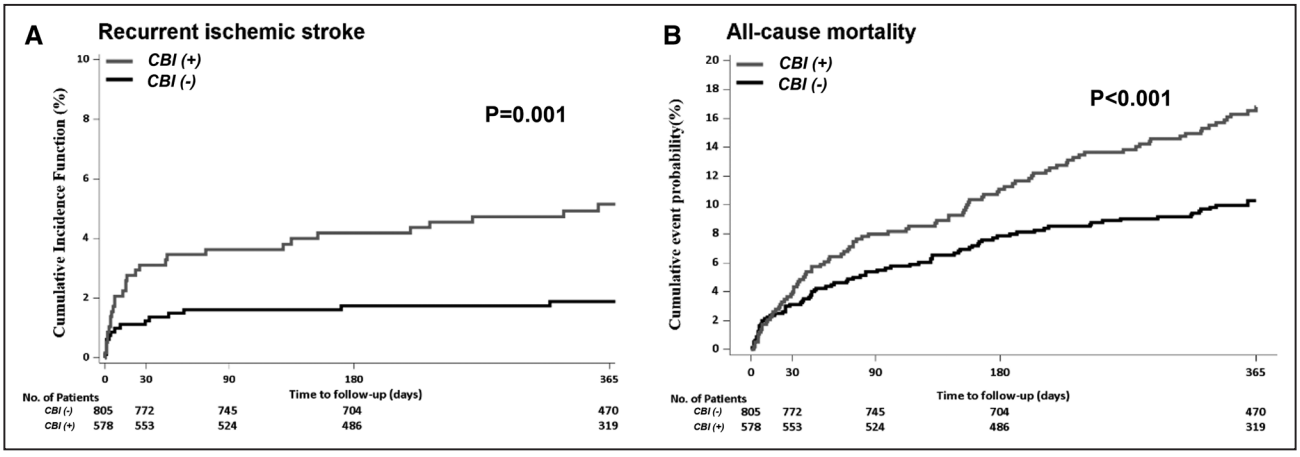

Figure 2. Cumulative incidence curves of outcome events according to covert brain infarction (CBI): cumulative incidence functions for recurrent ischemic stroke and Kaplan-Meier estimates for all-cause mortality.

Table 3. Unadjusted Cumulative Incidence of Outcome Events

Outcomes/study groups	No. of events/no. of patients	Cumulative incidence, 30 d, % (95% CI)	Cumulative incidence, 1 y, % (95% CI)
Recurrent ischemic stroke*			
CBI (+)	29/578	3.12 (1.92–4.77)	5.15 (3.53–7.20)
CBI (–)	15/805	1.24 (0.64–2.21)	1.89 (1.11–3.02)
All-cause mortality†			
CBI (+)	93/578	3.99 (2.39–5.59)	16.80 (13.67–19.92)
CBI (–)	80/805	3.12 (1.91–4.32)	10.31 (8.16–12.45)

CBI indicates covert brain infarction; and CIF, cumulative incidence function.
*Based on the CIF with nonstroke death as a competing event.
†Based on the Kaplan-Meier method.

with CBI were more likely to be older, have moderate to severe WMHs and have higher systolic blood pressure, which were consistent with the previous study on the general elderly population with CBI.[21]

The apparently different risk between the EA and non-EA pattern CBIs might be explained by that the most of recurrent stroke among anticoagulated AIS patients with AF had an embolic pattern.[22] The increased risk of all-cause mortality by the non-EA pattern CBI was also suggested before by the study that lacunar infarcts increased the risk of mortality in patients with atherosclerotic disease.[23]

The necessity of a risk stratification tool to predict stroke recurrence in AIS patients with AF is overt in various clinical settings including deciding when to start anticoagulation,[24] and determining whether to administer anticoagulants in patients with hemorrhages or cerebral microbleeds.[25,26] However, we should acknowledge that the use of our extensive clinical database failed to improve the limited predictability of the convention risk prediction models for stroke recurrence in AF.[3] Neuroimaging parameters other than CBI could be considered in estimating the risk of stroke recurrence in AIS patients with AF. Furthermore, as brain MRI is widely used in the elderly population without stroke for various purposes, the role of CBI in stroke risk estimation for AF in general population should be explored more extensively.

Limitations

This study has limitations: First, 7.2% of the patients who gave consent to the study were not analyzed owing to absence or poor quality of MRI scan. Many of those excluded from the analysis had severe neurologic deficits or serious other medical conditions (Table S3). Bias due to excluding critically ill patients could be possible. However,

Table 4. Hazard Ratios of CBI and CBI Patterns for Recurrent Ischemic Stroke and All-Cause Mortality

	Model 1	Model 2		
	CBI*	EA pattern CBI only*	Non-EA pattern CBI only*	Both CBIs*
Recurrent ischemic stroke (subdistribution model)†				
aHR (95% CI)	2.91 (1.44–5.88)	2.76 (1.32–5.77)	1.44 (0.40–5.16)	5.39 (2.25–12.91)
P value for PH assumption	0.40	0.15	0.64	0.61
C-index (95% CI) ‡	0.67 (0.63–0.77)	0.68 (0.63–0.79)		
Recurrent ischemic stroke (Cox frailty model)†				
aHR (95% CI)	2.93 (1.53–5.58)	2.77 (1.37–5.60)	1.47 (0.42–5.15)	5.51 (2.37–12.80)
P value for PH assumption	0.22	0.15	0.86	0.41
C-index (95% CI)‡	0.67 (0.62–0.77)	0.67 (0.63–0.78)		
All-cause mortality (Cox frailty model)§				
aHR (95% CI)	1.32 (0.97–1.80)	1.12 (0.77–1.61)	1.74 (1.09–2.78)	1.78 (1.08–2.93)
P value for PH assumption	0.06	0.054	0.85	0.12
C-index (95% CI)‡	0.81 (0.79–0.85)	0.82 (0.79–0.85)		

aHR indicates adjusted hazard ratio; CBI, covert brain infarction; C-index, concordance index; EA, embolic-appearing; NIHSS, National Institutes for Health Stroke Scale; and PH, proportional hazards.
*With the CBI (–) group as a reference.
†Adjusted for age, diabetes, current smoking, discharge anticoagulant, discharge antiplatelet, white matter hyperintensities (moderate to severe), and CHA_2DS_2-VASc score.
‡CI estimation is based on the percentile bootstrap method with 1000 replications.
§Adjusted for initial NIHSS and initial systolic blood pressure in addition to covariates listed above.

the 1-year cumulative incidence of recurrent stroke in the excluded patients was numerically lower compared to the analyzable population (2.4% versus 3.9%). Second, the cumulative incidence of recurrent stroke in the analyzable population was relatively low; 2.8% for stroke/TIA at 3 months (data not shown). It was much lower than 7.6% for the recurrent ischemic event (ischemic stroke, TIA, and systemic embolism) in an international multicenter observational study.[27] However, it was similar to 2.8% to 3.1% for recurrent stroke or systemic embolism in the Japanese stroke cohort with AF.[28] Intensive risk factor control and high rate of NOAC prescription in the participating centers that were mostly university hospitals or regional stroke centers could explain the low recurrence rate. Third, center effect could not be adjusted in the Fine and Gray model. To examine the robustness of the results, the Cox frailty model with adjustment for center clustering was applied and reported similar hazards of CBI. Fourth, cerebral ischemic burdens including new CBI, WMH progression, and cognitive decline were not evaluated in this study, which calls for caution in interpretation.[29] Moreover, more detailed information relating to AF, such as patterns and types of AF, left atrial enlargement, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) was not available. In addition, a possibility of overlapped stroke causes was undetermined.[30] Lacunes in the cortical medullary artery territory were classified into the EA pattern CBIs, based on the previous research[31] that they had a higher chance of having proximal embolic sources than lacunes in the penetrating artery territory, but this classification may be debatable. Further research is warranted. Lastly, the participating centers were university hospitals or regional stroke centers, and therefore, selection bias could be present. However, the risk of bias may have been minimized as the participating centers serve as regional stroke centers with high-density catchments for stroke admissions, and the age and sex distribution of our registry was nearly identical to that of a national report.[32]

In conclusion, our study suggests that in AIS patients with AF, a neuroimaging marker, CBI, is a familiar and useful marker for the prediction of stroke recurrence. These results warrant elucidation of the role of CBI in stroke risk estimation in stroke-free individuals with AF.

ARTICLE INFORMATION

Received January 30, 2022; final revision received September 2, 2022; accepted September 20, 2022.

The podcast and transcript are available at https://www.ahajournals.org/str/podcast.

Affiliations

Department of Neurology and Cerebrovascular Center (D.Y.K., S.-G.H., H.-G.J., K.-J.L., B.J.K., M.-K.H., H.-J.B.) and Department of Neurosurgery, Seoul National University Bundang Hospital (H.-G.J.), Seoul National University College of Medicine, Seongnam, Republic of Korea. Department of Neurology, Korea University Guro Hospital, Seoul, Republic of Korea (K.-J.L.). Department of Neurology, Chonnam National University Hospital, Gwangju, Republic of Korea (K.-H.C., J.-T.K.). Department of Neurology, Chungbuk National University Hospital, Cheongju, Republic of Korea (D.-I.S.). Department of Neurology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Republic of Korea (J.K.C., D.H.K.). Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Republic of Korea (D.-E.K., W.-S.R.). Artificial Intelligence R&D, JLK Corp, Seoul, Republic of Korea (W.-S.R.). Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Republic of Korea (J.-M.P.). Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Republic of Korea (K.K.). Department of Neurology, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Republic of Korea (J.G.K., S.J.L.). Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea (M.-S.O., K.-H.Y., B.-C.L.). Department of Neurology, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea (H.-K.P., K.-S.H., Y.-J.C.,). Department of Neurology, Jeju National University Hospital, Jeju National University School of Medicine, Republic of Korea (J.C.C.). Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea (S.I.S., J.-H.H.). Department of Neurology, Seoul Medical Center, Republic of Korea (T.H.P.). Department of Neurology, Soonchunhyang University Hospital, Seoul, Republic of Korea (K.B.L.). Department of Neurology, Ulsan University Hospital, Ulsan University College of Medicine, Republic of Korea (J.-H.K., W.-J.K.). Department of Neurology, Yeungnam University Hospital, Daegu, Republic of Korea (J.L.). Clinical Research Center, Asan Medical Center, Seoul, Republic of Korea (J.S.L.). Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea (J.L.). Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL (P.B.G.).

Sources of Funding

This study was supported in part by Bristol-Myers Squibb Korea and the Korea Centers for Disease Control and Prevention (no. 2020ER620200f). The funding sources did not participate in any part of the study, from conception to article preparation.

Disclosures

None.

Supplemental Material

Tables S1–S3
Figure S1
References 33–35

REFERENCES

1. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM, Andresen D, Camm AJ, Davies W, Capucci A, Olsson B, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest.* 2010;137:263–272. doi: 10.1378/chest.09-1584
2. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc.* 2013;2:1–10. doi: 10.1161/JAHA.113.000250
3. Kim BJ, Lee KJ, Park EL, Tanaka K, Koga M, Yoshimura S, Itabashi R, Cha JK, Lee BC, Akiyama H, et al. Prediction of recurrent stroke among ischemic stroke patients with atrial fibrillation: development and validation of a risk score model. *PLoS One.* 2021;16:e02583771–e02583715. doi: 10.1371/journal.pone.0258377
4. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, Wright C, Beiser AS, Seshadri S, Pandya A, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke.* 2016;47:719–725. doi: 10.1161/STROKEAHA.115.011889
5. Cha MJ, Park HE, Lee MH, Cho Y, Choi EK, Oh S. Prevalence of and risk factors for silent ischemic stroke in patients with atrial fibrillation as determined by brain magnetic resonance imaging. *Am J Cardiol.* 2014;113:655–661. doi: 10.1016/j.amjcard.2013.11.011
6. Kalantarian S, Ay H, Gollub RL, Lee H, Retzepi K, Mansour M, Ruskin JN. Association between Atrial fibrillation and silent cerebral infarctions: A systematic review and meta-analysis. *Ann Intern Med.* 2014;161:650–658. doi: 10.7326/M14-0538
7. Miki K, Nakano M, Aizawa K, Hasebe Y, Kimura Y, Morosawa S, Akashi T, Morishita Y, Miyata S, Fukuda K, et al. Risk factors and localization of silent cerebral infarction in patients with atrial fibrillation. *Hear Rhythm.* 2019;16:1305–1313. doi: 10.1016/j.hrthm.2019.03.013

8. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e44–e71. doi: 10.1161/STR.0000000000000116
9. Van Latum JC, Van Kooten F, Koudstaal PJ, Van Gijn J, Kappelle LJ, Algra A. Silent brain infarction in nonrheumatic atrial fibrillation. *Neurology*. 1996;46:159–165. doi: 10.1212/WNL.46.1.159
10. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, Cha JK, Kim DH, Nah HW, Han MK, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke*. 2015;17:38–53. doi: 10.5853/jos.2015.17.1.38
11. Lee KJ, Kim BJ, Han MK, Kim JT, Choi KH, Shin DI, Yeo MJ, Cha JK, Kim DH, Nah HW, et al. Effect of heart rate on stroke recurrence and mortality in acute ischemic stroke with atrial fibrillation. *Stroke*. 2020;51:162–169. doi: 10.1161/STROKEAHA.119.026847
12. Zhu YC, Dufouil C, Tzourio C, Chabriat H. Silent brain infarcts: a review of MRI diagnostic criteria. *Stroke*. 2011;42:1140–1145. doi: 10.1161/STROKEAHA.110.600114
13. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
14. Park HK, Lee JS, Hong KS, Cho YJ, Park JM, Kang K, Lee SJ, Kim JG, Cha JK, Kim DH, et al. Statin therapy in acute cardioembolic stroke with no guidance-based indication. *Neurology*. 2020;94:e1984–e1995. doi: 10.1212/WNL.0000000000009397
15. Lee HL, Kim JT, Lee JS, Kim BJ, Park JM, Kang K, Lee SJ, Kim JG, Cha JK, Kim DH, et al. CHA2DS2-VASc score in acute ischemic stroke with atrial fibrillation: results from the clinical research collaboration for stroke in Korea. *Sci Rep*. 2021;11:1–10. doi: 10.1038/s41598-020-80874-1
16. Sposato LA, Cerasuolo JO, Cipriano LE, Fang J, Fridman S, Paquet M, Saposnik G. Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence. *Neurology*. 2018;90:e924–e931. doi: 10.1212/WNL.0000000000005126
17. Ghaznawi R, Geerlings MI, Jaarsma-Coes M, Hendrikse J, de Bresser J. Association of white matter hyperintensity markers on MRI and long-term risk of mortality and ischemic stroke: the SMART-MR study. *Neurology*. 2021;96:e2172–e2183. doi: 10.1212/WNL.0000000000011827
18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbrouckef JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ*. 2007;85:867–872. doi: 10.1136/bmj.39335.541782.AD
19. Weber R, Weimar C, Wanke I, Möller-Hartmann C, Gizewski ER, Blatchford J, Hermansson K, Demchuk AM, Forsting M, Sacco RL, et al. Risk of recurrent stroke in patients with silent brain infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) imaging substudy. *Stroke*. 2012;43:350–355. doi: 10.1161/STROKEAHA.111.631739
20. European Atrial Fibrillation Trial Study. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255–1262. doi: 10.1016/0140-6736(93)92358-Z
21. Longstreth WT, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ, O'Leary D, Carr J, Furberg CD. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002;33:2376–2382. doi: 10.1161/01.str.0000032241.58727.49
22. Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, De Marchis GM, Polymeris A, Zedde ML, Yaghi S, et al. Causes and risk factors of cerebral ischemic events in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants for stroke prevention: the RENo study. *Stroke*. 2019;50:2168–2174. doi: 10.1161/STROKEAHA.119.025350
23. Conijn MMA, Kloppenborg RP, Algra A, Mali WPTM, Kappelle LJ, Vincken KL, Van Der Graaf Y, Geerlings MI. Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: The second manifestations of arterial disease-magnetic resonance (SMART-MR) study. *Stroke*. 2011;42:3105–3109. doi: 10.1161/STROKEAHA.110.594853
24. Wilson D, Ambler G, Banerjee G, Shakeshaft C, Cohen H, Yousry TA, Salman RAS, Lip GYH, Houlden H, Brown MM, et al. Early versus late anticoagulation for ischaemic stroke associated with atrial fibrillation: multicentre cohort study. *J Neurol Neurosurg Psychiatry*. 2019;90:320–325. doi: 10.1136/jnnp-2018-318890
25. Paciaroni M, Bandini F, Agnelli G, Tsivgoulis G, Yaghi S, Furie KL, Tadi P, Becattini C, Zedde M, Abdul-Rahim AH, et al. Hemorrhagic transformation in patients with acute ischemic stroke and atrial fibrillation: time to initiation of oral anticoagulant therapy and outcomes. *J Am Heart Assoc*. 2018;7:1–10. doi: 10.1161/jaha.118.010133
26. Wilson D, Ambler G, Lee KJ, Lim JS, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2019;18:653–665. doi: 10.1016/S1474-4422(19)30197-8
27. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF study. *Stroke*. 2015;46:2175–2182. doi: 10.1161/STROKEAHA.115.008891
28. Arihiro S, Todo K, Koga M, Furui E, Kinoshita N, Kimura K, Yamagami H, Terasaki T, Yoshimura S, Shiokawa Y, et al. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: the SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. *Int J Stroke*. 2016;11:565–574. doi: 10.1177/1747493016632239
29. Kühne M, Krisai P, Coslovsky M, Rodondi N, Müller A, Beer JH, Ammann P, Auricchio A, Moschovitis G, Hayoz D, et al. Silent brain infarcts impact on cognitive function in atrial fibrillation. *Eur Heart J*. 2022;1:9. doi: 10.1093/eurheartj/ehac020
30. Gutierrez J, Gil-Guevara A, Ramaswamy S, DeRosa J, Di Tullio MR, Cheung K, Rundek T, Sacco RL, Wright CB, Elkind MSV. Classification of covert brain infarct subtype and risk of death and vascular events. *Stroke*. 2020;51:90–98. doi: 10.1161/STROKEAHA.119.026068
31. Yonemura K, Kimura K, Minematsu K, Uchino M, Yamaguchi T. Small centrum ovale infarcts on diffusion-weighted magnetic resonance imaging. *Stroke*. 2002;33:1541–1544. doi: 10.1161/01.str.0000016961.01086.94
32. Park TH, Ko Y, Lee SJ, Lee KB, Lee J, Han MK, Park JM, Kim DE, Cho YJ, Hong KS, et al. Gender differences in the age-stratified prevalence of risk factors in Korean ischemic stroke patients: a nationwide stroke registry-based cross-sectional study. *Int J Stroke*. 2014;9:759–765. doi: 10.1111/ijs.12146
33. Vynckier J, Kaesmacher J, Wardlaw JM, Roten L, Beyeler M, Belachew NF, Grunder L, Seiffge DJ, Jung S, Gralla J, et al. Phenotypes of chronic covert brain infarction in patients with first-ever ischemic stroke: a cohort study. *Stroke*. 2022;53:558–568. doi: 10.1161/STROKEAHA.121.034347
34. Loos CMJ, Staals J, Wardlaw JM, Van Oostenbrugge RJ. Cavitation of deep lacunar infarcts in patients with first-ever lacunar stroke: a 2-year follow-up study with MR. *Stroke*. 2012;43:2245–2247. doi: 10.1161/STROKEAHA.112.660076
35. Liao S, Deng Z, Wang Y, Jiang T, Kang Z, Tan S. Different mechanisms of two subtypes of perforating artery infarct in the middle cerebral artery territory: a high-resolution magnetic resonance imaging study. *Front Neurol*. 2018;9:1–8. doi: 10.3389/fneur.2018.00657