Stroke is a clinically heterogeneous entity. Based on the heart disease and stroke statistics from the American Heart Association, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhages account for 87%, 10%, and 3% of all strokes, respectively.1 Approximately a quarter of all ischemic strokes are cryptogenic.2 Moreover, patients with atrial fibrillation (AF) had severe clinical presentation or sequelae of cerebral infarction compared to those without AF; hence, early detection of AF significantly improves patient prognosis and reduces the overall healthcare costs.3 Previous studies have reported that premature atrial contractions (PACs) and non-sustained atrial tachycardia (NSAT) observed on 24-hour Holter monitoring may predict undiagnosed AF.4,5 We investigated whether frequent PACs predicted new-onset AF and recurrent stroke in cryptogenic stroke patients with concomitant NSAT.

In cryptogenic stroke patients, early detection of new-onset atrial fibrillation (AF) and recurrent stroke is required to prevent poor clinical outcomes. Therefore, we investigated the predictors of new-onset AF and recurrent stroke in cryptogenic stroke patients without previously diagnosed AF. In total, 390 patients who were diagnosed with stroke and non-sustained atrial tachycardia (NSAT) on 24-hour Holter monitoring were followed up to assess new-onset AF and recurrent stroke. The 5-year event-free survival as well as the predictors of recurrent stroke or new-onset AF were investigated. Based on receiver operating characteristic analysis, frequent premature atrial contractions (PACs) were defined as PACs >44 beats/day. The median follow-up period was 35 months. The composite event rate was 11.5%. In Kaplan-Meier analysis, the 5-year cumulative incidence of composite events was higher in cryptogenic stroke patients with frequent PACs than in those without frequent PACs. Multivariate analysis revealed that current smoking, increased left atrial volume index, and frequent PACs were poor prognostic predictors of composite event, and frequent PACs were an independent poor prognostic factor of new-onset AF in cryptogenic stroke patients. Therefore, frequent PACs might be associated with poor clinical outcomes (new-onset AF and recurrent stroke) in cryptogenic stroke patients with concomitant NSAT.

Key Words: Cryptogenic stroke, premature atrial contraction, clinical outcome, atrial fibrillation, recurrent stroke

Frequent Premature Atrial Contractions as a Poor Prognostic Factor in Cryptogenic Stroke Patients with Concomitant Non-Sustained Atrial Tachycardia

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months. Based on a standard 12-lead ECG recording or a sin-
toms and undergo a standard 12-lead ECG recording every 3
more precisely. After enrollment, all of the patients regularly
brain imaging. New-onset AF is a working diagnosis in patients
transesophageal echocardiography. Therefore, in the
Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classi-
fication,6 etiologies of the enrolled patients were small vessel
disease and other determined and undetermined etiologies.
NSAT was diagnosed by 24-hour Holter monitoring on current
NSAT was defined as ≥3 consecutive PACs with a heart rate of >100 beats/min for <30 s. PAC was defined based
the following electrocardiographic parameters: 1) a short-
ened RR interval (≥25% reduction in interval duration), 2) oc-
currence of a P wave, and 3) QRS width <0.12 s. Within 7 days of
admission, all of the enrolled patients underwent transthoracic
echocardiography, transesophageal echocardiography, and
24-hour Holter monitoring. The enrolled patients were admit-
ted at three tertiary hospitals (Severance Hospital, Gangnam
Severance Hospital, and Kyung Hee University Hospital). This
study complied with the Declaration of Helsinki and was ap-
proved by the Institutional Review Board of the Gangnam Se-
verance Hospital, Seoul, South Korea (3-2020-0260). Written in-
fomed consent was obtained from all patients.

The exclusion criteria were as follows: 1) history of stroke or
tient ischemic attack; 2) history of a brain hemorrhage,
brain tumor, and cerebrovascular malformations; 3) known
tachyarrhythmias, including supraventricular tachyarrhyth-
mia; 4) status post of a permanent pacemaker; 5) presence of
atherosclerotic plaques involving the aorta or aortic arch and
the carotid artery; 6) history of structural heart disease; 7) sys-
tolic dysfunction (ejection fraction (EF); <50%); and 8) history
of neoplasm.

Patients were categorized into those without events (n=345)
and those with events (n=45). Electronic medical records of
the patients and relevant data were collected. After the first isch-
emic stroke event, the enrolled patients underwent standard
ECG, 24-hour Holter monitoring, and echocardiography to
identify cardioembolic sources of stroke. After that, antiplate-
let agents (aspirin, clopidogrel, or triflusal) were prescribed.
Recurrence stroke was defined as the occurrence of neurologi-
cal symptoms associated with objective evidence of lesions on
brain imaging. New-onset AF is a working diagnosis in patients
without a history of AF; until the pattern of AF can be defined
more precisely. After enrollment, all of the patients regularly
visited the outpatient clinics after discharge to check for symp-
toms and undergo a standard 12-lead ECG recording every 3
months. Based on a standard 12-lead ECG recording or a sin-
gle-lead ECG tracing lasting 30 seconds, heart rhythm with no
discernible repeating P waves and irregular RR intervals (when
atrioventricular conduction is not impaired) was diagnosed as
clinical AF.

According to the current American Society of Echocardiogra-
phy guidelines, all of the patients underwent Doppler echocar-
diography to measure the following echo parameters: 1) peak
early (E); 2) late diastolic mitral inflow velocities; 3) early dia-
static mitral annulus peak velocity (e') from the septal aspect of
the mitral annulus in the apical four-chamber view; 4) E/e' ratio,
with an E/e' ratio of >14 defined as the presence of dia-
stolic dysfunction; 5) EF, which was calculated by Modified
Simpson rule; 6) the left atrial (LA) anteroposterior diameter,
which was measured in a parasternal long-axis view at end-sys-
tole to determine the left atrium size; 7) LA volume, which was
measured by the ellipse method from the apical four-chamber
and parasternal long-axis views at ventricular end-systole; and
8) LA volume index (LAVi), which was used to adjust LA vol-
ume regarding body surface area.

Categorical and continuous variables are presented as num-
bars (percentages) and mean±standard deviation, respective-
ly. Baseline clinical characteristics were compared between
patients with and without composite events using Student's t-
test for continuous variables and the chi-square test for cate-
gorical variables. A p-value <0.05 was considered statistically
significant. The Youden index based on receiver operating char-
acteristic was used to determine the optimal cutoff value for
composite events. Based on the area under the receiver operat-
ing characteristic curve value (0.602), PACs >44 beats/day
were defined as frequent PACs (sensitivity: 71% and specifici-
ity: 52%). Kaplan-Meier survival curves and log-rank test were
used to compare the 5-year cumulative incidence of compos-
ite events between patients with and without frequent PACs.
Univariate and multivariate Cox proportional hazards regres-
sion analyses were performed to determine independent poor
predictors of composite events. Variables with a p-value <0.20
in univariate analysis or those considered relevant predictors
of clinical events were included in the multivariate analysis. All
statistical analyses were performed using the SPSS software
version 25.0 (IBM Corp., Armonk, NY, USA).

The mean age of the 390 patients was 67 years. No statistically
significant intergroup differences were noted in the base-
line clinical characteristics, including the mean age (p=0.110).
However, compared to patients without clinical events, those
with clinical events had a larger LA diameter (36.2 mm vs. 37.7
mm, p=0.044), LA volume (40.5 mm3 vs. 46.1 mm3, p=0.003),
and LAVi (24.1 mm3/m2 vs. 28 mm3/m2, p=0.005) (Table 1). The
median follow-up period was 35 months, and the composite
event rate was 11.5% (45/390). With regard to individual clini-
cal events, the rate of new-onset AF was 3.1%, and that of stroke
recurrence was 9%. Kaplan-Meier analysis revealed that the 5-
year cumulative incidence of composite events (new-onset
AF and recurrent stroke) was significantly higher among cryp-
togenic stroke patients with frequent PACs than among those
without frequent PACs (15.2% vs. 7.2%, log-rank \(p=0.003\)) (Fig. 1A). In addition, individual Kaplan-Meier analysis revealed that compared to cryptogenic stroke patients without frequent PACs, those with frequent PACs had a higher rate for new-onset AF (4.8% vs. 1.1%, log-rank \(p=0.006\)) (Fig. 1B) and recurrent stroke (11.4% vs. 6.1%, log-rank \(p=0.031\)) (Fig. 1C).

Univariate and multivariate Cox proportional hazard regression analyses were performed to investigate the predictors of composite events in cryptogenic stroke patients (Table 2). Univariate analysis revealed that age [hazards ratio (HR): 1.03, 95% confidence interval (CI): 1.00–1.06, \(p=0.049\)], LAVi (HR: 1.07, 95% CI: 1.03–1.10, \(p=0.002\)), and frequent PACs (HR: 2.62, 95% CI: 1.37–5.02, \(p=0.004\)) were poor predictors for composite event in cryptogenic stroke patients. Multivariate analysis revealed that cigarette smoking status (HR: 2.07, 95% CI: 1.12–3.84, \(p=0.021\)), LAVi (HR: 1.05, 95% CI: 1.01–1.08, \(p=0.006\)), and frequent PACs (HR: 2.30, 95% CI: 1.16–4.56, \(p=0.017\)) were independent poor prognostic factors in cryptogenic stroke patients with concomitant NSAT after adjusting for confounders such as age, sex, EF diastolic dysfunction (E/e’ >14), LAVi, hypertension, diabetes, coronary artery disease, chronic kidney disease, cigarette smoking status, and frequent PACs. Additionally, multivariate analysis for individual events revealed that compared with cryptogenic stroke patients without frequent PACs, those with frequent PACs had a higher risk of new-onset AF (HR: 5.34, 95% CI: 1.10–25.85, \(p=0.037\)) but not of stroke recurrence (HR: 1.99, 95% CI: 0.94–4.20, \(p=0.072\)).

The main findings of this study are as follows: 1) frequent PACs are a poor prognostic factor for clinical outcomes in cryptogenic stroke patients and 2) frequent PACs are associated with new-onset AF in cryptogenic stroke patients. In context, we suggest that cryptogenic stroke patients with risk factors for poor predictors should be considered for close and prolonged follow-up with cardiac rhythm monitoring to improve clinical outcomes.

We found that frequent PACs were a poor prognostic factor for clinical outcomes in cryptogenic stroke patients with NSAT and no previously diagnosed AF. The definition of frequent PACs remains unclear. Previous studies have defined frequent PACs based on their study results, which represent a subjective interpretation,\(^8\)-\(^10\); nevertheless, compared to cryptogenic stroke patients without frequent PACs, those with frequent PACs had poor clinical outcomes.\(^8\)-\(^10\) Another study reported that the PAC burden detected by Holter monitoring might be associated with clinical outcomes.\(^11\)

Although various studies have reported an association between frequent PACs and poor clinical outcome, the exact pathomechanism remains unclear. In our study, frequent PACs were associated with poor clinical outcomes in composite event and new-onset AF, but not with recurrent stroke. Plausible reasons may

### Table 1. Patient Characteristics

|                      | Total (n=390) | Composite outcomes | p     |
|----------------------|--------------|--------------------|-------|
|                      |              | No event (n=345)   | Event (n=45) |
| Age (yr)             | 66.7±11.9    | 66.4±11.7          | 69.4±13.0 | 0.110 |
| Male sex             | 219 (56.2)   | 195 (56.5)         | 24 (53.3) | 0.806 |
| Hypertension         | 273 (70.0)   | 237 (68.7)         | 36 (80.0) | 0.167 |
| Diabetes             | 107 (27.4)   | 99 (28.7)          | 8 (17.8)  | 0.172 |
| Dyslipidemia         | 160 (41.0)   | 143 (41.4)         | 17 (37.8) | 0.757 |
| Chronic kidney disease | 17 (4.4)    | 13 (3.8)           | 4 (8.9)   | 0.232 |
| Vascular disease     | 12 (3.1)     | 10 (2.9)           | 2 (4.4)   | 0.916 |
| Coronary artery disease | 41 (10.5)   | 37 (10.7)          | 4 (8.9)   | 0.905 |
| Cigarette smokers    | 148 (37.9)   | 127 (36.8)         | 21 (46.7) | 0.264 |

Echocardiographic parameters

|                  | Total (n=390) | No event (n=345) | Event (n=45) | p     |
|------------------|--------------|------------------|--------------|-------|
| LA diameter (mm) | 36.4±4.5     | 36.2±4.4         | 37.7±5.0     | 0.044 |
| LA volume (mm\(^3\)) | 41.2±11.8 | 40.5±11.5        | 46.1±12.9    | 0.003 |
| LA volume index (mm\(^3\)/m\(^2\)) | 24.5±5.9 | 24.1±5.5         | 28.0±8.6     | 0.005 |
| LVEF (%)         | 66.6±8.8     | 66.7±8.7         | 66.0±9.1     | 0.612 |
| LV mass index (g/m\(^2\)) | 105.1±28.9 | 112.4±40.2       | 13.5±6.2     | 0.082 |
| E/e’             | 12.0±4.5     | 11.8±4.1         | 13.5±6.2     | 0.082 |
| PACs (n)         | 541.0±2565.7 | 537.4±2608.8     | 568.5±2233.7 | 0.939 |
| Frequent PACs    | 210 (53.8)   | 178 (51.6)       | 32 (71.1)    | 0.017 |

Medication

|                  | Total (n=390) | No event (n=345) | Event (n=45) | p     |
|------------------|--------------|------------------|--------------|-------|
| Aspirin          | 301 (77.2)   | 264 (76.5)       | 37 (82.2)    | 0.504 |
| Triflusal        | 203 (52.1)   | 182 (52.8)       | 21 (46.7)    | 0.542 |
| Clopidogrel      | 30 (7.7)     | 29 (8.4)         | 1 (2.2)      | 0.243 |

LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PAC, premature atrial contractions.

Data are presented as n (%).
be that PACs are known precursors of AF, which is a potential risk factor for stroke.\textsuperscript{5,12} Previous studies have reported an association between PACs and AF in cryptogenic stroke patients\textsuperscript{12-14} and proved that frequent PACs or consecutive supraventricular extrasystoles, such as NSAT, are associated with a higher prevalence of AF.\textsuperscript{12-14} In our results, frequent PACs was defined as PACs >44 beats/day using the Youden index based on the receiver operating characteristic. The cut-off value used in our study was relatively small compared to that in the aforementioned study. However, despite the relatively small number of PAC, our results revealed that patients with frequent PACs had a potential risk of hidden AF. Therefore, intensive observation with a 12-lead ECG recording or the usage of a loop recorder for patients who have frequent PAC may offer better clinical outcomes by early detection of new-onset AF.

In addition, our results revealed that increased LAVi was a poor predictor of clinical outcomes. Previous studies have suggested LAVi as a risk factor for cardioembolic stroke.\textsuperscript{15,16} Also, Atrial stretch\textsuperscript{17} and atrial tissue alterations\textsuperscript{18} in an enlarged left atrium are associated with disturbances in impulse propagation in patients with AF suggesting that left atrium enlargement may increase the atrial ectopy rate and, consequently, the risk of stroke.\textsuperscript{19} In addition, the association between smoking status and recurrent stroke is statistically significant.

The smoking aggravates atherosclerosis and stroke occurrence by an increase of oxidative stress, endothelial dysfunction, and inflammation.\textsuperscript{20,21} In addition, smoking increases the risk of recurrent stroke.\textsuperscript{22} Furthermore, we suggest that patients with the abovementioned risk factors should be considered as having a high risk of poor clinical outcomes. Therefore, close monitoring of frequent PACs with 24-hour Holter monitoring or wearable devices for detecting arrhythmia may contribute to better clinical outcomes in cryptogenic stroke patients.

This study had some limitations. First, since this was a retrospective study based on data from three tertiary referral hospitals, the possibility of selection and referral bias cannot be excluded. Second, the study population was relatively small, and the study lacked follow-up 24-hour Holter monitoring. Third, the statistical model in the multivariate analysis may not have accurately analyzed unmeasured confounding factors, such as the patients’ general health condition and the three-dimensional techniques used in transthoracic echocardiography. Therefore, frequent PACs are significantly associated with poor clinical outcomes in cryptogenic stroke patients with concomitant NSAT.

Table 2. Adjusted Multivariate Risk of Frequent PACs for Subsequent 5-Year Clinical Events

| Event rate at 5 year (unadjusted) | Without frequent PACs (n=180) | With frequent PACs (n=210) | Adjusted HR of frequent PACs (95% CI) | p value |
|----------------------------------|-----------------------------|-----------------------------|--------------------------------------|--------|
| Composite events                 | 7.2% (13)                   | 15.2% (32)                  | 2.30 (1.16–4.56)                     | 0.017  |
| New-onset atrial fibrillation    | 1.1% (2)                    | 4.8% (10)                   | 5.34 (1.10–25.85)                    | 0.037  |
| Recurrent stroke                 | 6.1% (11)                   | 11.4% (24)                  | 1.99 (0.94–4.20)                     | 0.072  |

HR, hazard ratio; PAC, premature atrial contraction; CI, confidence interval.
Rates are Kaplan-Meier estimates at 5 year (number of events). P value corresponds to the adjusted HR (95% CI). All clinical endpoints were adjusted by age, sex, EF, diastolic dysfunction (E/e’ >14), LAVi, hypertension, diabetes, coronary artery disease, chronic kidney disease, cigarette smoking status, and frequent PACs.
AUTHOR CONTRIBUTIONS

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