An Approach to Working Up Cases of Embolic Stroke of Undetermined Source

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Background—From a therapeutic viewpoint, it is important to differentiate the underlying causes of embolism in patients with cryptogenic stroke, such as aortic arch atheroma, patent foramen ovale, and paroxysmal atrial fibrillation. We investigated the clinical and radiological characteristics of these 3 common causes of cryptogenic embolism to develop models for decision making in etiologic workups.

Methods and Results—A total of 321 consecutive patients with acute infarcts from cryptogenic embolism were included. Patients were divided into 3 groups—aortic arch atheroma (n=40), patent foramen ovale (n=153), and paroxysmal atrial fibrillation (n=128)—based on extensive cardiologic workups. We used a multinomial logistic regression analysis to detect the clinical and diffusion-weighted imaging factors associated with the probability of aortic arch atheroma, patent foramen ovale, and paroxysmal atrial fibrillation. Clinical and radiological features differed among the groups. The patent foramen ovale group had a healthy vascular risk factor profile and showed posterior circulation involvement compared with other groups (P<0.01). In contrast, paroxysmal atrial fibrillation–related strokes had higher initial National Institutes of Health Stroke Scale (NIHSS) scores and larger lesions than the other groups (P<0.001). The aortic arch atheroma group had clinical features similar to those of the paroxysmal atrial fibrillation group but showed small lesions scattered in multiple vascular territories (P<0.001). Multivariate regression analysis revealed that age, initial NIHSS score, lesion size (≥20 mm), multiple (≥3) lesions, and involvement of posterior circulation or multiple vascular territories differentiated the 3 groups (pseudo, R²=0.656). The prediction ability of this model was validated in the external validation cohort (n=117, area under the curve 0.78).

Conclusions—Our data indicate that patients with cryptogenic embolic stroke show distinct clinical and radiological features depending on the underlying causes. (J Am Heart Assoc. 2016;5:e002975 doi:10.1161/JAHA.115.002975)

Key Words: cerebral infarction • diagnosis • embolic stroke of undetermined etiology • embolism
(TEE), for example, may reveal high-risk sources with indication for oral anticoagulation, improvident use may inadver-
tently lead to a rise in cases with ≥2 determined causes. Patent foramen ovale (PFO) is prevalent in both the general
population and among stroke patients, whereas aortic arch
atheroma (AAA) is commonly observed in elderly patients with
multiple vascular risk factors. The probability of having PFO or
AAA as a cause of, or coincident with, stroke should be
weighted in patients with embolic stroke of undetermined source along with PFO or AAA.6

Diagnostic investigations of suspected cases of embolic stroke of undetermined source, particularly with advanced
diagnostic techniques, should be guided and chosen in
accordance with patient characteristics at the time of clinical
presentation. The cost-effectiveness of advanced diagnostic
technologies will greatly depend on the appropriate selection
of patients for the various diagnostic tests. Kent and
colleagues recently reported on the clinical and imaging
characteristics of PFO that are likely to be stroke related or
incidental, using the Risk of Paradoxical Embolism (RoPE)
score7; however, no studies have evaluated the probability of
PAF, PFO, and AAA in patients with embolic stroke of
undetermined source. In the current study, we investigated
the clinical and radiological characteristics of these 3
common causes of embolic stroke of undetermined source to
develop a prediction model to help with decision making
during etiologic workups.

Methods

Patients and Workups

Two separate data sets from different hospitals were used to
develop and validate a prediction model. For model develop-
ment, we prospectively recruited patients with acute ischemic
stroke who were admitted to the Samsung Medical Center (a
tertiary university hospital in Seoul, Republic of Korea) from
September 2008 through September 2014. We used a
prospective cohort from the Ajou University Hospital (a
tertiary university hospital in Suwon, Republic of Korea) during
the same period to test the model’s performance. From
patients who experienced focal or lateralizing neurological
symptoms within 7 days from onset and had relevant lesions
on diffusion-weighted imaging (DWI), we enrolled patients
with stroke due to an undetermined cause at the time of
admission. All patients underwent ECG and brain magnetic
resonance imaging and magnetic resonance angiography in
the emergency room. We excluded patients if they had a
determined cause of stroke before admission, based on the
Stop Stroke Study Trial of Org 10172 in Acute Stroke
Treatment (SSS-TOAST; eg, significant stenosis of relevant
arteries on magnetic resonance angiography or atrial fibrilla-
tion [usually permanent] on the first ECG). Local institutional
review boards approved this study. All participants or patient
guardians provided informed consent.

The following data were systematically collected: demo-
graphic information; medical history of vascular risk factors
such as hypertension, diabetes mellitus, dyslipidemia, and
smoking history; and initial National Institutes of Health
Stroke Scale (NIHSS) scores. In addition, we performed
extensive workups, including repetitive ECGs, transthoracic
echocardiography or TEE, echo bubble tests or transcranial
right-to-left shunt tests, multidetector row computed tomog-
raphy (MDCT), and cardiac telemetry (≥72 hours). The
transcranial right-to-left shunt test is based on the intracranial
detection of intravenously injected microemboli. The size and
functional relevance of a right-to-left shunt can be assessed
more easily using transcranial Doppler ultrasound, with
sensitivity and specificity similar to TEE.8

Based on the results of the extensive cardiology workups,
patients were divided into 3 groups: AAA (n=40), PFO
(n=153), and PAF (n=128) (Figure 1). AAA was considered
as a cause of stroke if vulnerable AAA was observed on the
TEE or MDCT. Vulnerable AAA was defined as aortic plaques
in the ascending aorta or proximal arch that met ≥1 of the
following criteria: (1) ≥4 mm of intima–media thickness on
TEE or ≥6 mm of thickness adjacent to the aortic wall on
MDCT or (2) ulcerated plaque or (3) mobile plaque on TEE or
soft plaque on MDCT.9,10 We performed the TEE or transcran-
ial Doppler ultrasound agitated saline test or MDCT to
evaluate PFO. PFO was deemed present when 1 of following
criteria was observed: (1) the passage of >3 microbubbles to
the left atrium within 3 cardiac cycles after complete
opacification of the right atrium on the TEE, (2) microembolic
signals within 40 seconds after injection of agitated saline
with microbubbles on the transcranial Doppler ultrasound, or
(3) a distinct flap in the left atrium at the expected location of
the septum primum or a continuous column of contrast
material connecting both atria or jet of contrast material into
the right atrium on the MDCT.11–13 Patients in the PAF group
were those who had no history or ECG findings of atrial
fibrillation at admission, but PAF was diagnosed using
repetitive ECGs or 72-hour cardiac telemetry. If patients
had PAF plus PFO or AAA, patients were classified as
belonging to the PAF group because the current evidence-
based classification system classifies PAF as a high-risk
embolic source and PFO and AAA as low or uncertain sources
of embolism.14 Few patients had both AAA and PFO, and they
were excluded from this analysis.

Image Analysis

All participants underwent 3-T magnetic resonance imaging
including DWI (Achieva; Phillips Medical System). In the
development set, the DWI parameters were as follows: repetition time 3000 ms, echo time 80 ms, matrix number 128×128, 2 b values of 0 and 1000 s/mm², slice thickness 5 mm, interslice gap 2 mm, 22 axial slices, and field of view 240 mm. In the validation set (Intera, Achieva; Philips Healthcare), the parameters were as follows: repetition time 3300, echo time 77 ms, matrix number 128×128, 2 b values of 0 and 1000 s/mm², slice thickness 5 mm, 28 axial slices, and field of view 220 mm. We analyzed lesions noted on DWI in terms of their size, number, and distribution. The largest diameter of each lesion was measured, and each lesion was divided into small or large lesions based on a threshold of 20 mm. We manually counted the number of lesions on DWI. We evaluated DWI lesion distribution based on the involved structure (eg, cortex, subcortex, or both) or the involved vascular territory (eg, anterior or posterior circulation). The involvement of multiple vascular territories was noted when multiple lesions on DWI were located (1) in unilateral anterior and posterior circulation, (2) in bilateral anterior circulation, or (3) in bilateral anterior and posterior circulation.

Figure 1. Patient selection. Among 368 patients excluded due to undetermined etiology, 21 had 2 of 3 embolic source categories. AAA indicates aortic arch atheroma; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PAF, paroxysmal atrial fibrillation; PFO, patent foramen ovale; TIA, transient ischemic attack.
Statistical Analysis

Descriptive demographic, clinical, and radiological data are shown as mean±SD or numbers and frequencies, as appropriate. We analyzed the differences among the groups using a chi-square or Mann–Whitney test for discrete variables and 1-way ANOVA or Kruskal–Wallis tests for continuous variables. We used a multinomial regression analysis to detect the clinical and DWI factors associated with the 3 groups: AAA, PFO, and PAF. To develop the prediction model, we used a generalized logit model for the nominal response data after selecting the variables with \( P < 0.05 \) in the univariate analysis with the development data set. Multicollinearity was checked using a variance inflation factor; there were no variables with a variance inflation factor >10. The Bonferroni method was used to correct for multiple testing of three. The prediction model was validated externally in a different cohort (n=117).

All analyses were performed using commercially available SPSS version 20 (IBM Corp), SAS version 9.3 (SAS Institute), and R version 3.1.1 (R Foundation for Statistical Computing). A 2-sided \( P < 0.05 \) was considered statistically significant.

Results

Clinical Characteristics

Of the patients with embolic stroke of undetermined source at the time of admission, we included 321 patients with 1 of 3

Table 1. Clinical and Radiological Characteristics

|                         | AAA (n=40) | PFO (n=153) | PAF (n=128) | P Value |
|-------------------------|------------|-------------|-------------|---------|
| **Clinical characteristics** |            |             |             |         |
| Age, years, median (IQR) | 72.5 (68.0–78.8) | 56.0 (46.0–66.0) | 72.0 (63.0–80.0) | <0.001 |
| Male sex, n (%)          | 29 (72.5)  | 107 (69.9)  | 70 (54.7)   | 0.015   |
| Hypertension, n (%)      | 33 (82.5)  | 57 (37.3)   | 88 (68.8)   | <0.001  |
| Diabetes mellitus, n (%) | 6 (15.0)   | 24 (15.7)   | 23 (18.0)   | 0.844   |
| Dyslipidemia, n (%)      | 16 (40.0)  | 34 (22.2)   | 35 (27.3)   | 0.087   |
| Coronary artery disease, n (%) | 2 (5.0) | 6 (3.9) | 12 (9.4) | 0.162 |
| Current smoker, n (%)    | 15 (37.5)  | 47 (30.7)   | 17 (13.3)   | 0.001   |
| Metabolic syndrome, n (%)| 4 (10.0)   | 19 (12.4)   | 15 (11.7)   | 0.971   |
| Initial NIHSS, median (IQR) | 1 (0–3) | 1 (0–4) | 7 (2–16) | <0.001 |
| **Radiological characteristics** | | | | |
| Size                     |            |             |             |         |
| Largest diameter, mm, median (IQR) | 11.8 (8.1–14.4) | 16.4 (9.4–38.4) | 47.9 (27.2–74.3) | <0.001 |
| ≥20 mm, n (%)            | 7 (17.5)   | 63 (41.2)   | 107 (83.6)  | <0.001  |
| Composition              |            |             |             | <0.001  |
| Small lesions only, n (%)| 31 (77.5)  | 75 (49.0)   | 13 (10.2)   |         |
| Small and large lesions, mixed, n (%) | 1 (2.5) | 52 (34.0) | 83 (64.8) |         |
| Large lesions only, n (%) | 8 (20.0)  | 26 (17.0)   | 32 (25.0)   |         |
| Distribution             |            |             |             |         |
| Involved vascular territory |        |             |             |         |
| Posterior circulation, n (%) | 5 (12.5) | 65 (42.5) | 21 (16.4) | <0.001 |
| Multiple vascular territories, n (%) | 19 (47.5) | 17 (11.1) | 9 (7.0) | <0.001 |
| Involved structure        |            |             |             |         |
| Cortical lesions only, n (%) | 9 (22.5) | 33 (21.6) | 39 (30.5) | 0.211 |
| Subcortical lesions only, n (%) | 9 (22.5) | 58 (37.9) | 15 (11.7) | <0.001 |
| Multiplicity              |            |             |             |         |
| Number of lesions, median (IQR) | 4 (2–13) | 1 (1–3) | 1 (1–2) | <0.001 |
| ≥3 lesions, n (%)         | 29 (72.5)  | 49 (32.5)   | 30 (23.4)   | <0.001 |

AAA indicates aortic arch atheroma; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PAF, paroxysmal atrial fibrillation; PFO, patent foramen ovale.

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etiologies: AAA in 40 (12.5%), PFO in 153 (47.7%), and PAF in 128 (39.9%) patients. Table 1 shows the clinical characteristics of these 3 groups. Patients with PFO were younger than patients in the other 2 groups (PFO: aged 55.5 years; AAA: aged 72.9 years; PAF: aged 71.6 years; \( P<0.001 \)). Hypertension was more frequent in the AAA group \( (P<0.001) \). The proportion of current smokers was lowest among the PAF–stroke patients. PAF–stroke patients experienced the most severe neurological deficits at presentation (median NIHSS score: PAF 7 [interquartile range 2–16]; AAA 1 [interquartile range 0–3]; PFO 1 [interquartile range 0–4]; \( P<0.001 \)).

Radiological Characteristics

The DWI lesion patterns were different among the 3 groups (Table 1 and Figure 2). Lesions in the AAA group were smaller than lesions in the other groups (largest lesion diameter: AAA: 11.8 mm; PFO: 16.4 mm; PAF: 47.9 mm; \( P<0.001 \)). Most of the patients (77.5%) in the AAA group had only small lesions, whereas patients in the PAF group showed larger lesions; many of them (64.8%) had no small lesions. Involved vascular territories and anatomical structures were also different. Approximately half of the patients (47.5%) with AAA showed lesions in multiple vascular territories, whereas involvement of a single vascular territory was more frequent in the PFO and PAF groups (88.9% and 93.0%, respectively; \( P<0.001 \)). A higher proportion of patients in the PFO group had lesions involving posterior circulation compared with other groups (PFO: 42.5%; AAA: 12.5%; PAF: 16.4%; \( P<0.001 \)). More than one-third of PFO patients (37.9%) had lesions restricted to the subcortical areas \( (P<0.001) \). In terms of lesion multiplicity, the AAA group had a greater number of lesions compared with the PFO and PAF groups (median DWI lesion number: AAA: 4; PFO: 1; PAF: 1; \( P<0.001 \)). Thirty-two patients (80.0%) in the AAA group showed multiple lesions on DWI, whereas more than half of the patients in the other groups had a single lesion (PFO: 55.6%; PAF: 60.9%).

The Prediction Model for AAA, PFO, and PAF

The prediction model was constructed using the development data set (\( n=321 \)). We selected the following aforementioned variables: age, hypertension, current cigarette smoking, initial NIHSS score, the presence of large lesions (largest lesion diameter \( \geq 20 \) mm), subcortical involvement, posterior circulation involvement, multiple vascular territory involvement, and lesion multiplicity (\( \geq 3 \) lesions) (Table 2). NIHSS scores were transformed using a natural log considering its skewed distribution. Age, hypertension, initial NIHSS score, large lesion presence, posterior circulation involvement, multiple vascular territory involvement, and lesion multiplicity were independent predictors of AAA, PFO, and PAF \( (\text{pseudo, } R^2=0.656) \). Based on these results, the probability equations for each group were generated:
Table 2. Multinomial Logistic Regression Analysis for AAA, PFO, and PAF

|                      | PFO vs AAA* | PAF vs PFO* | PAF vs AAA* |
|----------------------|-------------|-------------|-------------|
| **Chi-Square**       | **df**      | **P Value** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| Age                  | 40.9        | 2           | <0.001      | 1.08 (1.04–1.12) | 0.001 | 0.95 (0.89–1.01) | 0.164 |
| NIHSS                | 8.3         | 2           | 0.016       | 1.43 (0.7–2.93) | 0.694 | 1.53 (0.95–2.47) | 0.098 | 2.19 (1.06–4.55) | 0.030 |
| Hypertension         | 8.7         | 2           | 0.013       | 0.26 (0.07–1.04) | 0.059 | 2.24 (0.96–5.23) | 0.068 | 0.59 (0.14–2.51) | 1.000 |
| Current smoking      | 5.0         | 2           | 0.081       | 0.4 (0.11–1.45) | 0.261 | 0.65 (0.24–1.76) | 0.915 | 0.26 (0.06–1.1) | 0.075 |
| Large lesion (≥20 mm)| 20.8        | 2           | <0.001      | 3.21 (0.72–14.42) | 0.189 | 4.12 (1.56–10.88) | 0.002 | 13.24 (2.82–62.2) | <0.001 |
| Involving posterior  | 7.4         | 2           | 0.025       | 3.86 (0.72–20.79) | 0.166 | 0.4 (0.15–1.06) | 1.000 | 1.56 (0.26–9.17) | 0.072 |
| circulation          |             |             |             |                  |       |             |       |                  |       |
| Involving subcortex  | 2.6         | 2           | 0.266       | 0.69 (0.14–3.32) | 1.000 | 0.55 (0.19–1.58) | 0.528 | 0.38 (0.07–2.03) | 0.503 |
| Multiple vascular    | 9.4         | 2           | 0.009       | 0.23 (0.05–1.02) | 0.054 | 0.53 (0.11–2.49) | 0.983 | 0.12 (0.02–0.69) | 0.011 |
| territories          |             |             |             |                  |       |             |       |                  |       |
| Multiple lesions (≥3 lesions) | 11.7  | 2 | 0.003 | 0.44 (0.11–1.87) | 0.530 | 0.33 (0.12–0.9) | 0.025 | 0.15 (0.03–0.67) | 0.007 |

AAA indicates aortic arch atheroma; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PFO, patent foramen ovale.

*Indicates reference group used in the analyses.

The following equations for the PFO and PAF prediction scores were generated using the results from a generalized logit model (Table 3): prediction score (PFO)=10.200–0.124×age (yr)+0.366×ln(NIHSS score+1)–1.357×hypertension+1.321×large lesion+1.090×posterior lesion–0.905×multiple lesion–1.255×multiple territory; Prediction score (PFO)=-3.104–0.038×age (yr)+0.799×ln(NIHSS score+1)–0.567×hypertension+2.883×large lesion+0.112×posterior lesion–1.951×multiple lesion–1.794×multiple territory (for categorical variables, “1” was entered if the variable was indicated; otherwise, “0” was entered) (Data S1). The area under the curve of the prediction model was 0.79 (95% CI 0.76–0.82) based on the development data set, which we used for internal validation.

Table 3. Multivariable Associations of the Selected Factors With AAA, PFO, and PAF

|                      | AAA* vs PFO | AAA* vs PAF | PFO* vs PAF |
|----------------------|-------------|-------------|-------------|
|                      | **P Value** | **Coefficient** | **P Value** | **Coefficient** | **P Value** | **Coefficient** |
| Intercept            | 10.200      | 3.104       | –7.096      |
| Age                  | <0.001      | –0.124      | 0.438       | –0.038       | <0.001      | 0.086       |
| NIHSS                 | 0.655       | 0.366       | 0.024       | 0.799       | 0.087       | 0.433       |
| Hypertension          | 0.396       | –1.357      | 0.982       | –0.567      | 0.070       | 0.790       |
| Large lesion (≥20 mm) | 0.095       | 1.321       | <0.001      | 2.883       | <0.001      | 1.561       |
| Involving posterior  | 0.252       | 1.090       | >0.999      | 0.112       | 0.041       | –0.979      |
| circulation          |             |             |             |             |             |             |
| Multiple vascular    | 0.101       | –1.255      | 0.031       | –1.794      | >0.999      | –0.540      |
| territories          |             |             |             |             |             |             |
| Multiple lesions (≥3 lesions) | 0.101  | –0.905      | 0.002       | –1.951      | 0.030       | –1.046      |

AAA indicates aortic arch atheroma; NIHSS, National Institutes of Health Stroke Scale; PAF, paroxysmal atrial fibrillation; PFO, patent foramen ovale.

*Indicates reference group used in the analyses.

NIHSS was transformed using natural log, ln(NIHSS+1).
External Validation of the Prediction Model

The clinical and radiological characteristics from the validation data set (n = 117) were comparable with the development data set (Table 4). The prediction ability of the model was adequate in the validation cohort, with an area under the curve of 0.78 (95% CI 0.68–0.86). When a patient was allocated to the highest predicted probability among the 3 groups, the accuracy was 72.7%. Three representative cases with application of prediction models for AAA, PFO, and PAF are shown in Figure 3.

Discussion

In the present study, we observed distinct clinical and radiological characteristics for AAA, PFO, and PAF patients. Based on these characteristics, we developed an equation to predict the most probable etiology underlying cryptogenic embolisms.

Our data showed that the clinical features and lesion topography (infarct pattern and distribution) might provide clues regarding the causes of embolic stroke of undetermined source. This knowledge of the clinical and radiological features of embolic strokes of undetermined source will help physicians understand the pathogenic mechanisms involved in stroke development. Interestingly, vascular risk factor profile and infarct pattern were quite distinct among the 3 causes of embolic stroke of undetermined source. PFO primarily consisted of younger patients with a relatively healthy risk factor profile and posterior distribution, whereas AAA consisted of elderly patients with a high-risk profile and small cortical or border zone infarcts. PAF consisted of elderly patients with a relatively healthy risk factor profile (compared with those with AAA) and large cortical infarcts.

Our results are in line with previous PFO studies investigating the clinical characteristics and DWI patterns of PFO-related stroke from component databases in the RoPE study and the autopsy study of cholesterol emboli from vulnerable AAA. A brain single-photon emission computed tomography study showed that during the Valsalva maneuver, the rate of blood flow in the posterior circulation was higher than that in the anterior circulation, which could be a possible explanation.

Table 4. Comparison of Clinical and Radiological Characteristics Between the Development Data Set and the Validation Data Set

| Clinical characteristic                      | Samsung Medical Center (n=321) | Ajou University Hospital (n=117) | P Value |
|--------------------------------------------|--------------------------------|---------------------------------|---------|
| Age, years, median (IQR)                   | 66.0 (54.5–75.0)               | 62.0 (50.0–73.0)                | 0.081   |
| Male sex, n (%)                            | 206 (64.2)                     | 73 (62.4)                       | 0.732   |
| Hypertension, n (%)                        | 178 (55.5)                     | 71 (60.7)                       | 0.328   |
| Diabetes mellitus, n (%)                   | 53 (16.5)                      | 15 (12.8)                       | 0.345   |
| Dyslipidemia, n (%)                        | 85 (26.5)                      | 27 (23.1)                       | 0.470   |
| Coronary artery disease, n (%)             | 20 (6.2)                       | 10 (8.5)                        | 0.396   |
| Current smoker, n (%)                      | 79 (24.6)                      | 25 (21.4)                       | 0.480   |
| Metabolic syndrome, n (%)                  | 101 (31.9)                     | 47 (40.2)                       | 0.105   |
| Initial NIHSS, median (IQR)                | 3 (1–8)                        | 3 (1–7)                         | 0.661   |

| Radiological characteristics               |                                |                                 |         |
|--------------------------------------------|--------------------------------|---------------------------------|---------|
| Size                                        |                                |                                 |         |
| Largest diameter, ≥20 mm, n (%)             | 117 (55.1)                     | 75 (64.1)                       | 0.093   |
| Distribution                                |                                |                                 |         |
| Involved vascular territory                 |                                |                                 |         |
| Posterior circulation, n (%)               | 91 (28.3)                      | 29 (24.8)                       | 0.459   |
| Multiple vascular territories, n (%)        | 45 (14.0)                      | 14 (12.0)                       | 0.578   |
| Involved structure                          |                                |                                 |         |
| Cortical lesions only, n (%)                | 81 (25.2)                      | 38 (32.8)                       | 0.119   |
| Subcortical lesions only, n (%)             | 82 (25.5)                      | 25 (21.4)                       | 0.368   |
| Multiplicity                                |                                |                                 |         |
| Number of lesions, ≥3 lesions, n (%)        | 108 (33.9)                     | 33 (28.2)                       | 0.264   |

IQR indicates interquartile range; NIHSS, National Institutes of Health stroke scale.
Figure 3. Examples applying the prediction model to real clinical practice. A, A male patient aged 78 years had multiple small infarcts in multiple vascular territories. According to the prediction model, the probabilities for AAA, PFO, and PAF were 0.94, 0.05, and 0.01, respectively. We performed ECG, 72-hour Holter monitoring, and a transcranial Doppler shunt test; the results were negative. Multidetector row computed tomography revealed thick atheroma in the ascending aorta. B, A female patient aged 29 years had a right PCA infarction. There was no lesion outside the right PCA territory. The probability of PFO was 0.97. On transesophageal echocardiography, PFO with right-to-left shunt was observed. C, This is a case of a territorial right middle cerebral artery infarction. The patient was aged 74 years; initial NIHSS was 17. The PAF probability was 0.94. Although we did not find an abnormality on serial ECGs, 72-hour cardiac telemonitoring showed paroxysmal atrial fibrillation. AAA indicates aortic arch atheroma; NIHSS, National Institutes of Health Stroke Scale; PAF, paroxysmal atrial fibrillation; PCA, posterior cerebral artery; PFO, patent foramen ovale.
for the posterior predominance of paradoxical embolism. In contrast, because the clots from the left atrium or left atrial appendix are usually large (fibrin-containing), atrial fibrillation is associated with more severe ischemic strokes and longer (>60 minutes) transient ischemic attacks compared with arteroembolic strokes from the carotid artery or aortic arch (cholesterol-containing). Clot components reportedly determine infarct patterns; an autopsy study revealed that emboli containing fibrin often cause large cortical infarcts, whereas emboli containing cholesterol crystals frequently result in small border zone infarcts.

When investigating the underlying causes of embolic stroke of undetermined source, physicians need to decide on the type and extent of the ancillary procedures they will use to document a precise embolic source for proper secondary preventive management. In clinical practice, routinely ordering diagnostic tests, including TEE, and workups for paradoxical embolism and deep vein thrombosis, aortogenic embolism, and prolonged cardiac telemonitoring is neither indicated nor possible. TEE is considered the gold standard for the evaluation of embolic stroke of undetermined source; however, routine application of TEE is often limited in patients with acute stroke because of acute illness, mental change, coagulopathy or bleeding tendency, and lack of patient cooperation. The use of more noninvasive diagnostic techniques, such as the MDCT to detect aortogenic embolism or transcranial right-to-left shunt test to detect paradoxical embolism, would be practical alternatives. In contrast, current guidelines recommend performing cardiac monitoring for at least 24 hours to detect PAF; however, an atrial fibrillation detection rate of 24-hour Holter monitoring does not seem to be sufficient, so long-term cardiac rhythm monitoring should be considered in patients with a high probability of having PAF.

Moreover, the yield of diagnostic tests may differ among patients, depending on the probability of having PFO, AAA, and PAF as a cause of stroke. The yield (positive predictive value and probability of stroke cause) of cardiac telemonitoring, for example, and the workup for paradoxical embolism and deep vein thrombosis are very different. Based on a report by the US Centers for Medicare and Medicaid Services, aggregate cost for intensive embolic source evaluation in a single ischemic stroke patient can be >$2000 (ie, ECG, $17; complete transthoracic echocardiography, $229; transcranial Doppler ultrasound, $290; diagnostic TEE, $308; MDCT, $420; and cardiac telemetry, $680). Considering the increasing number of stroke patients, inadvertent etiologic evaluations could be a great burden to the economy. Consequently, selecting appropriate cardiologic workups for individual patients based on the probability equation would improve the cost-effectiveness of advanced diagnostic technologies and may help with timely etiologic investigation and accurate diagnosis.

Limitations
The current study has the advantage of incorporating derivation and external validation data, but it also has several limitations. Most important, not all patients in this study underwent the same diagnostic workups. Although all patients underwent DWI and magnetic resonance angiography, the cardiac workups, which included TEE, MDCT, and cardiac telemonitoring, varied among patients, depending on the physician’s preference in real-world practice. Patients who were likely to have aortogeniic or paradoxical embolism, for example, received additional TEE more often, whereas those who were suspected of having PAF received cardiac telemonitoring more often. Nevertheless, the external validation analysis using data from a different medical center suggested that the physician’s preference did not significantly influence our conclusions. In addition, we hypothesized that it is important to differentiate embolism cause in patients with embolic stroke of undetermined source because different treatment strategies are required (eg, plaque stabilizer [ie, statin] for AAA, closure [in some cases] for PFO, and anticoagulation for PAF); however, this is beyond the scope of the current analysis. Further studies with prospective follow-up data are needed to test this hypothesis. Last, these data are from 2 centers in South Korea; therefore, the generalizability of our results may be limited. Future studies with a prospective design including different ethnic populations are warranted.

Conclusions
Our data indicate that patients with embolic stroke of undetermined source showed distinct clinical and radiological features depending on the underlying stroke cause. Specific diagnostic tests for aortocardiac sources could be guided by such features. Our probability equations can aid decision making by identifying patients who are likely to have PAF during hospitalization in the first days of stroke onset or, conversely, those likely to have aortogenic pathology or paradoxical embolic sources. Continuous efforts are needed to refine the approach to working up cases of suspected embolic stroke of undetermined source, incorporating other biomarkers, such as B-type natriuretic peptide or genetic risk factors.

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Disclosures
None.

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