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Letter to the Editor

Patent Foramen Ovale May Decrease the Risk of Left Atrial Thrombosis in Stroke Patients With Atrial Fibrillation

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Dear Sir:

Atrial fibrillation (AF) and patent foramen ovale (PFO) are potential causes of stroke.[1-3] When a patient has both AF and PFO, the risk of stroke/thromboembolism from one of these conditions may be affected by the other.[4] However, this issue has rarely been investigated.

AF is often accompanied by left atrial (LA)/LA appendage (LAA) thrombus and spontaneous echo contrast (SEC), which increase the risk of embolism[1,2,5] and are associated with poor clinical outcomes in stroke patients.[6] Blood stasis in the LA/LAA is the main mechanism for developing LA/LAA thrombus and SEC in patients with AF.[1,2] Although shunt flow through the PFO may also affect LA/LAA hemodynamics,[7] whether PFO influences LA/LAA thrombosis remains unclear. This study investigated the risk of LA/LAA thrombus or SEC in stroke patients with both AF and PFO.

This single-center retrospective cross-sectional study included patients with acute ischemic stroke who had nonvalvular AF and underwent transesophageal echocardiography (TEE) between 2011 and 2019.[4] Patients who received LAA occlusion or PFO closure were excluded. The presence of PFO, LA/LAA thrombus, and SEC was determined using TEE. The measured echocardiographic parameters were LAA emptying velocity (LAAV), LA volume index, left ventricular ejection fraction, and ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (no. 4-2022-1131), and the need for informed consent was waivered owing to its retrospective nature. Detailed information on the study population and echocardiographic evaluation are presented in the Supplementary Methods. Statistical analysis was performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC, USA). Multivariable logistic regression analyses were performed to compare the frequencies of LA/LAA thrombus or SEC between patients with and without PFO. Mediation analysis was performed to evaluate echocardiographic parameters for explaining the relationship between PFO and LA/LAA thrombus or SEC.[8]

Of the 1,469 stroke patients with AF, 696 with nonvalvular AF who underwent both TEE and TTE were included (Supplementary Figure 1) (median age=73 years, 59.2% male). Among them, 145 (20.8%) had PFO. LA/LAA thrombus or SEC was observed in 331 (47.6%) patients (thrombus in 82 [11.8%] and SEC in 321 [46.1%]).

LA/LAA thrombus or SEC was less frequent in patients with PFO than in those without (37.2% vs. 50.3%, *P*=0.007) (Table 1). In multivariable backward regression analysis, PFO was independently associated with a lower prevalence of LA/LAA thrombus or SEC (adjusted odds ratio [OR] 0.65, 95% confidence interval [CI] 0.44–0.96, *P*=0.028) (Table 2 and Supplementary Table 1). Additionally, PFO with high-risk features (a large shunt or atrial septal aneurysm) showed a stronger association (OR 0.39, 95% CI 0.16–0.94, *P*=0.037) (Table 2). LAAV was significantly higher in patients with PFO than in those without (35.0 [21.8–53.0] cm/s vs. 27.6 [18.3–46.5] cm/s, *P*=0.005) (Table 1).

In the mediation analysis of echocardiographic parameters, LAAV was the only significant mediator for the effect of PFO on LA/LAA thrombus or SEC (91.1% mediation, *P*=0.031) (Figure 1 and Supplementary Table 2). The mediating effect was stronger in PFO patients with high-risk features (95.5% mediation, *P*=0.001) (Supplementary Table 3).

Table 1. Comparison of characteristics between patients with and without PFO

	PFO (n=145)	No PFO (n=551)	*P*
Demographics			
Age (yr)	73.0 [62.0–78.0]	73.0 [66.0–79.0]	0.258
Male sex	94 (64.8)	318 (57.7)	0.145
Hypertension	111 (76.6)	442 (80.2)	0.392
Diabetes	41 (28.3)	177 (32.1)	0.431
Dyslipidemia	26 (17.9)	103 (19.0)	0.869
Old ischemic stroke	24 (16.6)	101 (18.3)	0.708
Congestive heart failure	7 (4.8)	49 (8.9)	0.153
Ischemic heart disease	54 (37.2)	185 (33.6)	0.466
Current smoker	17 (11.7)	72 (13.1)	0.771
CHA_2DS_2-VASc score	3.0 [2.0–4.0]	4.0 [2.0– 5.0]	0.062
NIHSS at admission	4.0 [1.0–10.0]	4.0 [1.0–10.0]	0.401
Anticoagulation	23 (15.9)	136 (24.7)	0.032
Echocardiography parameters			
LAAV (cm/s)	35.0 [21.8–53.0]	27.6 [18.3–46.5]	0.005
LVEF (%)	54.0 [50.0–59.0]	56.0 [50.0–61.0]	0.162
LAVI (mL/m^2)	48.1 [37.6–61.2]	51.0 [39.5–65.0]	0.113
E/E'	12.5 [10.0–15.1]	13.0 [10.0–16.3]	0.272
LA/LAA thrombus or SEC	54 (37.2)	277 (50.3)	0.007

Values are presented as median [interquartile range] or number (%).
PFO, patent foramen ovale; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74, and sex category (female); NIHSS, National Institutes of Health Stroke Scale; LAAV, left atrial appendage emptying velocity; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E/E', early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; LA, left atrial; LAA, left atrial appendage; SEC, spontaneous echo contrast.

This study showed that PFO was associated with a lower prevalence of LA/LAA thrombus or SEC in stroke patients with nonvalvular AF, with the relationship likely to be mediated by higher LAAV.

In this study, LA/LAA thrombus or SEC was less frequent in patients with PFO than in those without. This result is in line with those of a previous study, which showed that LA/LAA thrombus or SEC was less frequent in patients with severe mitral stenosis and a coexisting PFO.[9] Although the cause-effect relationship remains uncertain, these findings suggest that PFO has a beneficial role in reducing LA/LAA thrombosis in patients with heightened thrombotic conditions. Stroke patients with determined etiologies, including AF, had a lower risk of recurrent stroke when they had a PFO.[4] It was speculated that PFO might be the actual etiology of stroke in some patients; therefore, the generally low-recurrence risk in PFO-associated stroke might be related to the decreased risk of stroke recurrence in such patients.[4] However, other factors may also be responsible for this low stroke risk. In AF, the presence of LA/LAA thrombus or SEC is an indicator of increased stroke risk.[1,2] Our findings suggest that coexisting PFO in patients with AF may reduce the risk of thromboembolism.

We also found that LAAV was significantly higher in patients with PFO than in those without. LAAV is a quantitative parameter for estimating thromboembolic risk, and a low LAAV has been associated with a higher risk of LA/LAA thrombus or SEC and thromboembolism.[1,2] Our findings suggest that intermittent shunt flow through the PFO may affect the flow dynamics in the LA/LAA, which was exhibited as a higher LAAV. These flow changes may act favorably to reduce blood stasis within the LA/LAA in patients with AF.

In this study, the decreased risk of LA/LAA thrombus or SEC in

Table 2. Prediction of left atrial thrombus or SEC according to PFO and high-risk features*

	Univariable		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
PFO (vs. no PFO)								
PFO	0.59 (0.40–0.85)	0.006	0.61 (0.42–0.90)	0.012	0.65 (0.44–0.96)	0.029	0.65 (0.44–0.96)	0.028
PFO considering high-risk features								
No PFO	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
PFO without high-risk features	0.66 (0.44–0.996)	0.048	0.68 (0.45–1.02)	0.063	0.72 (0.47–1.10)	0.125	0.72 (0.48–1.10)	0.130
PFO with high-risk features	0.33 (0.14–0.79)	0.013	0.38 (0.16–0.92)	0.031	0.39 (0.16–0.96)	0.041	0.39 (0.16–0.94)	0.037

Logistic regression analysis was performed to determine the association between PFO, and LA/LAA thrombus or SEC. Model 1 was adjusted for age, male sex, and CHA_2DS_2-VASc score. Model 2 was adjusted for Model 1 factors, along with hypertension, diabetes, dyslipidemia, old ischemic stroke, congestive heart failure, ischemic heart disease, current smoking, and anticoagulation. Model 3 was adjusted using a backward regression analysis.
SEC, spontaneous echo contrast; PFO, patent foramen ovale; OR, odds ratio; CI, confidence interval; LA, left atrial; LAA, left atrial appendage; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74, and sex category (female).
*High-risk features indicate the presence of either an atrial septal aneurysm or a large-shunt size.[3]

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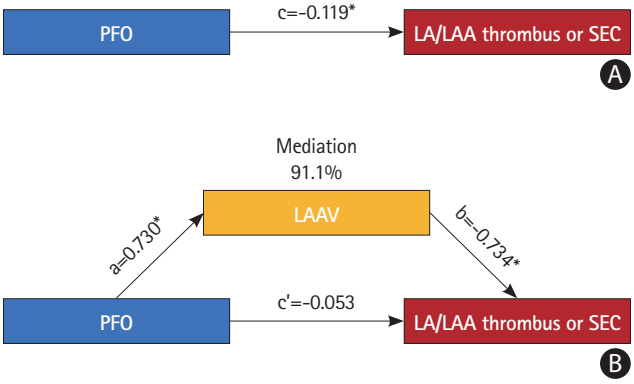

Figure 1. Mediation of effects of PFO on LA/LAA thrombus or SEC. Pathway of mediation analysis showing how echocardiographic parameters mediate the effect of PFO on LA/LAA thrombus or SEC. (A) The direct effect of PFO on LA/LAA thrombus or SEC and (B) LAAV mediation of the effect of PFO on LA/LAA thrombus or SEC. Comparable coefficients: a, the effect of PFO on LAAV; b, effect of LAAV on LA/LAA thrombus or SEC; c, direct association between PFO and LA/LAA thrombus or SEC (without adjusting for LAAV); and c', association between PFO and LA/LAA thrombus or SEC adjusting for LAAV. The degree of mediation is shown as Baron and Kenny's proportion of effect mediation (%). PFO, patent foramen ovale; LA, left atrial; LAA, left atrial appendage; SEC, spontaneous echo contrast; LAAV, left atrial appendage emptying velocity. *P<0.05.

patients with PFO was almost exclusively explained by the increased LAAV. The mediating effect was stronger in PFO patients with high-risk features. Atrial remodeling and blood stasis are the key mechanisms of thrombosis in AF.[1,2] Considering the crucial role of slow flow in LA/LAA in thrombosis[1,2] and similar other demographic and clinical factors between patients with and without PFO, PFO-related changes in the LAAV may have played a major role in lowering the risk of thrombosis in this study population.

Ischemic stroke may recur even after PFO closure, and AF is a known potential procedure-related complication after PFO closure.[7,10] Our findings suggest that measuring LAAV may be necessary in patients undergoing PFO closure because the procedure may further decrease LAAV in patients with low LAAV, thereby may increasing the risk of LA thrombosis and ischemic stroke.

This study had several limitations. TEE could not be performed in nearly half of the stroke patients because of the requirement for patient cooperation. Consequently, this study included patients with milder strokes (Supplementary Table 4). The generalizability of the findings of this study may be limited because they were based on data from a single university hospital with a single ethnicity.

In conclusion, coexisting PFO decreased the risk of LA/LAA thrombus or SEC in stroke patients with AF, mainly by reducing blood stasis.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.01179.

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Conflicts of interest

MB report research grants from Daewoong Pharmaceutical. All other authors report no potential conflicts of interest.

Author contribution

Conceptualization: MB, JHH. Study design: MB, JHH. Methodology: MB, CYS, SYG, JHH. Data collection: MB, CYS, SYG, YDK, HSN, JHH. Investigation: MB, JHH. Statistical analysis: MB, SJ, HSL. Writing—original draft: MB, JHH. Writing—review & editing: MB, CYS, SYG, YDK, HSN, JHH. Funding acquisition: MB, JHH. Approval of final manuscript: all authors.

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Supplementary Methods

Study population and evaluation

This retrospective cross-sectional study used data from a stroke registry that enrolled patients with acute ischemic stroke.[1,2] The registry enrolled consecutive patients with acute ischemic stroke or transient ischemic attack within 7 days of symptom onset who were admitted to the Stroke Center of Severance Hospital, Yonsei University, Seoul, South Korea. This study included consecutive patients with nonvalvular atrial fibrillation (AF) and patent foramen ovale (PFO) on transesophageal echocardiography (TEE) between November 2011 and December 2019. Upon admission, all patients underwent brain computed tomography (CT) and/or magnetic resonance imaging with cerebral angiographic studies (CT angiography, magnetic resonance angiography, and digital subtraction angiography); standard blood tests; and chest radiography. Cardiac evaluations included 12-lead electrocardiography (ECG), continuous ECG monitoring during the stay in a stroke unit, 24-hour Holter monitoring, transthoracic echocardiography (TTE), TEE, and heart CT.

Echocardiography evaluation and PFO, atrial thrombus, and spontaneous echo contrast

TTE and TEE were performed within 2 weeks of the initial stroke using commercially available echocardiography machines. TTE was performed using a Vivid E9 ultrasound system (GE Medical Systems, Chicago, IL, USA; Philips iE33; Philips Healthcare, Amsterdam, the Netherlands) with a 2.5–3.5 MHz probe. Standard 2D and Doppler measurements were performed according to the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging.[3] The left ventricular ejection fraction (LVEF) was measured using the biplane Simpson's method in the apical four- and two-chamber views. LVEF <52% for males and <54% for females indicated abnormal left ventricular (LV) systolic function.[3] In a case of LVEF measured using the M-mode method, the LVEF value minus eight was calculated to substitute LVEF as the biplane method.[4] Left atrial volume index (LAVI) was measured using the biplane-modified Simpson method in both the apical four- and two-chamber views and indexed to the body surface area. The upper normal limit for 2D echocardiographic LAVI was 34 mL/m^2 for both sexes.[3] If LAVI was measured using the prolate ellipse method, LAVI plus seven was calculated for each patient, and the value was regarded as the LAVI of the Simpson method.[5] A ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (E/E') >15 indicated an increase in the LV filling pressure.[6]

TEE was performed using either an iE33 xMATRIX ultrasound system (Philips, Andover, MA, USA) or Acuson SC2000 ultrasound system (Siemens, Mountain View, CA, USA) equipped with a multiplane 5-MHz transducer. TEE was part of the standard and routine evaluation for stroke patients in the study hospital, except for those with decreased consciousness, impending brain herniation, poor systemic condition, and inability to accept an esophageal transducer due to swallowing difficulty, tracheal intubation, or lack of willingness to provide informed consent.[2,7] If the patients could be trained to perform the Valsalva maneuver, they were properly instructed before the TEE procedure. A contrast test was performed using an agitated saline solution. A PFO was considered present if any microbubbles were seen in the left cardiac chambers within three cardiac cycles of the maximum right atrium enhancement or if a turbulent color jet was seen within the atrial septum on color Doppler images. The physiological shunt size was defined as the maximal number of bubbles observed in the left atrium (LA) either at rest or after the Valsalva maneuver within three cardiac cycles. Shunt size was classified into small (≤20 bubbles) and large (>20 bubbles).[8,9] Atrial septal aneurysm was defined as ≥10 mm of excursion from midline.[9] All segments of the thoracic aorta, including the ascending and descending aorta and aortic arch, were evaluated for the presence of plaques. The LA appendage (LAA) was observed on the best image between 45° and 90°, including 2D color Doppler images and pulsed-wave Doppler. The LAA emptying velocity (LAAV) was defined as the mean of three consecutive values of peak end-diastolic emptying velocity obtained using pulsed-wave Doppler at the LAA ostium in the TEE view. Spontaneous echo contrast (SEC) was defined as a smoke-like swirling pattern observed in LA or LAA after adjusting for the optimal gain setting.[10] LAAV of >40 cm/s indicated normal blood flow velocity.[11]

Echocardiographic parameters, LAAV, LAVI, LVEF, and E/E', which have been suggested to be associated with LA/LAA thrombus and SEC, were assessed.[12-14] All echocardiographic parameters were used as continuous variables, except in the demographic table.

Statistical analyses

Statistical analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS (version 9.4; SAS Institute, Cary, NC, USA). Univariable analysis was performed using the independent t-test, analysis of variance, or Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables, as appropriate. As 17 patients had missing values for the E/E', median imputation was applied to replace the missing values with a median value of 13.

Multivariable logistic regression analyses were performed to determine the association between PFO and atrial thrombus/SEC.

Model 1 was adjusted for age, male sex, and the CHA_2DS_2-VASc score. Model 2 was adjusted for Model 1 factors along with hypertension, diabetes, dyslipidemia, old ischemic stroke, congestive heart failure, ischemic heart disease, current smoking status, and anticoagulation. Model 3 was adjusted using a backward regression analysis. We also performed multivariable logistic regression models considering PFO with and without high-risk features.

To determine potential echocardiographic parameters among LAAV, LAVI, LVEF, and E/E', as a mediator of the relationship between PFO and LA/LAA thrombus or SEC, mediation analysis was performed. This effect was calculated using a comparable coefficient. To perform the mediation analysis, the following pathways were evaluated: (a) the effect of PFO on LAAV; (b) the effect of LAAV on atrial thrombus/SEC; (c) the direct association between PFO and LA/LAA thrombus or SEC (without adjusting for LAAV); and (c') the association between PFO and LA/LAA thrombus or SEC when adjusting for LAAV. Baron and Kenny's proportion of the mediation effect (%) was calculated.[15]

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Supplementary Table 1. Predictors for left atrial thrombus or SEC

	Univariable		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographic variables								
Age (yr)	1.02 (1.01–1.04)	0.005	1.00 (0.98–1.02)	0.870	1.02 (0.99–1.05)	0.161	1.02 (1.01–1.04)	0.004
Male sex	0.87 (0.64–1.17)	0.359	1.17 (0.84–1.64)	0.350	0.86 (0.57–1.29)	0.461		
Hypertension	1.33 (0.92–1.93)	0.133			1.08 (0.66–1.77)	0.758		
Diabetes	1.43 (1.04–1.97)	0.030			1.25 (0.80–1.94)	0.335	1.29 (0.92–1.80)	0.136
Dyslipidemia	0.89 (0.61–1.29)	0.530			0.77 (0.51–1.14)	0.193		
Old ischemic stroke	1.70 (1.15–2.52)	0.008			1.46 (0.75–2.84)	0.264	1.54 (1.02–2.32)	0.042
Congestive heart failure	2.73 (1.51–4.93)	0.001			2.44 (1.26–4.72)	0.008	2.49 (1.36–4.55)	0.003
Ischemic heart disease	1.30 (0.95–1.78)	0.099			1.21 (0.86–1.69)	0.272		
Current smoker	1.57 (1.00–2.46)	0.050			2.10 (1.27–3.48)	0.004	1.98 (1.22–3.19)	0.005
CHA_2DS_2-VASc score	1.23 (1.12–1.35)	<0.001			1.03 (0.78–1.34)	0.852		
Anticoagulation	1.66 (1.16–2.37)	0.006			1.41 (0.96–2.06)	0.082	1.42 (0.97–2.08)	0.070
Patent foramen ovale	0.59 (0.40–0.85)	0.006	0.61 (0.42–0.90)	0.012	0.65 (0.44–0.96)	0.029	0.65 (0.44–0.96)	0.028

Logistic regression analysis was performed to determine the association between PFO, and left atrial thrombus or SEC. Model 1 was adjusted for age, male sex, and CHA_2DS_2-VASc score. Model 2 was adjusted for Model 1 factors, along with hypertension, diabetes, dyslipidemia, old ischemic stroke, congestive heart failure, ischemic heart disease, current smoking, and anticoagulation. Model 3 was adjusted using a backward regression analysis.
SEC, spontaneous echo contrast; OR, odds ratio; CI, confidence interval; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74, and sex category (female); PFO, patent foramen ovale.

Supplementary Table 2. Analysis of potential echocardiographic mediators of the effect of a patent foramen ovale on left atrial thrombus or spontaneous echo contrast

	Indirect association through mediator		
	Comparable coefficient (95% CI)	% Mediation	*P* for indirect effect
LAAV (cm/s)	-0.536 (-1.023 to -0.049)	91.08	0.031
LAVI (mL/m^2)	-0.189 (-0.521 to -0.064)	64.66	0.210
LVEF (%)	0.024 (-0.035 to 0.084)	24.65	0.418
E/E'	-0.007 (-0.215 to -0.035)	5.70	0.633

CI, confidence interval; LAAV, left atrial appendage emptying velocity; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E/E', early diastolic mitral inflow velocity to early diastolic mitral annulus velocity.

Supplementary Table 3. Analysis of potential echocardiographic mediators of the effect of PFO on left atrial thrombus or spontaneous echo contrast according to PFO with and without high-risk features*

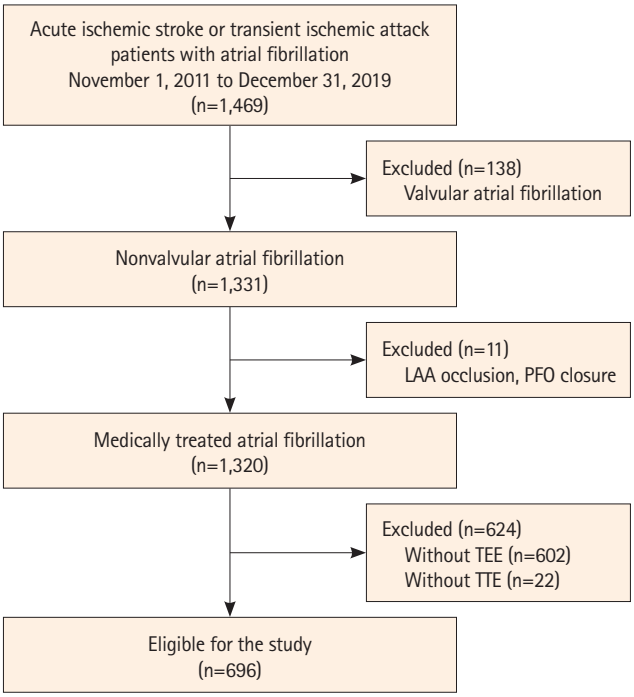
	Indirect association through mediators					
	PFO with high-risk features			PFO without high-risk features		
	Comparable coefficient (95% CI)	% Mediation	*P* for indirect effect	Comparable coefficient (95% CI)	% Mediation	*P* for indirect effect
LAAV (cm/s)	-0.636 (-1.003 to -0.269)	95.50	0.001	-0.292 (-0.939 to 0.354)	86.09	0.376
LAVI (mL/m^2)	-0.166 (-0.476 to 0.143)	60.55	0.291	-0.154 (-0.470 to 0.163)	68.06	0.341
LVEF (%)	-0.009 (-0.067 to 0.049)	7.01	0.765	0.031 (-0.028 to 0.091)	53.05	0.303
E/E'	-0.017 (-0.048 to 0.014)	12.90	0.282	0.001 (-0.028 to 0.028)	0.12	0.995

PFO, patent foramen ovale; CI, confidence interval; LAAV, left atrial appendage emptying velocity; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E/E', early diastolic mitral inflow velocity to early diastolic mitral annulus velocity.
*High-risk features indicated the presence of either an atrial septal aneurysm or a large-shunt size.[16]

Supplementary Table 4. Comparison of patients in whom TEE was performed or not performed

	TEE (n=718)	No TEE (n=602)	*P*
Demographics			
Age (yr)	73.0 [65.0–79.0]	78.0 [72.0–83.0]	<0.001
Male sex	427 (59.5)	317 (52.7)	0.015
Hypertension	574 (79.9)	493 (81.9)	0.409
Diabetes	224 (31.2)	235 (39.0)	0.003
Dyslipidemia	138 (19.2)	125 (20.8)	0.528
Previous ischemic stroke	130 (18.1)	142 (23.6)	0.017
Congestive heart failure	69 (9.6)	92 (15.3)	0.002
Ischemic heart disease	246 (34.3)	161 (26.7)	0.004
Current smoker	91 (12.7)	60 (10.0)	0.146
CHA_2DS_2-VASc score	5.0 [4.0–6.0]	6.0 [5.0–6.0]	<0.001
NIHSS at admission	4.0 [1.0–10.0]	11.0 [3.0–18.0]	<0.001
Anticoagulation	161 (22.4)	125 (20.8)	0.508

Values are presented as median [interquartile range] or number (%).
TEE, transesophageal echocardiography; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74, and sex category (female); NIHSS, National Institutes of Health Stroke Scale.



Supplementary Figure 1. Patient selection. LAA, left atrial appendage; PFO, patent foramen ovale; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

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