JoS JOURNAL OF STROKE

Journal of Stroke 2024;26(2):242-251
https://doi.org/10.5853/jos.2023.03265

Original Article

Device Closure or Antithrombotic Therapy After Cryptogenic Stroke in Elderly Patients With a High-Risk Patent Foramen Ovale

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Background and Purpose In young patients (aged 18–60 years) with patent foramen ovale (PFO)-associated stroke, percutaneous closure has been found to be useful for preventing recurrent ischemic stroke or transient ischemic attack (TIA). However, it remains unknown whether PFO closure is also beneficial in older patients.

Methods Patients aged ≥60 years who had a cryptogenic stroke and PFO from ten hospitals in South Korea were included. The effect of PFO closure plus medical therapy over medical therapy alone was assessed by a propensity-score matching method in the overall cohort and in those with a high-risk PFO, characterized by the presence of an atrial septal aneurysm or a large shunt.

Results Out of the 437 patients (mean age, 68.1), 303 (69%) had a high-risk PFO and 161 (37%) patients underwent PFO closure. Over a median follow-up of 3.9 years, recurrent ischemic stroke or TIA developed in 64 (14.6%) patients. In the propensity score-matched cohort of the overall patients

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Received: October 3, 2023
Revised: January 13, 2024
Accepted: January 15, 2024

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(130 pairs), PFO closure was associated with a significantly lower risk of a composite of ischemic stroke or TIA (hazard ratio [HR]: 0.45; 95% confidence interval [CI]: 0.24–0.84; *P*=0.012), but not for ischemic stroke. In a subgroup analysis of confined to the high-risk PFO patients (116 pairs), PFO closure was associated with significantly lower risks of both the composite of ischemic stroke or TIA (HR: 0.40; 95% CI: 0.21–0.77; *P*=0.006) and ischemic stroke (HR: 0.47; 95% CI: 0.23–0.95; *P*=0.035).
Conclusion Elderly patients with cryptogenic stroke and PFO have a high recurrence rate of ischemic stroke or TIA, which may be significantly reduced by device closure.

Keywords Cryptogenic stroke; Patent foramen ovale; Device closure; Stroke prevention; Elderly patients

Introduction

Since the initial clinical reports of the high prevalence of patent foramen ovale (PFO) in young stroke patients (age <55 years),[1,2] the association between PFO and cryptogenic stroke has been a highly debated topic. Successful clinical introduction of percutaneous device closure of the PFO has further complicated the situation, and landmark randomized clinical trials have shown that PFO closure can effectively reduce the recurrence rate of ischemic stroke or transient ischemic attack (TIA).[3-9] Thus, current practice guidelines recommend antithrombotic therapy or device closure of the PFO for preventing recurrent ischemic stroke in patients with PFO-associated ischemic stroke.[10-12] Moreover, a recent meta-analysis of pooled individual patient data from all 6 landmark randomized clinical trials shows that among patients aged 18 to 60 years with PFO-associated stroke, a multivariable causal classification system (PFO-Associated Stroke Causal Likelihood [PASCAL] classification system) combining individual vascular risk factors and stroke pattern with high-risk anatomical features of PFO (e.g., atrial septal aneurysm, large-sized shunt), is useful in predicting the likelihood of risk reduction for recurrent ischemic stroke with device closure.[13]

Despite these promising results, there is a lack of evidence on whether device closure is also helpful for preventing recurrent ischemic stroke in elderly (>60 years) patients with PFO and cryptogenic stroke. This is because the current guidelines mention an age limit of <60 years in endorsing the use of device closure, which is based on a meta-analysis of case-control studies published in 2000 in which the benefits of device closure in stroke patients older than 55 years were relatively unclear.[14] As a result, most randomized controlled trials on this issue exclusively enrolled patients aged <60 years.[3-8]

In contrast, one randomized clinical trial performed in South Korea did not employ any age limitation,[9] which was possible because the Korean healthcare policy does not have an age limitation in the reimbursement of medical insurance fees for percutaneous device closure of PFO. As a result, institutions in South Korea have adopted an individualized heart-brain team approach to determine whether medical therapy alone or device closure is more suitable for patients with PFO. This approach has facilitated the collection of clinical data on older cryptogenic stroke patients with PFO who have undergone device closure. In this study, we evaluated whether percutaneous device closure of PFO was beneficial in preventing recurrent ischemic stroke in cryptogenic stroke patients aged over 60 years, with a particular focus on those who had a high-risk PFO.

Methods

Subjects

This is a multicenter, retrospective study. Ten South Korean stroke centers (Asan Medical Center, Severance Hospital, Chungnam National University Hospital, Kyung Hee University Hospital, Ulsan University Hospital, Seoul National University Bundang Hospital, Daejeon St. Mary's Hospital, Hanyang University Medical Center, Gyeongsang National University Changwon Hospital, and Chungbuk National University Hospital) that are actively performing device closure of PFO participated in this study. The study included consecutive patients aged ≥60 years with cryptogenic ischemic stroke who were diagnosed with PFO through a standardized evaluation protocol including transesophageal echocardiography (TEE) who were admitted to the aforementioned centers between January 2008 and December 2020. Patients who had been involved in the multidisciplinary team[15] were carefully selected for this study. The decision to choose between PFO closure or medical therapy for an individual was made through consensus, which took into account the interpretation of neuro- and cardiac imaging, the possibility of other sources of cardiac embolism, the presence of comorbidities, assessment of PFO morphology, and the procedural risk of PFO closure at each participating center.

An ischemic stroke was defined as an acute focal neurologic

deficit associated with evidence of relevant infarction on magnetic resonance imaging of the brain, regardless of the duration of the symptoms. The index stroke was regarded as cryptogenic after the exclusion of other identifiable mechanisms of stroke (e.g., large-artery disease, cardioembolic infarction, small-vessel disease, other determined etiologies such as arterial dissection or moyamoya disease) through a standardized evaluation conducted at each center. Large-artery disease was defined when there was relevant significant (≥50%) steno-occlusion in the intracranial or extracranial arteries evaluated by computed tomography angiography, magnetic resonance angiography, or ultrasonography. Patients with significant atherothrombosis (plaque thickness of ≥4 mm) in the thoracic aorta were also considered in this category. Cardiac origin of embolism was considered when there was a cardiac condition with a high embolic risk, such as atrial fibrillation, valvular heart disease (presence of a prosthetic valve or moderate-to-severe rheumatic mitral stenosis), acute myocardial infarction with a mural thrombus, endocarditis, or systolic heart failure with an ejection fraction of ≤40%. To rule out cardiac embolism, electrocardiography, Holter monitoring (24 hr or 72 hr), and transthoracic echocardiography were performed at the discretion of an attending physician. A stroke caused by small vessel disease was defined as a small (<1.5 cm in diameter) and deep (e.g., basal ganglia, thalamus, brainstem) infarction, without evidence of relevant large artery disease or cardiac embolism.

In these patients with cryptogenic stroke, TEE was performed in all cases to detect the PFO, and to assess the morphologic characteristics of the atrial septum and right-to-left shunting through the PFO with agitated saline while the patient was undergoing a Valsalva maneuver. High-risk PFOs were defined when there was an atrial septal aneurysm (i.e., protrusion of the dilated segment of the septum at least 10 mm beyond the level surface of the atrial septum) or a large shunt (>20 bubbles in the left atrium).

Treatment and study endpoints

All patients received antiplatelet therapy or anticoagulation therapy chosen by the attending physicians at each participating center. Percutaneous device closure of PFO was considered through a shared decision-making process and closure was performed by experienced interventional cardiologists using contemporary devices, such as the Amplatzer PFO Occluder, Cocoon PFO Occluder, and Figulla Flex II PFO Occluder. After PFO closure, patients were generally recommended to take a dual antiplatelet regimen (aspirin 100 mg/day in combination with clopidogrel 75 mg/day) for at least 6 months; however, the attending physicians could choose to continue either antiplatelet therapy or anticoagulation therapy after considering the risk-to-benefit ratio for each patient.

The clinical, laboratory, and outcome data, other than ischemic stroke or TIA, were determined by analyzing the medical records and through telephone contact by research coordinators. The occurrence of ischemic stroke or TIA was verified by neurologists at each center based on the clinical findings and relevant neuroimaging studies. TIA was defined as a neurological deficit lasting less than 24 hours regardless of imaging findings.

Although follow-up strategies varied from center to center, most of the patients regularly visited the outpatient clinic in the neurology departments. Patients who underwent PFO closure also visited the department of cardiology. Follow-up information was obtained from reviewing medical records. In patients who were not being followed at the participating centers (n=58), telephone contact was made in addition to the chart review. All the chart reviews and telephone contacts were conducted between December 2020 and April 2022. The primary outcome was a composite of recurrent ischemic stroke or TIA. Secondary outcomes included death; ischemic stroke; a composite of ischemic stroke, TIA, and systemic embolization; intracranial bleeding; major bleeding according to the Thrombolysis in Myocardial Infarction definition;[16] and atrial fibrillation. This study was approved by the Institutional Review Board of Asan Medical Center (Approval No. 2019-0778) and each participating centers, with a waiver for the requirement of written informed consent.

Statistical analysis

Descriptive statistics for continuous variables are presented as mean±standard deviation and were compared using Student's t-test. Categorical variables are presented as numbers and percentages and were tested using the Pearson chi-square or Fisher's exact test, as appropriate. Rates of outcomes were evaluated using incidence rates and presented as the number of cases per 100 person-years (PY). Unadjusted hazard ratios (HRs) for the PFO closure group, compared with the medical therapy alone group, were estimated using Cox's proportional hazards regression analyses. Survival curves were generated using the Kaplan-Meier method.

Considering the differences in the characteristics of patients who received PFO closure and those who received medical therapy alone in registry data, propensity-score matching was used to select patients with similar baseline who might be equally suitable for the two treatment strategies. Propensity scores were estimated nonparametrically by fitting a logistic regression model using variables such as age, sex, body-mass index, hypertension, diabetes, dyslipidemia, chronic kidney disease, smoking status, prior stroke or TIA, migraine, prior deep vein thrombosis or pulmonary thromboembolism, history of cancer, superficial infarc-

https://doi.org/10.5853/jos.2023.03265

tion, and presence of a high-risk PFO. Propensity score matching was performed using a 1:1 matching protocol without replacement (greedy-matching algorithm) and with a caliper width equal to 0.2 times the standard deviation of the logit of the propensity score. Standardized differences were estimated for the covariates before and after matching, and a significant improvement in baseline was achieved after matching (Supplementary Table 1). Cox proportional hazards regression model with robust standard errors that accounts for the clustering of the pairs was used to compare the risks of outcomes in the matched cohort. Considering the higher likelihood of a causal relationship between high-risk PFO features and paradoxical embolization, we also compared the relative treatment effect of PFO closure and medical therapy alone in patients with a high-risk PFO. A formal test of interaction was conducted to assess if there were differences in the effects of treatment modalities between different patient enrollment periods (<2016 vs. ≥2016 based on the median of index stroke year). To adjust for the potential impact of participating centers (Supplementary Table 2), we conducted a separate analysis in each matched cohort using the Cox proportional hazards regression model with a shared frailty factor.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All reported *P* values are two-sided, and those smaller than <0.05 were considered significant.

Results

Patient characteristics

A total of 437 patients met the eligibility criteria and were included in the current analysis; the mean age was 68.1±6.4 years, 262 (60%) were men, and 303 (69%) had a high-risk PFO. After the index stroke, 161 (37%) patients received PFO closure, and 276 (63%) patients underwent medical therapy alone. The baseline patient characteristics are presented in Table 1. The PFO closure group and the medical therapy alone group did not have significant differences with regard to sex, body mass index, and key clinical factors such as diabetes, smoking status, prior stroke, history of venous thromboembolism, and history of cancer. However, compared with the medical therapy alone group, the PFO closure group was younger (69.2 vs. 66.2 years; *P*<0.001), had a higher Risk of Paradoxical Embolism score (3.8±1.2 vs. 4.2±1.2, *P*<0.001), a higher prevalence of migraine (1.4% vs. 5.6%; *P*=0.030), and high-risk features of PFO including atrial septal aneurysm (18.8% vs. 30.4%; *P*=0.008) and large-sized shunt (51.8% vs. 88.2%; *P*<0.001). Medications in each group during follow-up were summarized in the Supplementary Table 3.

Table 1. Baseline characteristics of the overall patients

	Medical therapy alone (n=276)	PFO closure (n=161)	$P^{\dagger}$
Age (yr)	69.2±6.7	66.2±5.2	<0.001
Male sex	164 (59.4)	98 (60.9)	0.766
Body mass index (kg/m^2)	23.8±3.1	24.0±2.6	0.472
Medical history			
Hypertension	170 (61.6)	84 (52.2)	0.068
Diabetes	69 (25.0)	30 (18.6)	0.157
Current smoker	56 (20.3)	25 (15.5)	0.268
Hyperlipidemia	89 (32.2)	44 (27.3)	0.281
Chronic kidney disease*	12 (4.3)	3 (1.9)	0.270
Prior stroke	61 (22.1)	39 (24.2)	0.610
Prior transient ischemic attack	19 (6.9)	7 (4.3)	0.280
Prior DVT or PTE	9 (3.3)	1 (0.6)	0.147
Migraine	4 (1.4)	9 (5.6)	0.030
History of cancer	31 (11.2)	22 (13.7)	0.549
Qualifying event			0.584
Vertebrobasilar territory	95 (34.4)	49 (30.4)	
Multiple territories	60 (21.7)	33 (20.5)	
Cortical infarction	158 (57.2)	109 (67.7)	0.031
PFO morphology			
Atrial septal aneurysm	52 (18.8)	49 (30.4)	0.008
Large sized shunt	143 (51.8)	142 (88.2)	<0.001
RoPE score	3.8±1.2	4.2±1.2	<0.001
Antithrombotic therapy at 30 days after stroke			
Antiplatelet alone	231 (83.7)	146 (90.7)	0.057
Anticoagulant alone	28 (10.1)	10 (6.2)	0.218
Both	11 (4.0)	5 (3.1)	0.835
None	6 (2.2)	0	0.145

Data are presented as mean±standard deviation or n (%).
PFO, patent foramen ovale; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; RoPE, Risk of Paradoxical Embolism.
*Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2; †*P*-value by Pearson chi-square test, Fisher's exact test, Student's t-test, or Cochran-Mantel-Haenszel shift test, as appropriate.

Clinical outcomes

During a median clinical follow-up duration of 3.9 years (interquartile range 2.1–7.5 years), primary endpoint occurred in 64 (14.6%) patients. Ischemic stroke, TIA, intracranial bleeding, and major bleeding occurred in 52 (11.9%), 16 (3.7%), 11 (2.5%), and 24 (5.5%) patients, respectively. The overall incidence rate of ischemic stroke or TIA was 3.98 cases per 100 PY in the medical therapy alone group and 2.24 cases per 100 PY in the PFO closure group. The incidence rate of ischemic stroke was 3.12 cases per 100 PY in the medical therapy alone group and 1.91 cases per 100 PY in the PFO closure group. The results of clinical outcomes are shown in Supplementary Table 4 and Supple-

mentary Figure 1. The risk of ischemic stroke or TIA was significantly lower in the PFO closure group (hazard ratio [HR] 0.52; 95% confidence interval [CI] 0.29–0.95; *P*=0.034). Of note, 10 patients who initially received medical therapy underwent PFO closure after stroke recurrence, and 2 patients who initially received PFO closure developed procedure-related strokes. The risks of intracranial (HR 0.40; 95% CI 0.09–1.86; *P*=0.243) or major bleeding (HR 0.62; 95% CI 0.25–1.58; *P*=0.319) were not significantly different between the two groups. The risks of death (HR 0.19; 95% CI 0.04–0.81; *P*=0.025) and the composite outcome of ischemic stroke, TIA, or systemic embolization (HR 0.55; 95% CI 0.31–0.99; *P*=0.046) were significantly lower in the PFO closure group, whereas the rate of atrial fibrillation was higher in the PFO closure group (HR 2.28; 95% CI 1.08–4.82; *P*=0.030). The difference in rates of ischemic stroke outcomes was especially prominent in patients with a high-risk PFO; the PFO closure group showed significantly lower risks of recurrent ischemic stroke (HR: 0.36; 95% CI: 0.18–0.75; *P*=0.006) and the composite outcome of ischemic stroke or TIA (HR: 0.36; 95% CI: 0.19–0.69; *P*=0.002).

Propensity score–matched analyses in the overall cohort and high-risk PFO cohort

After conducting propensity score matching to create a cohort of patients with clinical equipoise for medical therapy and PFO closure at baseline, there were 130 and 116 pairs in the overall and high-risk PFO populations, respectively. The baseline characteristics of each matched cohort are provided in Table 2. The adjusted HRs for between-group comparisons in each cohort are shown in Table 3. In the overall cohort, the 5-year rates of ischemic stroke or TIA rates in the medical therapy alone group and the PFO closure group were 21.6% and 12.7%, respectively, resulting in incidence rates of 4.25 cases per 100 PY and 2.10 cases per 100 PY. Although the incidence of recurrent ischemic stroke was not significantly different between the groups (HR: 0.58; 95% CI: 0.30–1.12; *P*=0.107), there was a significant difference between the groups in the risk of a composite outcome of ischemic stroke or TIA (HR: 0.45; 95% CI: 0.24–0.84; *P*=0.012), favoring the PFO closure group (Figure 1). The risks of other secondary outcomes were comparable between the groups. In the analysis confined to the high-risk PFO population, the PFO closure group had significantly lower risks of a composite of ischemic stroke or TIA (HR: 0.40; 95% CI: 0.21–0.77; *P*=0.006) and ischemic stroke (HR: 0.47; 95% CI: 0.23–0.95; *P*=0.035) (Figure 2). No significant interaction effect was found between the relative effect of treatment modalities and different patient enrollment periods for each outcome (Supplementary Table 5). The results of the analysis adjusted for the participating center effect were

Table 2. Baseline characteristics of the propensity-matched cohorts

	Overall cohort			High-risk PFO cohort		
	Medical therapy alone (n=130)	PFO closure (n=130)	*P*†	Medical therapy alone (n=116)	PFO closure (n=116)	*P*†
Age (yr)	66.7±5.2	67.1±5.3	0.536	66.6±4.9	66.9±5.2	0.481
Male sex	89 (68.5)	85 (65.4)	0.572	78 (67.2)	75 (64.7)	0.648
Body mass index (kg/m^2)	23.9±2.9	24.0±2.6	0.810	23.8±2.7	23.8±2.4	0.960
Medical history						
Hypertension	76 (58.5)	78 (60.0)	0.789	65 (56.0)	68 (58.6)	0.675
Diabetes	25 (19.2)	25 (19.2)	>0.999	24 (20.7)	24 (20.7)	>0.999
Current smoker	25 (19.2)	23 (17.7)	0.715	23 (19.8)	22 (19.0)	0.847
Hyperlipidemia	41 (31.5)	38 (29.2)	0.668	36 (31.0)	34 (29.3)	0.758
Chronic kidney disease*	6 (4.6)	3 (2.3)	0.273	6 (5.2)	3 (2.6)	0.273
Prior stroke	29 (22.3)	31 (23.8)	0.758	24 (20.7)	26 (22.4)	0.746
Prior transient ischemic attack	7 (5.4)	6 (4.6)	0.782	5 (4.3)	5 (4.3)	>0.999
Prior DVT or PTE	3 (2.3)	1 (0.8)	0.341	3 (2.6)	1 (0.9)	0.341
Migraine	4 (3.1)	5 (3.8)	0.706	3 (2.6)	4 (3.4)	0.657
History of cancer	18 (13.8)	13 (10.0)	0.321	14 (12.1)	10 (8.6)	0.396
Cortical infarction	87 (66.9)	88 (67.7)	0.893	80 (69.0)	81 (69.8)	0.886
High-risk PFO morphology	116 (89.2)	116 (89.2)	>0.999	NA	NA	NA

Data are presented as mean±standard deviation or n (%).
PFO, patent foramen ovale; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; NA, not applicable.
*Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2; †*P*-value by conditional logistic regression.

https://doi.org/10.5853/jos.2023.03265

Table 3. Propensity-score matching analysis for clinical outcomes in the overall cohort and the high-risk PFO cohort

	Overall cohort					
	Medical therapy alone (n=130)		PFO closure (n=130)		HR (95% CI)†	*P*
	N (%)*	Incidence rate (100 PY, 95% CI)	N (%)*	Incidence rate (100 PY, 95% CI)		
Primary outcome						
Ischemic stroke or TIA	30 (23.1)	4.25 (2.77–6.53)	12 (9.2)	2.10 (1.05–4.19)	0.45 (0.24–0.84)	0.012
Secondary outcomes						
Death	8 (6.2)	1.17 (0.60–2.30)	2 (1.5)	0.38 (0.09–1.53)	0.40 (0.09–1.89)	0.247
Ischemic stroke	12 (16.9)	3.38 (2.17–5.26)	11 (8.5)	2.19 (1.17–4.11)	0.58 (0.30–1.12)	0.107
Vascular death	1 (0.8)	0.15 (0.02–1.02)	1 (0.8)	0.19 (0.03–1.37)	1.27 (0.11–15.04)	0.850
Ischemic stroke, TIA, or systemic embolization	31 (23.8)	4.48 (2.96–6.79)	13 (10.0)	2.31 (1.19–4.46)	0.47 (0.26–0.87)	0.017
Intracranial bleeding	5 (3.8)	0.67 (0.25–1.77)	2 (1.5)	0.29 (0.05–1.81)	0.46 (0.12–1.77)	0.258
Major bleeding	10 (7.7)	1.50 (0.79–2.82)	6 (4.6)	1.13 (0.50–2.56)	0.72 (0.27–1.90)	0.505
Atrial fibrillation	7 (5.4)	1.12 (0.55–2.28)	12 (9.2)	2.52 (1.40–4.54)	1.97 (0.76–5.09)	0.162
	High-risk PFO cohort					
	Medical therapy alone (n=116)		PFO closure (n=116)		HR (95% CI)†	*P*
	N (%)*	Incidence rate (100 PY, 95% CI)	N (%)*	Incidence rate (100 PY, 95% CI)		
Primary outcome						
Ischemic stroke or TIA	28 (24.1)	4.41 (2.80–6.95)	10 (8.6)	1.92 (0.90–4.12)	0.40 (0.21–0.77)	0.006
Secondary outcomes						
Death	6 (5.2)	0.98 (0.45–2.12)	2 (1.7)	0.42 (0.10–1.69)	0.55 (0.11–2.72)	0.461
Ischemic stroke	22 (19.0)	3.81 (2.45–5.94)	9 (7.8)	1.99 (0.99–3.99)	0.47 (0.23–0.95)	0.035
Vascular death	0	-	1 (0.9)	-	NE	NE
Ischemic stroke, TIA, or systemic embolization	29 (25.0)	4.66 (3.00–7.24)	11 (9.5)	2.15 (1.04–4.43)	0.42 (0.22–0.81)	0.009
Intracranial bleeding	4 (3.4)	0.58 (0.21–1.56)	1 (0.9)	0.09 (0.00–9.51)	0.29 (0.05–1.59)	0.154
Major bleeding	9 (7.8)	1.51 (0.77–2.94)	4 (3.4)	0.80 (0.29–2.25)	0.51 (0.17–1.54)	0.235
Atrial fibrillation	6 (5.2)	1.08 (0.50–2.31)	12 (10.3)	2.82 (1.55–5.10)	2.31 (0.85–6.24)	0.099

PFO, patent foramen ovale; PY, person-years; CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack; NE, non-estimable.
*Data are presented as crude number and event rates; †Hazard ratios are for the PFO closure group as compared with the medical therapy alone group. Cox proportional hazard model with robust standard errors to account for clustering in matched pairs.

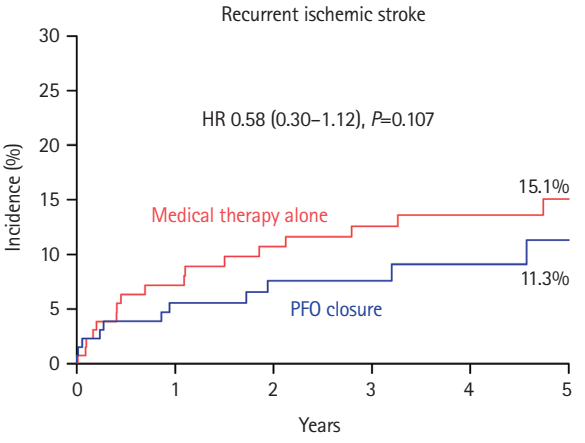
largely consistent with the unadjusted results (Supplementary Table 6).

Atrial fibrillation

Regarding the device closure procedure, 14 serious nonfatal complications occurred in 13 patients, which included puncture site hematomas (n=4), pericardial effusion (n=3), stroke (n=2), pericarditis (n=2), transient atrial fibrillation (n=2), and deep vein thrombosis (n=1). There were 28 new cases (13 in the medical therapy alone group and 15 in the PFO closure group) of atrial fibrillation during follow-up (5-year event rate: medical therapy alone group, 4.5% [0.95 cases per 100 PY] vs. PFO closure group, 9.6% [2.45 cases per 100 PY], *P*=0.026); in the PFO closure group, atrial fibrillation was detected within 45 days after the procedure in 5 patients. In the matched analysis of the high-risk PFO population, the risk of atrial fibrillation tended to be higher in the PFO closure group, albeit without statistical significance (HR: 2.31; 95% CI: 0.85–6.24; *P*=0.099).

Discussion

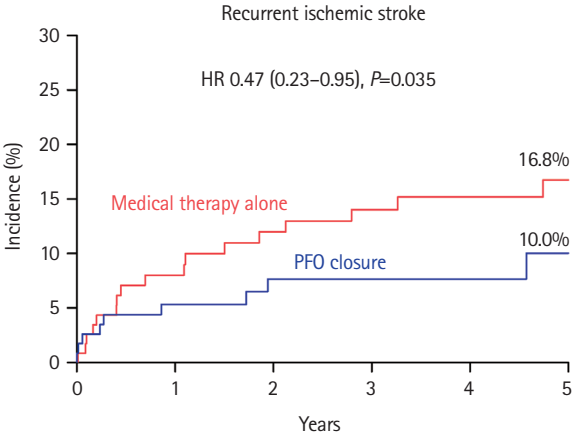
In this retrospective analysis of multicenter registry data, we found that the recurrence rate of ischemic stroke or TIA was as high as 14.6% in elderly patients with cryptogenic stroke and PFO. Importantly, a propensity-score matched analysis showed that elderly cryptogenic stroke patients with a high-risk PFO (e.g., atrial septal aneurysm, large-sized shunt) may significantly benefit from undergoing percutaneous PFO device closure to prevent the recurrence of ischemic events. Although the benefit of PFO closure in older patients has not been confirmed through

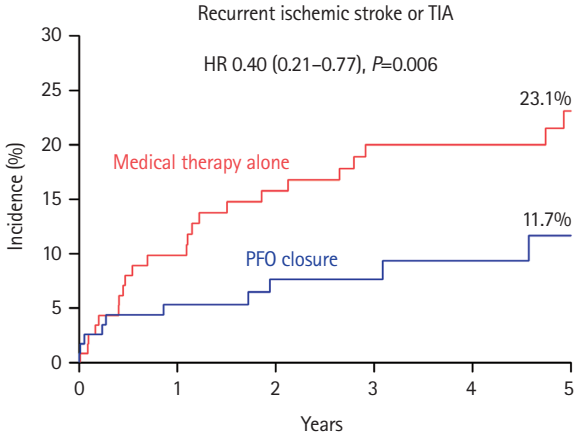


Number at risk						
Medical therapy alone	130	107	100	90	71	57
PFO closure	130	110	92	66	46	39

Number at risk						
Medical therapy alone	130	104	95	83	68	54
PFO closure	130	110	92	66	45	39

Figure 1. Recurrent ischemic stroke or transient ischemic attack (TIA) in the propensity-score matched overall cohort. PFO, patent foramen ovale; HR, hazard ratio.





Number at risk						
Medical therapy alone	116	95	89	80	63	51
PFO closure	116	97	80	57	44	37

Number at risk						
Medical therapy alone	116	93	85	74	60	48
PFO closure	116	97	80	57	44	37

Figure 2. Recurrent ischemic stroke or transient ischemic attack (TIA) in the propensity-score matched high-risk patent foramen ovale (PFO) cohort. HR, hazard ratio.

randomized clinical trials, our results may be useful in guiding shared and individualized decision-making for percutaneous device closure in this selected group of patients with cryptogenic stroke.

PFO remains open in approximately one-fourth of the general population, and its prevalence decreases gradually with increasing age, from 34% during the first three decades of life to 20% during the ninth decade.[17] Since the initial observational studies on the higher prevalence of PFO in patients with cryptogenic stroke, clinicians' interest has mainly been focused on the potential association between PFO and the development of ischemic stroke development in relatively young patients as well as the additive beneficial effect of PFO closure to prevent ischemic stroke recurrence thereof, with only a small number of studies including older cryptogenic stroke patients. However, a landmark study that used TEE in all consecutive ischemic stroke patients to

https://doi.org/10.5853/jos.2023.03265

overcome the selection bias of previous studies found that the association between the presence of PFO and cryptogenic stroke was present in patients aged ≥55 years as well as those aged <55 years.[18] A population-based clinical study using the less invasive transcranial Doppler ultrasound also reported that the association between right-to-left shunt on transcranial Doppler ultrasound and cryptogenic events remained significant in older ages, resulting in the substantial population burden of PFO-associated events.[19] Thus, age restrictions on access to diagnostic or therapeutic procedures in older patients with cryptogenic TIA or stroke should not hinder the necessary further clinical investigation on older patients to develop appropriate diagnostic and therapeutic management strategies.

Age is the single most important risk factor for stroke and the rate of stroke increases by 2-fold for every decade after the age of 55.[20-22] Age is also a strong predictor of stroke recurrence. In an analysis of a pooled dataset from 11 stroke registries, older age groups (60–80 years, >80 years) had significantly higher risks compared with the younger age group (<60 years) for recurrent ischemic stroke or TIA (HR 1.90, 95% CI 1.21–2.98; HR 2.71, 95% CI 1.57–4.70, respectively).[23] Age is also an important prognostic factor after cryptogenic stroke or TIA in patients with PFO who are receiving medical treatment alone: in a pooled analysis of 4 studies, increased risk of ischemic stroke recurrence with PFO was only evident in those aged 65 years or older (odds ratio 2.5, 95% CI 1.4–4.2, P=0.001).[24] Accordingly, in our study patients (mean age: 68.1 years), the overall incidence of ischemic stroke recurrence was 3.12 cases per 100 PY in the medical therapy alone group, which was higher than the incidence rates of 1.26 cases per 100 PY reported in randomized trials including young stroke patients (mean age, 46.5 years) or 2.37 cases per PY in observational cohorts with a mean age of 51.8 years.[24] Meanwhile, our incidence rate is comparable to that (3.27 cases per 100 PY) reported in large randomized clinical trials that included patients with a mean age over 60 years.[25,26] Considering that cases of PFO-associated stroke are common in older individuals, the clinical significance of conducting investigations to assess the potential benefits of PFO closure should not be underestimated or ignored.

Recently, a new classification called PASCAL was developed to integrate the Risk of Paradoxical Embolism score with two simple anatomical features of a high-risk PFO (PFO with atrial septal aneurysm and PFO with a large shunt [>20 bubbles in the left atrium]).[27] This system categorizes individuals based on the probability that the stroke was causally related to the PFO, allowing for a clearer distinction between patients who would benefit from device closure and those without, as shown in an analysis of pooled individual patient data from 6 randomized clinical trials.[13] In this study, we used the same criteria for high-risk PFO suggested in the PASCAL classification system and found that PFO closure was significantly beneficial in preventing recurrent ischemic stroke in elderly cryptogenic stroke patients with a high-risk PFO. On the other hand, the association between PFO closure and the development of atrial fibrillation may require more attention in elderly patients. Randomized trials that mostly enrolled patients aged ≤60 years suggested an increased incidence of atrial fibrillation after PFO closure; indeed, a pooled analysis of those trials reported that the rate of atrial fibrillation was 5.0% with device closure over a median follow-up of 57 months, which was significantly higher than 1.1% in those without device closure.[13] Because the atrial substrate for tachyarrhythmia progresses with age, the risk of atrial fibrillation triggered by the procedure or implanted device could be higher in older patients. In our study, the 5-year rate of atrial fibrillation was 9.6% in the PFO closure group, which was higher than that in the medical therapy group despite the younger age and relatively lower prevalence of risk factors. The observed incidence rate (2.45 cases per 100 PY) of our study was similar to that of a recent descriptive report by Alperi et al.,[28] which included 388 elderly (>60 years) patients who underwent PFO closure (2.66 cases per 100 PY). To date, the incidence, pattern, and impact of atrial fibrillation after PFO closure in this population are largely unknown. The ongoing Defense-Elderly study (ClinicalTrials.gov Identifier: NCT04285918) could provide valuable insights into this topic. Yet, considering the result of the ultimate endpoint of both PFO treatment and atrial fibrillation in our study, our findings suggest that instead of ruling out the use of device closure in elderly patients with cryptogenic stroke, the choice of treatment should be made through shared decision-making to effectively weigh the advantages and disadvantages of PFO closure in preventing secondary stroke, particularly in individuals with a high-risk PFO.

Several limitations should be recognized when interpreting the study results. First, despite careful patient selection and rigorous statistical adjustment, the treatment strategy in our registry was not randomized, which may introduce selection bias. Neurologists assessing the endpoints were not blinded to the management of PFO, which also limits the value of the comparison. Therefore, overall findings should be regarded as explorative and hypothesis-generating. Second, since the study included patients who actively participated in the multidisciplinary decision-making process, it was inevitable that the matched cohort predominantly consisted of high-risk PFO patients. Accordingly, comparing outcomes between treatments was not possible for patients with non-high-risk PFO; thus, our data only offer limited information about this population. Third, although our findings are in line with a previous subgroup analysis of a clinical trial that did

not impose age restrictions for patient enrollment,[29] there are some safety considerations regarding device closure that may diminish its potential benefits, including the increased background risk of stroke due to other causes and the potentially higher procedural risk in the elderly population.[30] In addition, as prolonged cardiac monitoring using an implantable loop recorder was not performed in our current study, there is a possibility of undiagnosed paroxysmal atrial fibrillation, which has a higher prevalence in the elderly population. However, since there is no solid evidence from randomized clinical trials supporting that the use of a loop recorder in reducing the rate of stroke recurrence,[31] we believe that this would not have significantly affected our main findings.

Conclusions

Elderly patients with cryptogenic stroke and PFO had a high recurrence rate of ischemic stroke or TIA, and device closure was associated with a significant risk reduction in the risk of recurrent events, particularly in those with a high-risk PFO. Limiting the use of device closure should be reconsidered, and individualized decision-making for percutaneous device closure is necessary for this specific group of patients with cryptogenic stroke.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.03265.

Funding statement

This research was supported in part by a grant of the Korean Health Technology R&D Project through the Korean Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0481, HC21C0139).

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: PHL, JSK (Jung-Sun Kim), JKS, SUK, JSK (Jong S. Kim). Study design: PHL, JSK (Jung-Sun Kim), JKS. Methodology: PHL, JSK (Jung-Sun Kim), SUK, BJK, JSL, JSK (Jong S. Kim). Data collection: PHL, JSK (Jung-Sun Kim), JKS, SHK, BJK, BJS, JSW, SHA, JWS, JYK, KL, SYL, RH, SJ, JYJ, JHB, YDK, SHH, JSK (Jong S. Kim). Investigation: PHL, JSK (Jung-Sun Kim), JKS, SHK, BJK, BJS, JSW, SHA, JWS, JYK, KL, SYL, RH, SJ, JYJ, JHB, YDK, SHH, JSK (Jong S Kim). Statistical analysis: PHL, JSL. Writing—original draft: PHL, JKS. Writing—review & editing: PHL, JSK (Jung-Sun Kim), JKS, JSK (Jong S Kim). Funding acquisition: JKS, SUK. Approval of final manuscript: all authors.

Acknowledgments

We thank the research coordinators at each participating centers for their help in collecting and ensuring the accuracy and completeness of clinical data.

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Supplementary Table 1. Standardized differences of clinically relevant variables between the treatment groups before and after propensity-score matching

	Overall cohort		High-risk PFO cohort	
	ASD before matching	ASD after matching	ASD before matching	ASD after matching
Age (yr)	0.51	0.06	0.53	0.07
Male sex	0.03	0.07	0.02	0.06
Body mass index	0.07	0.03	0.02	0.01
Hypertension	0.19	0.03	0.21	0.05
Diabetes	0.16	0.00	0.11	0.00
Hyperlipidemia	0.11	0.05	0.19	0.04
Chronic kidney disease	0.14	0.13	0.17	0.13
Current smoker	0.12	0.04	0.04	0.02
Prior stroke	0.05	0.04	0.00	0.04
Prior TIA	0.11	0.04	0.08	0.00
Migraine	0.23	0.04	0.19	0.05
Prior DVT or PTE	0.19	0.13	0.21	0.13
History of cancer	0.07	0.12	0.06	0.11
Cortical infarction	0.22	0.02	0.07	0.02
High-risk PFO	0.86	0.00		

An ASD >0.2 was considered as a serious imbalance.
PFO, patent foramen ovale; ASD, absolute standardized difference; TIA, transient ischemic attack; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

Supplementary Table 2. Patient numbers who underwent PFO device closure and antithrombotic medical treatment only at each participating center

Centers	Antithrombotic therapy only (n=276)	PFO closure (n=161)
D01	0	3
D02	16	19
D03	13	6
D04	0	23
D05	80	76
D06	104	8
D07	30	2
D08	33	16
D09	0	5
D10	0	3

PFO, patent foramen ovale.

Supplementary Table 3. Medications in each group during follow-up

	Total patients		*P*
	Medication-only group (n=276)	PFO closure group (n=161)	
At 30 days			
Antiplatelet alone	231/276 (83.7)	146/161 (90.7)	0.057
Anticoagulant alone	28/276 (10.1)	10/161 (6.2)	0.218
Both	11/276 (4.0)	5/161 (3.1)	0.835
None	6/276 (2.2)	0	0.145
At 6 months			
Antiplatelet alone	217/260 (83.5)	142/156 (91.0)	0.043
Anticoagulant alone	24/260 (9.2)	6/156 (3.8)	0.063
Both	10/260 (3.8)	6/156 (3.8)	>0.999
None	9/260 (3.5)	2/156 (1.3)	0.305
At 12 months			
Antiplatelet alone	199/249 (79.9)	126/152 (82.9)	0.544
Anticoagulant alone	24/249 (9.6)	6/152 (3.9)	0.057
Both	13/249 (5.2)	9/152 (5.9)	0.942
None	13/249 (5.2)	10/152 (6.6)	0.729
	Matched cohort		*P*
	Medication-only group (n=130)	PFO closure group (n=130)	
At 30 days			
Antiplatelet alone	107/130 (82.3)	117/130 (90.0)	0.106
Anticoagulant alone	15/130 (11.5)	8/130 (6.2)	0.190
Both	6/130 (4.6)	5/130 (3.8)	>0.999
None	2/130 (1.5)	0	0.478
At 6 months			
Antiplatelet alone	103/124 (83.1)	112/126 (88.9)	0.252
Anticoagulant alone	15/124 (12.1)	5/126 (4.0)	0.033
Both	4/124 (3.2)	7/126 (5.6)	0.555
None	2/124 (1.6)	2/126 (1.6)	>0.999
At 12 months			
Antiplatelet alone	93/117 (79.5)	99/122 (81.1)	0.873
Anticoagulant alone	14/117 (12.0)	4/122 (3.3)	0.022
Both	6/117 (5.1)	9/117 (7.4)	0.653
None	4/117 (3.4)	10/117 (8.2)	0.195

PFO, patent foramen ovale.

https://doi.org/10.5853/jos.2023.03265

Supplementary Table 4. Crude analysis of clinical outcomes in the overall and high-risk PFO population

	Overall cohort					
	Medical therapy alone (n=276)		PFO closure (n=161)		HR (95% CI)†	*P*
	N (%)*	Incidence rate (100 PY, 95% CI)	N (%)*	Incidence rate (100 PY, 95% CI)		
Primary outcome						
Ischemic stroke or TIA	50 (18.1)	3.98 (3.02–5.26)	14 (8.7)	2.24 (1.33–3.79)	0.52 (0.29–0.95)	0.034
Secondary outcomes						
All-cause death	24 (8.7)	1.71 (1.15–2.55)	2 (1.2)	0.30 (0.07–1.20)	0.19 (0.04–0.81)	0.025
Ischemic stroke	40 (14.5)	3.12 (2.29–4.25)	12 (7.5)	1.91 (1.09–3.37)	0.56 (0.30–1.08)	0.083
Ischemic stroke, TIA, or systemic embolization	51 (18.5)	4.08 (3.10–5.37)	15 (9.3)	2.42 (1.46–4.01)	0.55 (0.31–0.99)	0.046
Intracranial bleeding	9 (3.3)	0.65 (0.34–1.25)	2 (1.2)	0.30 (0.08–1.21)	0.40 (0.09–1.86)	0.243
Major bleeding	18 (6.5)	1.33 (0.84–2.12)	6 (3.7)	0.91 (0.41–2.03)	0.62 (0.25–1.58)	0.319
Atrial fibrillation	13 (4.7)	0.95 (0.55–1.64)	15 (9.3)	2.45 (1.48–4.06)	2.28 (1.08–4.82)	0.030
	High-risk PFO cohort					
	Medical therapy alone (n=156)		PFO closure (n=147)		HR (95% CI)†	*P*
	N (%)*	Incidence rate (100 PY, 95% CI)	N (%)*	Incidence rate (100 PY, 95% CI)		
Primary outcome						
Ischemic stroke or TIA	37 (23.7)	5.54 (4.01–7.64)	12 (8.2)	2.08 (1.18–3.66)	0.36 (0.19–0.69)	0.002
Secondary outcomes						
All-cause death	11 (7.1)	1.43 (0.79–2.58)	2 (1.4)	0.32 (0.08–1.30)	0.25 (0.05–1.14)	0.074
Ischemic stroke	31 (19.9)	4.48 (3.15–6.37)	10 (6.8)	1.72 (0.93–3.21)	0.36 (0.18–0.75)	0.006
Ischemic stroke, TIA, or systemic embolization	38 (24.4)	5.74 (4.18–7.89)	13 (8.8)	2.27 (1.32–3.91)	0.38 (0.20–0.72)	0.003
Intracranial bleeding	7 (4.5)	0.93 (0.45–1.96)	1 (0.7)	0.16 (0.02–1.15)	0.16 (0.02–1.30)	0.087
Major bleeding	15 (9.6)	2.06 (1.24–3.41)	4 (2.7)	0.65 (0.24–1.74)	0.29 (0.10–0.88)	0.028
Atrial fibrillation	8 (5.1)	1.08 (0.54–2.16)	15 (10.2)	2.67 (1.61–4.43)	2.20 (0.93–5.19)	0.073

PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.
*Data are presented as crude number and event rates; †Hazard ratios are for the PFO closure group as compared with the medical therapy alone group.

Supplementary Table 5. Interaction effects between treatment modalities and different patient enroll periods in the overall and high-risk PFO population

Outcomes	Overall population						
	HR (95% CI)	*P*	Index stroke year <2016		Index stroke year ≥2016		*P* for interaction effect
			HR (95% CI)	*P*	HR (95% CI)	*P*	
Primary outcome							
Ischemic stroke or TIA	0.45 (0.24–0.84)	0.012	0.54 (0.22–1.29)	0.164	0.32 (0.13–0.80)	0.014	0.422
Secondary outcomes							
Death	0.40 (0.09–1.89)	0.247	NE	-	NE	-	-
Ischemic stroke	0.58 (0.30–1.12)	0.107	0.66 (0.26–1.64)	0.367	0.43 (0.16–1.20)	0.107	0.557
Ischemic stroke, TIA, or systemic embolization	0.47 (0.26–0.87)	0.017	0.59 (0.26–1.35)	0.212	0.32 (0.13–0.80)	0.014	0.333
Intracranial bleeding	0.46 (0.12–1.77)	0.258	0.49 (0.05–4.60)	0.531	0.40 (0.04–4.54)	0.461	0.918
Major bleeding	0.72 (0.27–1.90)	0.505	1.19 (0.33–4.34)	0.790	0.30 (0.06–1.56)	0.152	0.229
Atrial fibrillation	1.97 (0.76–5.09)	0.162	2.25 (0.64–7.96)	0.209	1.55 (0.39–6.19)	0.538	0.688
Outcomes	High-risk PFO population						
	HR (95% CI)	*P*	Index stroke year <2016		Index stroke year ≥2016		*P* for interaction effect
			HR (95% CI)	*P*	HR (95% CI)	*P*	
Primary outcome							
Ischemic stroke or TIA	0.40 (0.21–0.77)	0.006	0.45 (0.17–1.16)	0.097	0.31 (0.12–0.80)	0.016	0.583
Secondary outcomes							
Death	0.55 (0.11–2.72)	0.461	NE	-	NE	-	-
Ischemic stroke	0.47 (0.23–0.95)	0.035	0.50 (0.19–1.36)	0.176	0.37 (0.13–1.09)	0.072	0.698
Ischemic stroke, TIA, or systemic embolization	0.42 (0.22–0.81)	0.009	0.50 (0.21–1.23)	0.131	0.31 (0.12–0.81)	0.016	0.462
Intracranial bleeding	0.29 (0.05–1.59)	0.154	NE	-	NE	-	-
Major bleeding	0.51 (0.17–1.54)	0.235	0.69 (0.13–3.57)	0.657	0.31 (0.06–1.67)	0.173	0.535
Atrial fibrillation	2.31 (0.85–6.24)	0.099	2.16 (0.61–7.63)	0.234	2.47 (0.51–11.96)	0.261	0.892

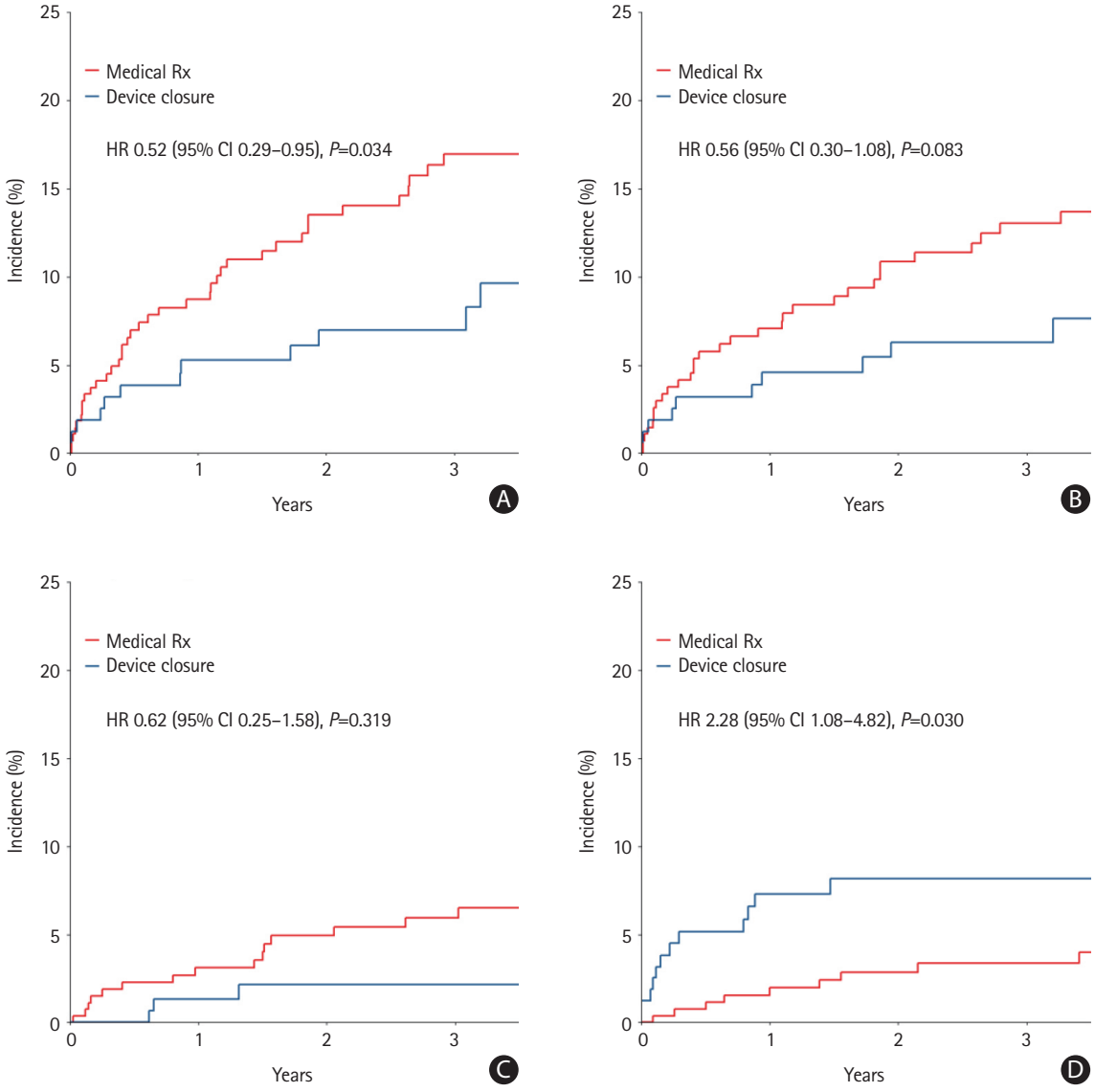
Hazard ratios are for the PFO closure group as compared with the medical therapy alone group.
PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; NE, non-estimable.

Supplementary Table 6. Hazard ratios adjusted for the participating center effect in the propensity-score matched cohorts

	Overall cohort			High-risk PFO cohort		
	HR*	95% CI	*P*	HR*	95% CI	*P*
Primary outcome						
Ischemic stroke or TIA	0.37	0.21–0.96	0.005	0.33	0.16–0.71	0.004
Secondary outcome						
Death	0.41	0.08–1.97	0.264	0.55	0.11–2.86	0.479
Ischemic stroke	0.45	0.21–0.96	0.038	0.37	0.16–0.85	0.018
Ischemic stroke, TIA, or systemic embolization	0.39	0.20–0.77	0.007	0.36	0.18–0.75	0.006
Intracranial bleeding	0.42	0.08–2.23	0.310	0.27	0.03–2.42	0.241
Major bleeding	0.44	0.14–1.37	0.155	0.33	0.09–1.22	0.097
Atrial fibrillation	1.82	0.70–4.74	0.223	2.24	0.83–6.06	0.113

PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.
*Hazard ratios are for the PFO closure as compared with the medical therapy alone group. Cox proportional hazards regression with a shared frailty factor.

https://doi.org/10.5853/jos.2023.03265



Supplementary Figure 1. Cumulative incidence of clinical outcomes. (A) Stroke or TIA. (B) Ischemic stroke. (C) Major bleeding. (D) Atrial fibrillation. TIA, transient ischemic attack; HR, hazard ratio; CI, confidence interval.