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Cryptogenic Stroke and High-Risk Patent Foramen Ovale

The DEFENSE-PFO Trial

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ABSTRACT

BACKGROUND Recent reports showing the favorable role of patent foramen ovale (PFO) closure in patients with cryptogenic stroke have raised the issue of selecting optimal candidates.

OBJECTIVES This study, DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale), evaluated whether the benefits of PFO closure can be determined on the basis of the morphologic characteristics of the PFO, as evaluated by transesophageal echocardiography.

METHODS Patients with cryptogenic stroke and high-risk PFO were divided between a transcatheter PFO closure and a medication-only group. High-risk PFO included PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium ≥10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥2 mm. The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction–defined major bleeding during 2 years of follow-up.

RESULTS From September 2011 until October 2017, 120 patients (mean age: 51.8 years) underwent randomization. PFO size, frequency of septal aneurysm (13.3% vs. 8.3%; $p = 0.56$), and hypermobility (45.0% vs. 46.7%; $p > 0.99$) were similar between the groups. All PFO closures were successful. The primary endpoint occurred exclusively in the medication-only group (6 of 60 patients; 2-year event rate: 12.9% [log-rank $p = 0.013$]; 2-year rate of ischemic stroke: 10.5% [$p = 0.023$]). The events in the medication-only group included ischemic stroke ($n = 5$), cerebral hemorrhage ($n = 1$), Thrombolysis In Myocardial Infarction–defined major bleeding ($n = 2$), and transient ischemic attack ($n = 1$). Nonfatal procedural complications included development of atrial fibrillation ($n = 2$), pericardial effusion ($n = 1$), and pseudoaneurysm ($n = 1$).

CONCLUSIONS PFO closure in patients with high-risk PFO characteristics resulted in a lower rate of the primary endpoint as well as stroke recurrence. (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale [DEFENSE-PFO]; NCT01550588) (J Am Coll Cardiol 2018;71:2335–42)

The potential association between patent foramen ovale (PFO) and cryptogenic stroke has been a controversial issue for several decades (1–12). Since the successful clinical introduction of a safe transcatheter closure technique, this challenging issue has become an open and rapidly evolving question regarding the clinical benefit of closing a PFO after a cryptogenic stroke.

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ABBREVIATIONS AND ACRONYMS

MRI = magnetic resonance imaging

PFO = patent foramen ovale

TEE = transesophageal echocardiography

TIMI = Thrombolysis In Myocardial Infarction

We have witnessed the publication of articles with the opposite results in the past 5 years (13–18). Along with U.S. Food and Drug Administration approval of the Amplatzer PFO Occluder (St. Jude Medical, St. Paul, Minnesota), the current consensus is that the key to appropriate device use is a comprehensive assessment to select the optimal candidates for the procedure. A deliberate and systematic evaluation by both a neurologist and a cardiologist has been recommended to exclude small-vessel disease, an intracardiac embolic source, stroke associated with major intracranial and extracranial vascular disorders, and hypercoagulable status. This approach mainly focuses on finding exclusionary factors for the application of a stringent definition of cryptogenic stroke.

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Although PFO shows a variable degree of shunt amount and is reported to have a cumulative risk of stroke with atrial septal aneurysm, it remains elusive whether the potential benefit gained from device closure of a PFO can also be determined on the basis of the morphologic characteristics of the PFO. In our previous study, we observed that the anatomic features of the atrial septal abnormalities associated with PFO, as evaluated by transesophageal echocardiography (TEE), were quite diverse and that high-risk PFO as defined by TEE findings, including PFO size, the presence of an atrial septal aneurysm, or hypermobility, was useful in predicting stroke recurrence (19). Considering the high prevalence of PFO in the general population and in patients with cryptogenic stroke, transcatheter device closure confined to patients with cryptogenic stroke and characteristic PFO morphology associated with a higher stroke recurrence rate would be a more appropriate approach to enhance the benefits of PFO closure. To test the hypothesis, this multicenter, randomized, open-label trial (DEFENSE-PFO [Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale]) was performed.

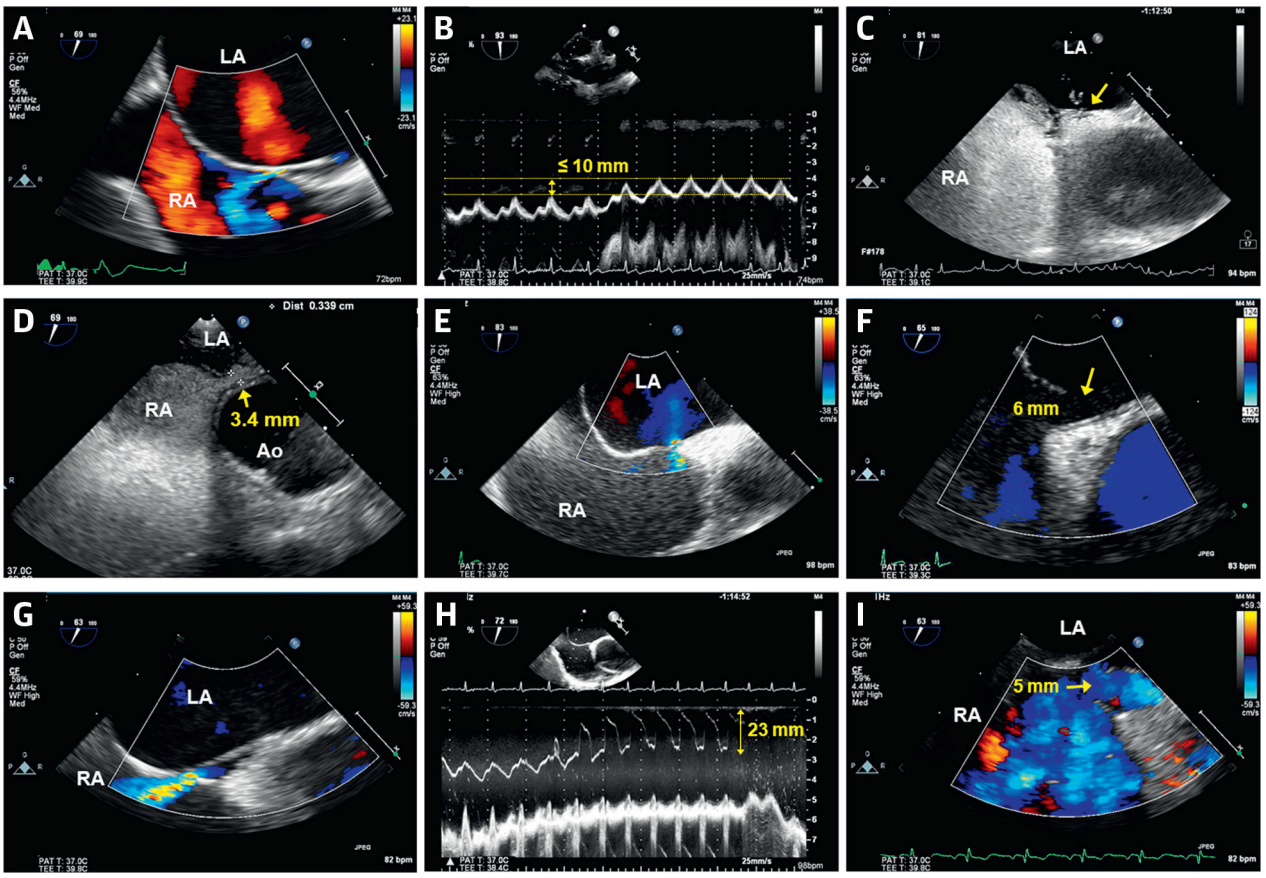
METHODS

STUDY DESIGN. The DEFENSE-PFO trial was an investigator-initiated, multicenter, randomized, open-label, superiority trial that compared combined transcatheter PFO closure and medical therapy alone in patients with cryptogenic stroke and high-risk PFO. The trial was conducted at 2 sites in South Korea from June 2011 through October 2017. The trial was approved by the Institutional Review Board at each participating site, and all patients provided written informed consent. Investigators affiliated with the Asan Medical Center, Seoul, South Korea, were responsible for the management and monitoring of the data. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

PATIENT SELECTION. Patients were eligible for the trial if they had experienced an ischemic stroke within the previous 6 months with no identifiable cause other than a high risk PFO with right-to-left shunting. An ischemic stroke was defined as an acute focal neurologic deficit, presumably caused by ischemia, that either resulted in clinical symptoms lasting 24 h or more or was associated with evidence of relevant infarction on magnetic resonance imaging (MRI) of the brain. For a stringent definition of cryptogenic stroke, a standardized evaluation was performed to rule out other identifiable mechanisms of stroke, such as large-artery atherosclerotic disease, an established cardioembolic source, small-vessel occlusive disease, a hypercoagulable disorder requiring anticoagulation, or arterial dissection. To assess whether large-artery atherosclerotic disease was a potential source of stroke, imaging of the intracranial arteries, cervical arteries, and aortic arch was performed in all patients by means of computed tomography angiography, magnetic resonance angiography, or ultrasonography; patients with at least 50% stenosis of a major vessel or with occlusion of a major vessel were excluded from the trial. Patients were also excluded if they had had a stroke as a result of small-vessel occlusive disease, which was defined as the presence of a small, deep infarction (<1.5 cm in diameter) or a typical clinical lacunar syndrome. Holter monitoring or prolonged monitoring of the cardiac rhythm was performed to rule out paroxysmal atrial fibrillation.

A standardized TEE protocol (19) was used to assess the morphologic characteristics of the atrial septum and right-to-left shunting through a high-risk PFO with agitated saline while the patient was at rest or while a Valsalva maneuver was being performed. As described previously (19), a high-risk PFO included a PFO with an atrial septal aneurysm (protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium ≥10 mm), or PFO size (maximum separation of the septum primum from the secundum during the Valsalva maneuver) ≥2 mm on TEE (**Figure 1**). Patients with a history of myocardial infarction or unstable angina, a history of intracranial bleeding, pre-existing

FIGURE 1 Representative TEE Images Showing Low-Risk and High-Risk PFO

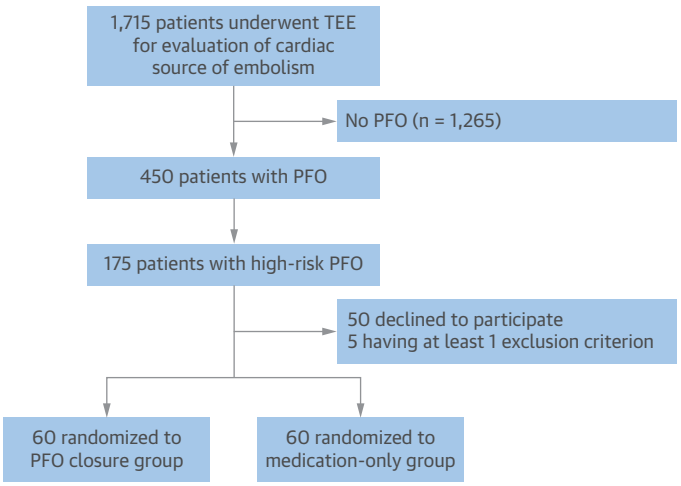


Low-risk patent foramen ovale (PFO) is characterized by **(A)** the absence of aneurysmal changes of the interatrial septum **(B)** with limited motion and **(C)** separation of the septum primum and the secundum, resulting in a small PFO size and shunt during the Valsalva maneuver **(arrow)**. High-risk PFO is characterized by **(D)** PFO size of >3 mm **(arrow)** or **(E)** the presence of atrial septal aneurysm with **(F)** hypermobility of the septum during the Valsalva maneuver resulting in a large PFO size **(arrow). (G)** Some patients without a characteristic atrial septal aneurysm may show exaggerated motion of the atrial septum during the Valsalva maneuver, resulting in **(H)** septal excursion >10 mm and **(I)** a large PFO size **(arrow)**. Ao = aorta; LA = left atrium; RA = right atrium; TEE = transesophageal echocardiography.

neurological disorders, left ventricular systolic dysfunction with aneurysm or akinesia, contraindications to antiplatelet therapy, or an underlying malignant disease were excluded.

RANDOMIZATION AND TREATMENTS. After morphologic assessment of PFO and the adjacent atrial septum, eligible patients were randomly assigned in a 1:1 ratio, using dedicated Internet-based software, to receive either transcatheter PFO closure (Amplatzer PFO Occluder) or medical therapy alone. Randomization was not stratified according to participating center or morphologic characteristics of PFO. Treatments were administered in an open-label fashion and were started as soon as possible. PFO closure was performed by experienced interventional cardiologists using a device approved by the Food and Drug Administration (Amplatzer PFO Occluder). All patients received either antiplatelet therapy or anticoagulation therapy chosen by the local investigator. Patients who underwent PFO closure were generally recommended to start a dual antiplatelet regimen (aspirin 100 mg/day in combination with clopidogrel 75 mg/day) for at least 6 months after the procedure. However, the local investigator or attending neurologists could choose to continue either antiplatelet therapy or anticoagulation therapy on the basis of the individual risk-to-benefit ratio. Antiplatelet therapy included aspirin, aspirin in combination with clopidogrel at a dose of 75 mg/day, or aspirin in combination with cilostazol at a dose of 200 mg/day. Warfarin was used to maintain the target international normalized ratio of 2.0 to 3.0. Clinical data were regularly recorded by the local investigator during regular clinic visits (1, 3, 6, 12, and 24 months).

FIGURE 2 Flow Diagram of the Study Group



Abbreviations as in Figure 1.

Follow-up MRI was recommended 6 months after randomization in both groups to diagnose asymptomatic ischemic stroke.

STATISTICAL ANALYSIS. On the basis of the results from a previous study (19), we assumed the event rate at 24 months would be 4% in the PFO closure group and 15% in the medication-only group. It was estimated that 99 patients in each group were needed to detect this difference with a statistical power of 80%. Expecting that approximately 10% of the patients would not return for follow-up, the total sample size was estimated to be 210 patients (105 patients per group) with a 2-sided alpha level of 0.05.

During the course of the current trial, which definitely had a lower than expected rate of patient recruitment, other trials of PFO closure reported a beneficial effect of PFO closure over medical therapy alone (16–18). Among them, the CLOSE (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) investigators used selection criteria of morphologic features of the atrial septum and PFO similar to those used in our study (17); these investigators selected a PFO with an associated atrial septal aneurysm or large interatrial shunt (the appearance of more than 30 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium). The CLOSE investigators demonstrated that the rate of stroke recurrence was lower among those patients assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone (hazard ratio: 0.03; 95% confidence interval: 0.00 to 0.26; $p < 0.001$). On the basis of this information and without knowledge of the event rates in the study group in the current trial, the investigators agreed to consider cessation of enrollment for the patients' safety and to consult the Institutional Review Board. Early termination of the trial was approved by the Board, and the Steering Committee decided to stop enrollment in November 2017 and pursue follow-up of all patients.

The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction (TIMI)-defined major bleeding during 2 years of follow-up. The analysis was performed in the intention-to-treat cohort, which included all patients who were randomly assigned to a treatment. An additional analysis was performed in the per-protocol cohort, which included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation. In addition to the composite of clinical events listed as the primary endpoint, the secondary endpoint included asymptomatic ischemic stroke on follow-up MRI, which was recommended to be performed 6 months after the randomization. Survival curves were estimated by means of the Kaplan-Meier method and were compared by the log-rank test.

RESULTS

PATIENTS. From September 2011 until October 2017, 450 patients had a diagnosis of cryptogenic stroke with PFO, and the frequency of high-risk PFO was 38.9% ($n = 175$). Fifty patients declined to participate in the trial, and 5 had at least 1 exclusion criterion. Finally, 60 patients (mean age 51.8 years) were randomly enrolled in each group (Figure 2). The baseline characteristics of both groups are summarized in Table 1, and these show no significant difference between the groups in terms of age, sex, medical history, qualifying event, modified Rankin scale at discharge (a measure of disability), and the anatomic characteristics of PFO and the atrial septum as evaluated by TEE.

INTERVENTION AND MEDICATIONS. Among the 60 patients in the combined PFO closure group, 7 declined the intervention. One single device (Amplatzer PFO Occluder) was used for PFO closure, and successful closure was achieved in all patients. One day after the procedure, transthoracic echocardiography was repeated to check the amount of the remnant shunt, and this imaging revealed minimal or no (<10 microbubbles) residual shunt in all but 4

TABLE 1 Baseline Characteristics of the Patients

	PFO Closure Group (N = 60)	Medication-Only Group (N = 60)	p Value
Age, yrs	49 ± 15	54 ± 12	0.06
Male	33 (55.0)	34 (56.7)	>0.99
Medical history			
Hypertension	12 (20.0)	17 (28.3)	0.39
Diabetes	6 (10.0)	8 (13.3)	0.78
Current smoker	10 (16.7)	16 (26.7)	0.27
Hypercholesterolemia	18 (30.0)	25 (41.7)	0.25
Qualifying event			0.28
Anterior circulatory territory	28 (46.7)	34 (56.7)	
Multiple territories	0 (0.0)	2 (3.3)	
Modified Rankin scale			0.74
0 or 1	47 (78.3)	45 (75.0)	
2 or 3	13 (21.7)	15 (25.0)	
Morphologic characteristics of PFO			
Shunt at rest			
No shunt	25 (41.7)	26 (43.3)	0.25
Left-to-right shunt	31 (51.7)	34 (56.7)	
Right-to-left shunt	3 (5.0)	0 (0.0)	
Bidirectional shunt	1 (1.7)	0 (0.0)	
PFO size, mm	3.2 ± 1.5	3.2 ± 1.1	0.85
Atrial septal aneurysm	5 (8.3)	8 (13.3)	0.56
Atrial septal hypermobility	28 (46.7)	27 (45.0)	>0.99

Values are mean ± SD or n (%).
PFO = patent foramen ovale.

TABLE 2 Changes in Antiplatelet or Anticoagulation Therapy During Follow-Up

	PFO Closure Group (N = 60)	Medication-Only Group (N = 60)	p Value
At 30 days			
Single-antiplatelet therapy	10.0 (6/60)	16.7 (10/60)	0.42
Dual-antiplatelet therapy	75.0 (45/60)	58.3 (35/60)	0.08
Warfarin	15.0 (9/60)	25.0 (15/60)	0.25
At 6 months			
Single-antiplatelet therapy	34.6 (18/52)	25.0 (13/52)	0.39
Dual-antiplatelet therapy	57.7 (30/52)	51.9 (27/52)	0.69
Warfarin	7.7 (4/52)	23.1 (12/52)	0.05
At 12 months			
Single-antiplatelet therapy	42.6 (20/47)	37.0 (17/46)	0.67
Dual-antiplatelet therapy	34.0 (16/47)	41.3 (19/46)	0.53
Warfarin	6.4 (3/47)	21.7 (10/46)	0.04
No antiplatelet therapy or warfarin	17.0 (8/47)	0.0 (0/46)	0.006

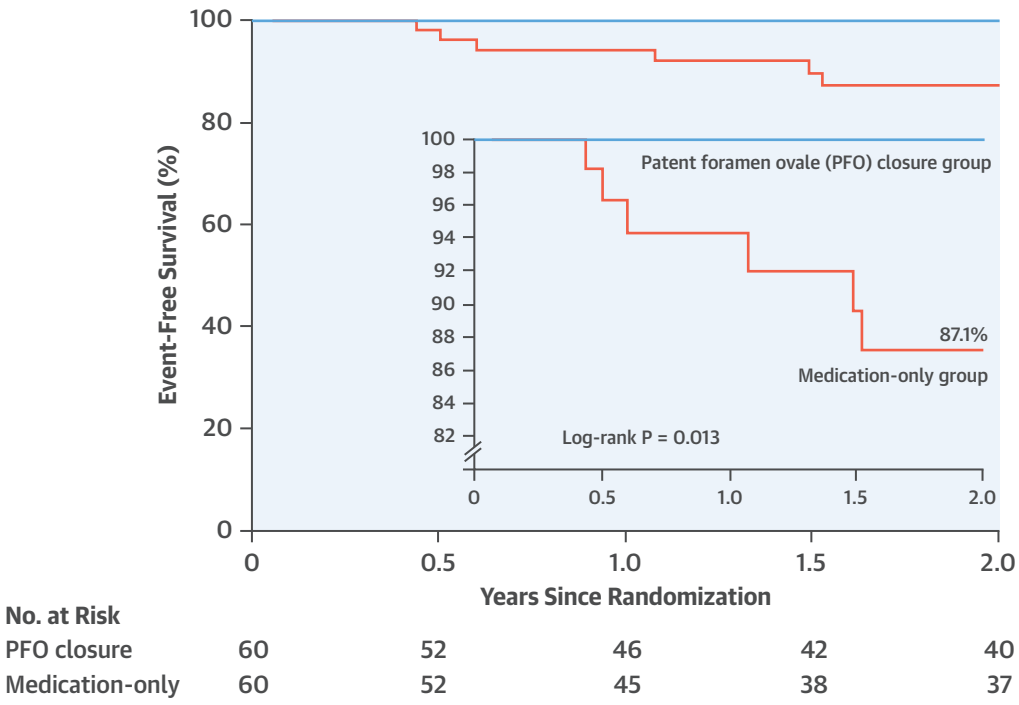
Values are % (n/N).
PFO = patent foramen ovale.

patients. Follow-up echocardiography was performed in 1 patient with severe residual shunt 2 months later, and this study showed disappearance of the residual shunt.

Temporal changes of the medications prescribed in the 2 groups are summarized in Table 2. Dual-antiplatelet therapy was the most frequently chosen medication in both groups at 30 days after randomization, and this trend continued for up to 12 months in the medication-only group. However, in the combined PFO closure group, single-antiplatelet therapy became the most frequent strategy after 6 months, and 17% (8 of 47) of patients stopped medication after the PFO closure. At the beginning, warfarin was prescribed in 25% of the patients in the medication-only group, and anticoagulation therapy continued in more than 20% until 12 months after the randomization. Thus, anticoagulation therapy was more frequently used in the medication-only group 6 months after the randomization.

OUTCOMES IN THE PFO CLOSURE GROUP VERSUS THE MEDICATION-ONLY GROUP. The median duration of follow-up was 2.8 years (interquartile range [IQR]: 0.9 to 4.1 years) in both groups (2.8 years [IQR: 0.9 to 4.2 years] in the PFO closure group vs. 2.8 years [IQR: 0.9 to 4.1 years] in the medication-only group). Major procedural complications occurred in 2 patients in the combined PFO closure group; these included development of pericardial effusion (n = 1) and pseudoaneurysm at the puncture site (n = 1). Atrial fibrillation developed in 1 patient 1 day after the procedure and in the other patient during follow-up. In the intention-to-treat cohort, no event of the primary endpoint occurred in the combined PFO closure group, whereas the primary endpoint occurred in 6 of 60 patients in the medication-only group (2-year event rate 12.9%; 95% confidence interval: 3.2 to 22.6; standard error 5.0), and the Kaplan-Meier curves showed a significant difference (log-rank p = 0.013) (Central Illustration). The events that occurred in the medication-only group included ischemic stroke (n = 5), cerebral hemorrhage (n = 1), TIMI-defined major bleeding (n = 2), and transient ischemic attack (n = 1) (Table 3). Major bleeding included 1 patient who developed spontaneous intracerebral hemorrhage during warfarin medication and another who showed hemorrhagic transformation of acute ischemic stroke during dual-antiplatelet therapy. Other ischemic strokes occurred during dual-antiplatelet therapy in 2 patients, single-antiplatelet therapy in 1, and warfarin in 1. Atrial septal aneurysm or hypermobility was present in 4 of 5 patients with recurrent stroke, and 3 patients showed new lesions in the vascular territory different from the initial lesion. The Kaplan-Meier 2-year cumulative estimate of the probability of stroke was 10.5% in the

CENTRAL ILLUSTRATION **Device Closure for High-Risk PFO: Kaplan-Meier Cumulative Estimates**



No. at Risk					
PFO closure	60	52	46	42	40
Medication-only	60	52	45	38	37

Lee, P.H. et al. J Am Coll Cardiol. 2018;71(20):2335–42.

Kaplan-Meier cumulative estimates of the primary endpoint in the patent foramen ovale (PFO) closure group versus the medication-only group.

medication-only group (95% confidence interval: 1.68 to 19.32; standard error 4.5; p = 0.023 when compared with the PFO closure group), a finding suggesting that the number of patients needed to treat to avoid 1 stroke at 2 years would be 10.

Seven patients randomized to the combined PFO closure group did not undergo the device closure, and 4 patients in the medication-only group underwent device closure during follow-up. Thus, a total of 109 patients were available for the per-protocol analysis. None of the 11 patients who changed treatment arms after randomization experienced the primary endpoint. The per-protocol analysis showed that the primary event occurred only in the medication-only group, and the event-free survival rates were significantly different (log-rank p = 0.016) (Online Figure 1).

Follow-up MRI was performed in 72 patients at a median of 6 months in both groups. The incidence of silent brain infarction was not significantly different between the groups (8.8% [3 of 34] in the PFO closure group vs. 18.4% [7 of 38] in the medication-only group; p = 0.24) (**Table 3**).

DISCUSSION

In this trial of PFO closure in a selected group of patients who had experienced a recent cryptogenic ischemic stroke and had high-risk PFO defined as PFO with an associated atrial septal aneurysm, hypermobility, or large size, the rate of the primary endpoint, including recurrent ischemic stroke, was significantly lower with closure of the PFO in combination with medical therapy than with medical therapy alone. This trial showed that 10 patients would need to be treated to avoid 1 stroke at 2 years.

The initial 3 randomized trials, published in 2012 and 2013, did not show the superiority of PFO closure over medical therapy alone for secondary prevention in patients with cryptogenic stroke and PFO (13–15). However, in a pooled analysis of individual participant data from the 3 trials, the rates of recurrent stroke were significantly lower in patients who underwent PFO closure than in those who received medical therapy alone (20). Last year, we witnessed the dramatic conversion from a negative to a positive

TABLE 3 Clinical Outcomes

2-Yr Outcome	PFO Closure Group (n = 60)	Medication-Only Group (n = 60)	p Value
Primary endpoint	0 (0.0)	6 (12.9)	0.013
Secondary endpoint			
Ischemic stroke	0 (0.0)	5 (10.5)	0.023
Vascular death	0 (0.0)	0 (0.0)	NA
TIMI-defined major bleeding	0 (0.0)	2 (4.9)	0.15
Hemorrhagic stroke	0 (0.0)	1 (2.5)	0.30
Transient ischemic attack	0 (0.0)	1 (2.0)	0.32
Systemic embolism	0 (0.0)	0 (0.0)	NA
New ischemic lesion on MRI	3/34 (8.8)	7/38 (18.4)	0.24

Values are n (%) (Kaplan-Meier estimates) or n/N (%).

MRI = magnetic resonance imaging; NA = not applicable; PFO = patent foramen ovale; TIMI = Thrombolysis In Myocardial Infarction.

outlook with respect to PFO closure (16–18). New trials with positive findings have a different study design in terms of medications and follow-up duration. Although warfarin was included in all old trials with negative findings, only antiplatelet therapy was the comparator in the Gore REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients) trial (16). In the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial, follow-up duration was the only parameter associated with the opposite results (2.1 vs. 5.9 years) (14,18). The potential role of risk stratification on the basis of the morphologic characteristics of PFO and the associated anatomic features of the adjacent atrial septum has remained elusive. Atrial septal aneurysm characterized by its hypermobility has been reported to be an independent risk factor for recurrent stroke in patients with PFO (19,21), and subgroup analysis of the previous trial with negative results showed that PFO closure was beneficial in patients with atrial septal aneurysm or substantial shunt size (15).

Our study is different from 2 of the trials with favorable conclusions for PFO device closure, in which the anatomic features of the atrial septum or PFO were not considered at all, and all patients with cryptogenic stroke presumably attributed to PFO were included (16,18). The only trial with stringent entry criteria similar to ours is the CLOSE trial (17), which required that patients have a large interatrial right-to-left shunt (more than 30 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium) or an atrial septal aneurysm (a septum primum excursion >10 mm). Both the CLOSE trial and our trial showed no occurrence of stroke in patients who underwent PFO closure, a finding suggesting that the beneficial effect of percutaneous device closure of PFO can be maximized by adding the morphologic characteristics of PFO, as evaluated by TEE, to the selection criteria for the procedure. Thus, in addition to the systematic and standardized evaluation for the exclusion of many clinical conditions needed to consider a stroke to be cryptogenic, morphologic evaluation to diagnose positive characteristics of PFO should be incorporated as an additional stringent criterion to enhance the benefit from PFO closure.

Selection of the appropriate medical treatment for patients with cryptogenic stroke and PFO still remains an unresolved and challenging issue. Our retrospective study (19) and a previous systemic review (22) suggested that anticoagulant therapy may be superior to antiplatelet therapy for the prevention of stroke recurrence in patients with PFO. However, the comparison of oral anticoagulant agents with antiplatelet agents has not been adequately addressed, even in the recently published clinical trial (17). It is interesting to see that differences in medication may be contributing factors that can explain the contradictory results on the beneficial effect of PFO closure in the previous clinical trials that included all eligible patients with stroke and PFO, without any selection criteria on the basis of shunt size or anatomic characteristics of the atrial septum such as septal aneurysm. In the previous trials with negative results (13–15), warfarin was included in the medication-only group, whereas in the recently published trial with positive results favoring PFO closure (16), the investigators included antiplatelet therapy only and did not include warfarin in the medication-only arm. In our study, warfarin was allowed to be included in the medication-only group at the attending neurologist's discretion, and 25% of the patients in the medication-only group continued to receive warfarin up to 1 year after the randomization. In the CLOSE trial (17), which included high-risk patients with PFO similar to our trial, antiplatelet therapy only was used with positive results. We believe that the difference in medication between our study and the CLOSE trial further supports the powerful beneficial effect of device closure of PFO in patients with cryptogenic stroke and high-risk PFO.

STUDY LIMITATIONS. The limitations of this trial included early termination for patient safety, thereby resulting in an underpowered study to provide the

hazard ratio. Although the current trial had a lower than expected rate of patient recruitment, publication of consecutive clinical trials favoring PFO closure was the main reason that our research members decided on early termination of this trial; more specifically, the report of the CLOSE trial with stringent entry criteria similar to ours made our neurologists, the gate keepers of the current study, concerned about potential safety issues in maintaining this trial. In addition, because this trial was conducted in only 2 centers, potential selection bias of the enrolled patients cannot be completely excluded.

CONCLUSIONS

We have confirmed that the morphologic characteristics of PFO and the adjacent atrial septum as evaluated by TEE are important determinants of the clinical benefit of percutaneous device closure of PFO in patients with cryptogenic stroke. In patients who had a recent cryptogenic stroke attributed to PFO with a large PFO, atrial septal aneurysm, or hypermobility, the rate of the primary composite endpoint as well as stroke recurrence was lower with combined PFO closure in combination with medication than with medication therapy alone.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with cryptogenic stroke, the benefit of closing a PFO is related to the size of the PFO and the morphology and mobility of the interatrial septum.

TRANSLATIONAL OUTLOOK: Future studies comparing the relative risks and benefits of device-based PFO closure with various antithrombotic drug regimens should stratify patients on the basis of the size of the defect and mobility of the interatrial septum to ensure comparable stroke risk.

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KEY WORDS cryptogenic stroke, echocardiography, patent foramen ovale

APPENDIX For a supplemental figure, please see the online version of this paper.