Comparison of Outcomes after Device Closure and Medication Alone in Patients with Patent Foramen Ovale and Cryptogenic Stroke in Korean Population

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**Purpose:** To compare the effectiveness of device closure and medical therapy in prevention of recurrent embolic event in the Korean population with cryptogenic stroke and patent foramen ovale (PFO).

**Materials and Methods:** Consecutive 164 patients (men: 126 patients, mean age: 48.1 years, closure group: 72 patients, medical group: 92 patients) were enrolled. The primary end point was a composite of death, stroke, transient ischemic attack (TIA), or peripheral embolism.

**Results:** Baseline characteristics were similar in the two groups, except age, which was higher in the medical group (45.3±9.8 vs. 50.2±6.1, \(p<0.0001\)), and risk of paradoxical embolism score, which was higher in the closure group (6.2±1.6 vs. 5.7±1.3, \(p=0.026\)). On echocardiography, large right-to-left shunt (81.9% vs. 63.0%, \(p=0.009\)) and shunt at rest/septal hypermobility (61.1% vs. 23.9%, \(p<0.0001\)) were more common in the closure group. The device was successfully implanted in 71 (98.6%) patients. The primary end point occurred in 2 patients (2 TIA, 2.8%) in the closure group and in 2 (1 death, 1 stroke, 2.2%) in the medical group. Event-free survival rate did not differ between the two groups.

**Conclusion:** Compared to medical therapy, device closure of PFO in patients with cryptogenic stroke did not show difference in reduction of recurrent embolic events in the real world’s setting. However, considering high risk of echocardiographic findings in the closure group, further investigation of the role of PFO closure in the Asian population is needed.

**Key Words:** Patent foramen ovale, device closure, ischemic strokes, transient ischemic attack

INTRODUCTION

Patent foramen ovale (PFO) has been recognized as a possible cause of ischemic stroke or transient ischemic attack (TIA). Recently published randomized controlled trials comparing PFO closure versus medical therapy have shown no difference in the risk of recurrent stroke or TIA between the two groups. However, meta-analyses, including non-randomized data or focusing on trials which used the Amplatzer closure device, indicate an evidence of a benefit of PFO closure in certain conditions. This study represents our experience with the Amplatzer PFO Occluder (St. Jude Medical, St. Paul, MN, USA) in Korean patients with PFO and history of prior cryptogenic ischemic stroke or TIA.
MATERIALS AND METHODS

Study population
This study is a prospective observational study from the Gil Medical Center PFO registry. From October 2010 to August 2014, 184 consecutive patients with stroke/recurrent TIA and PFO documented on transesophageal echocardiography (TEE) and no other identifiable cause of the ischemic event, such as no carotid or intracranial artery stenosis, no atrial fibrillation and no thrombus or atheromatous plaque at aortic arch, were analyzed. Of these patients, those who were aged 18–60 and underwent a PFO closure or medical therapy alone were enrolled in this study. PFO closure was performed according to Heart team’s discretion (consist of cardiologist, neurologist and radiologist) based on patient’s clinical data, echocardiographic findings and patient’s preference. Fifteen patients were excluded due to their age, and 5 patients were lost during the follow-up period (Fig. 1). Finally, 164 patients (men: 126 patients, mean age: 48.1±8.5 years) were eligible for this study. The closure group included 72 patients and 92 patients were included in the medical group (medical therapy only). This study was approved by the Institutional Review Board of the Gil Medical Center.

PFO closure procedures
The closure procedure was performed under general anesthesia. After femoral venous access, the PFO was crossed with a 5 Fr multipurpose catheter. The multipurpose catheter was advanced into the left upper pulmonary vein and exchanged over a 0.035 inch J-tipped stiff guidewire for an 8 Fr or 9 Fr guiding sheath. Procedural anticoagulation was initiated with 5000 unit intravenous heparin. The appropriate device size was selected based on TEE measurements of the distance between the PFO and the aortic root. Once selected, the device was advanced through the sheath to the tip and, subsequently, the sheath and device were pulled back as a unit from the left upper pulmonary vein into the left atrium. While maintaining the position of the device, the sheath was gently pulled back allowing deployment of the left atrial disk. Under TEE guidance, the expanded left atrial disk was then retracted together with the sheath to the atrial septum, and, following verification of septal abutment, the sheath was pulled back, further allowing deployment of the right atrial disk. Upon confirmation of successful positioning by both TEE and fluoroscopy, the device was released. Recommended antiplatelet therapy following the procedure included aspirin 100 mg daily and clopidogrel 75 mg daily for at least 3 months. Follow-up transthoracic echocardiography (TTE) or TEE with agitated saline test was performed between 1 and 3 months after the procedure. Procedural success was defined as successful implantation of device without any procedure-related complication and in-hospital mortality or morbidity.

In the medical group, antithrombotic therapy was left to the discretion of the treating physician and could have included anti-platelet therapy or oral anticoagulation.

Echocardiographic variables
Septal hypermobility refers to interatrial septal excursion during the cardiac cycle of 10 mm or more from the midline. Shunt refers to agitated saline contrast (bubbles) appearing in the left atrium within 3 cardiac cycles of right atrial opacification. The degree of shunting was defined as small if 3–9 contrast bubbles appeared, moderate if 10–30 contrast bubbles appeared, and large if more than 30 contrast bubbles appeared in the left atrium.8

Definitions and study end points
Definition of risk of paradoxical embolism (RoPE) score was based on the previously published data.9 The primary end point was a composite of death, ischemic stroke, TIA, or peripheral embolism. Secondary end points were individual components of the primary end point as well as cardiovascular death, new-onset atrial fibrillation, myocardial infarction (MI), hospitalization related to the PFO or its treatment, device problems and bleeding.

Statistical analysis
Continuous data are expressed as mean±standard deviation and normality tests were performed in each variable for determination of whether or not a data set is well-modeled by a normal distribution. The baseline characteristics of the two groups were compared using the two-sample t-test for continuous variables, and chi-square test and Fisher’s exact test for categorical variables. Analysis of longitudinal data for the primary end point as well as cardiovascular death, new-onset atrial fibrillation, myocardial infarction (MI), hospitalization related to the PFO or its treatment, device problems and bleeding.

RESULTS

Patient populations
Among the 164 eligible patients, 72 were assigned to the closure group and 92 to the medical group. Baseline characteristics were similar between the two groups, except age which was higher in the medical group and RoPE score which was higher.

Fig. 1. Diagram for detailed enrollment of patients.

http://dx.doi.org/10.3349/ymj.2016.57.3.621
in the closure group. On TEE, moderate to large right to left shunt were more common in the closure group compared to the medical group (81.9% vs. 63.0%, \( p =0.009 \)). The presence of shunt at rest or septal hypermobility was also more common in the closure group than in the medical group (61.1% vs. 23.9%, \( p<0.0001 \)) (Table 1).

Treatments and follow-up
Device implantation was attempted in 72 patients in the closure group and was completed in all patients. In most patients, a 5 Fr multipurpose catheter was passed easily through the PFO, but, in some patients, Swartz™ SL sheath (St. Jude Medical, Plymouth, MN, USA) was necessary for strong back-up support for passage of the guidewire through the PFO. In 12 patients, 18 mm devices were implanted, 25 mm devices in 56 patients, and 30 mm devices in 4 patients. One left atrial wall perforation occurred, but did not require additional management. Therefore, implantation was deemed successful in 71 of the 72 patients (98.6%). Between 1 and 3 months after the index procedure, 55 patients (76.4%) in the closure group underwent TTE or TEE with agitated saline test to confirm the residual shunt after PFO closure. Of these, the device was correctly positioned in all patients (47 with no shunt, 5 with minimal shunt, 1 with moderate shunt, and 2 with severe shunt). Effective closure was defined as closure with no or minimal shunting, and therefore, was achieved in 52 of the 55 patients (94.6%). Among the 92 patients in the medical group, all patients had antiplatelet or anticoagulant treatment at discharge, and none crossed over to the closure group during the follow-up period. From 3 months onward, the use of antiplatelet agent was significantly less frequent in the closure group than in the medical group (\( p=0.005 \)). Use of oral anticoagulation was rare, but similar in both groups (Table 2). The mean duration of follow-up was 22 months in the closure group and 20 months in the medical group.

Clinical outcomes
Primary end points occurred in 2 patients (2.8%) in the closure group and 2 patients (2.2%) in the medical group (\( p=1.000 \)) (Ta-

### Table 1. Baseline Clinical and Transesophageal Echocardiographic Characteristics

|                                | Closure (n=72) | Medication (n=92) | \( p \) value |
|--------------------------------|---------------|------------------|-------------|
| Age, yrs                       | 45.3±9.8      | 50.2±6.7         | 0.000       |
| Male, n (%)                    | 53 (73.6)     | 73 (79.3)        | 0.457       |
| BMI, mean±SD                   | 24.8±3.0      | 24.2±3.4         | 0.239       |
| Hypertension, n (%)            | 26 (36.1)     | 30 (32.6)        | 0.740       |
| Diabetes mellitus, n (%)       | 7 (9.7)       | 12 (13.0)        | 0.626       |
| Dyslipidemia, n (%)            | 7 (9.7)       | 11 (12.0)        | 0.802       |
| Smoker, n (%)                  | 38 (52.8)     | 58 (63.0)        | 0.204       |
| Coronary artery disease, n (%) | 3 (4.2)       | 0                | 0.083       |
| Peripheral arterial obstructive disease, n (%) | 0 | 1 (1.1) | 1.000 |
| Chronic obstructive lung disease, n (%) | 2 (2.8) | 0 | 0.191 |
| Cerebrovascular events         |               |                  | 0.508       |
| Stroke, n (%)                  | 67 (93.1)     | 88 (95.7)        |             |
| TIA, n (%)                     | 5 (6.9)       | 4 (4.3)          |             |
| RoPE score                     | 6.2±1.6       | 5.7±1.3          | 0.026       |
| Intertrial right-to-left shunt  |               |                  | 0.009       |
| Small, n (%)                   | 13 (18.1)     | 34 (37.0)        |             |
| Moderate to large, n (%)       | 59 (81.9)     | 58 (63.0)        |             |
| Shunt at rest or septal hypermobility, n (%) | 44 (61.1) | 22 (23.9) | 0.000 |

BMI, body mass index; TIA, transient ischemic attack; RoPE score, risk of paradoxical embolism score.

### Table 2. Medication during Follow-Up Period

|                                | Closure (n=72) | Medication (n=92) | \( p \) value |
|--------------------------------|---------------|------------------|-------------|
| Antiplatelet agent             | 47 (65.3)     | 78 (84.8)        | 0.005       |
| Aspirin, n (%)                 | 39 (54.2)     | 69 (75.0)        | 0.008       |
| Clopidogrel, n (%)             | 34 (47.2)     | 44 (47.8)        | 1.000       |
| Anticoagulation, n (%)         | 6 (8.3)       | 6 (6.5)          | 0.766       |
| Satin, n (%)                   | 42 (58.3)     | 69 (75.0)        | 0.029       |
| ACEI, n (%)                    | 2 (2.8)       | 5 (5.4)          | 0.468       |
| ARB, n (%)                     | 26 (36.1)     | 47 (51.1)        | 0.060       |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

### Table 3. Clinical Outcomes

|                                | Closure (n=72) | Medication (n=92) | \( p \) value |
|--------------------------------|---------------|------------------|-------------|
| Primary end point*, n (%)      | 2 (2.8)       | 2 (2.2)          | 1.000       |
| Cerebrovascular events, n (%)  | 2 (2.8)       | 1 (1.1)          | 0.582       |
| Stroke, n (%)                  | 0             | 1 (1.1)          |             |
| TIA, n (%)                     | 2 (2.8)       | 0                |             |
| Death                          | 0             | 1 (1.1)          | 1.000       |
| Cardiovascular, n (%)          | 0             | 1 (1.1)          |             |
| Non-cardiovascular, n (%)      | 0             | 0                |             |

TIA, transient ischemic attack.
*Composite of death, nonfatal stroke, TIA, or peripheral embolism.

http://dx.doi.org/10.3349/ymj.2016.57.3.621
Fig. 2 shows the corresponding Kaplan-Meier curves for the primary composite end point. In an analysis of the individual components of the primary end point, TIA occurred in 2 patients (2.0%) in the closure group, and one stroke (1.0%) occurred in the medical group. There was no peripheral embolic event in either group. One patient in the medical group (1.0%) and no patient in the closure group died due to MI at 3 months after enrollment. Otherwise, there was no evidence of device-associated thrombi or new-onset atrial fibrillation in either group. There was also no hospital admission related to PFO or bleeding complications in either group.

**DISCUSSION**

**Main findings**

In our study group, PFO closure with the Amplatzer PFO occluder for secondary prevention of stroke or TIA did not result in any difference in the risk of embolic events or death, as compared with medical therapy alone. Other findings of the current study are 1) the recurrence rate of embolic events in our patients was very low; only 1.8% during mean 20-month follow-up period, which is lower compared to other similar studies.\(^7\)-\(^4\) 2) During the follow-up period, the use of antiplatelet agent was lower in the closure group than in the medical group, which might be a crucial point in an Asian population like ours.

**PFO device closure and medical treatment: no definite superiority of one strategy**

Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy.\(^5\)-\(^6\) Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy. There was no peripheral embolic event in either group. One patient in the medical group (1.0%) and no patient in the closure group died due to MI at 3 months after enrollment. Otherwise, there was no evidence of device-associated thrombi or new-onset atrial fibrillation in either group. There was also no hospital admission related to PFO or bleeding complications in either group. Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy. Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy. Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy.

**Consideration for procedure-related problems and hemorrhagic tendency of Asian population on antithrombotic medication**

We should also be careful on the fact that the PFO closure procedure is associated with some risks such as bleeding, vascular injury, device embolization, thrombus formation on the device, and tamponade. In most studies, however, the data showed that it can be achieved at a high rate with low complication rates due to the procedure itself.\(^10\)-\(^12\) In our study, only one procedure-related complication, which did not require additional management, was noted. Also, there was no death or severe complication related to the procedure. This becomes highly relevant as the medical treatment for ischemic stroke or TIA associated with PFO may include dual antiplatelet and/or anticoagulation therapy with their known potential risks. In our study, the use of antiplatelet agent in the closure group was lower than in the medical group, which might be a crucial point in the Asian population, in which hemorrhagic stroke risk (especially with regard to long-term use of antiplatelet or anticoagulation therapy) tends to be higher than in Western populations.\(^7\),\(^13\) Currently, there are no studies proving benefit of a specification medication or duration of medication for secondary prevention of ischemic stroke in patients with PFO, and both anti-platelets and/or anticoagulation are considered reasonable options.\(^9\),\(^14\)-\(^16\) pointing that the risk of bleeding would be increased in a time dependent manner with these medications. Given the safe and effective closure observed with the Amplatzer PFO Occluder, as in our study, PFO closure may be a reasonable approach for patients requiring long-term anti-platelet or anticoagulation therapy. However, device-related complications (erosion, migration, thrombosis) during the follow-up period after the procedure as well as residual shunt all play a role in complications or recurrent events.\(^17\),\(^18\) Therefore, increasing efforts to optimize device characteristics are necessary.
Limitations
This study has several limitations as follows. First, this is a non-randomized study with different patient’s profile and medications between both groups, and the relatively small sample size and low event rate in a single center study render it difficult to generalize the findings to a larger population. Second, relatively short echocardiographic and clinical follow-up duration in a small population is inadequate for definitive assessment of the absolute risk for recurrent events and bleeding complication of antiplatelet or anticoagulation therapy. Third, selection bias and incomplete follow-up (e.g., shunt grade) make direct comparison of both groups impossible.

Conclusion
Our study comparing PFO closure, using the Amplatzer PFO Occluder and medical therapy alone, in patients with ischemic stroke or recurrent TIA did not show any significant difference in reduction of the risk of recurrent embolic events or death in the real world’s setting. However, further investigation of the efficacy and safety of PFO closure is needed in the Asian population, which is prone to bleeding from long-term use of antiplatelet or anticoagulation therapy.

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