

# Safety and efficacy of Cardi-O-fix occluder for percutaneous closure of a patent foramen ovale

## A single-center prospective study

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### Abstract

**Background:** Amplatzer occluder and Cardio-O-fix occluder are currently used in percutaneous closure of patent foramen ovale. However, there is still a lack of relevant reports comparison the differences between them. The aim of this study was to evaluate the short-term and mid-term safety and efficacy of the Cardi-O-fix occluder in preventing recurrent cerebrovascular events in patients with a patent foramen ovale (PFO).

**Methods:** We enrolled 246 patients (105 men) with a PFO from May 30, 2013 to March 30, 2015 in this single-center prospective study. All patients were treated by PFO interventional closure, with the Cardi-O-fix PFO occluder being used in 180 patients and the Amplatzer PFO occluder being utilized in the remaining 66 patients. After the procedure, we verified the safety and efficacy of different devices using contrast transthoracic echocardiography.

**Results:** Neither recurrent stroke nor death was encountered during the follow-up of 12 months. Transient ischemic attack (TIA) was noted in 2 patients (1.1%) in the Cardi-O-fix PFO occluder group, and 1 patient suffered from TIA (1.5%) in the Amplatzer PFO occluder group. Among them, only 1 patient exhibited a small right to left shunt (RLS). There was no statistical difference in recurrent cerebral ischemic events. Three cases of paroxysmal atrial fibrillation were observed in the Cardi-O-fix PFO occluder group. One reverted spontaneously to sinus rhythm and the other 2 cases had pharmacologic conversion to sinus rhythm. One case of paroxysmal atrial fibrillation occurred in the Amplatzer group, which underwent pharmacologic conversion to sinus rhythm. There was no significant difference between the 2 groups regarding incidence of arrhythmia. No occluder translocation, erosion, pericardial effusion, and puncture site bleeding were observed in the 2 groups within 12 months of follow-up. The complete closure rates of the Cardi-O-fix and Amplatzer PFO occluder devices at the 12 months after the procedure were 73.9% and 63.6%, respectively, and the effective closure rates were 90.6% and 86.4%, respectively. There was no statistically significant difference in the complete closure rate and effective occlusion rate ( $P > 0.05$ ) between the devices.

**Conclusions:** There was no significant difference in the short- and mid-term efficacy and safety between the Cardi-O-fix PFO occluder and Amplatzer PFO occluder. The efficacy and safety of the Cardi-O-fix occluder were comparable to those of the Amplatzer PFO occluder.

**Abbreviations:** CS = cryptogenic stroke, PFO = patent foramen ovale, RLS = right to left shunt, TIA = transient ischemic attack.

**Keywords:** Cardi-O-fix, Occluder, Patent foramen ovale

Editor: Wilhelm Mistiaen.

Author Contributions: EZ, GC, and YZ designed this study; WL, YD, HL, and XW collected and collated case data; EZ, WL, and XH extracted and confirmed the data; EZ, YZ, and GC analyzed data; EZ wrote the manuscript; YZ edited the manuscript.

The study was registered at <https://register.clinicaltrials.gov/>. The registration number was NCT02777359.

The authors declare no competing financial interests.

The authors disclose no conflicts of interest.

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Medicine (2017) 96:14(e6572)

Received: 21 February 2017 / Received in final form: 9 March 2017 / Accepted: 17 March 2017

<http://dx.doi.org/10.1097/MD.0000000000006572>

## 1. Introduction

A patent foramen ovale (PFO) allows for normal fetal circulation; however, it remains open after birth in approximately 25% of adults,<sup>[1]</sup> while in patients who have experienced a cryptogenic stroke (CS), the prevalence can be up to 34% to 77%.<sup>[2,3]</sup> Strokes with of indefinite causes account for approximately 30% to 40% of all strokes, even after a comprehensive work-up, and are regarded as cryptogenic strokes.<sup>[4]</sup> An increasing number of studies have shown that PFO has a significant positive correlation with the risk of having a CS,<sup>[5,6]</sup> which may possibly be due to paradoxical embolism development.<sup>[7]</sup> However, the probability of detecting the thrombus in clinical practice is extremely low, with most of the diagnoses of paradoxical embolisms being speculative. Although in the past 2 decades, most observational studies have proven that PFO closure can reduce cerebrovascular events, 3 prospective randomized controlled studies performed between 2012 and 2013 that assessed the ability of percutaneous closure of PFO to prevent CS rendered this consensus controversial.<sup>[8–10]</sup> A network meta-analysis indicated that PFO closure can prevent recurrence of CS in a manner that is dependent on the occluder devices, with the Amplatzer PFO occluder (AGA Medical/St Jude Medical, St. Paul,

MN) being found to be superior to drug therapy for the prevention of stroke recurrence.<sup>[11]</sup> The Cardi-O-fix PFO occluder (Starway Medical Technology, Beijing, China) is a China-made device that is currently approved by the China Food and Drug Administration (FDA). Nevertheless, there is still a lack of relevant reports in comparison with the Amplatzer occluder. In the present study, we evaluated the safety and efficacy of the Cardi-O-fix occluder in PFO occlusions in compared with the Amplatzer occluder. This study sought to verify the safety and efficacy of the 2 occluders from the perspective of clinical research, without involvement of the manufacturers of the equipment or other third-party intervention. The study was not subject to third-party intervention.

## 2. Materials and methods

### 2.1. Study population

We enrolled 246 patients with PFO (105 men, 141 women, mean age of  $49.3 \pm 1.9$  years) between May 30, 2013 and March 30, 2015 from the First Affiliated Hospital of Xi'an Jiaotong University in Shaanxi Province, China. One hundred eighty (76 men, mean aged 41.8 years) and 66 (29 men, mean aged 39.2 years) underwent treatment using the Cardi-O-fix PFO occluder and Amplatzer occluder implants, respectively. Occluder implantation technically succeeded in all patients. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University, and all patients or their relatives provided written informed consent. All CS patients were confirmed by computed tomography or magnetic resonance imaging. Cerebral angiography, carotid artery Doppler ultrasound, transthoracic echocardiography, and Holter examination were also performed to exclude lacunar infarction or other definite cause of thromboembolism before considering proceeding with percutaneous intervention. We included patients aged 18 to 60 years who were diagnosed with the following: CS or transient ischemic attack (TIA) that was complicated with PFO, and developed moderate to extensive right to left shunting (RLS) occurred, which recurred after antiplatelet or anticoagulant therapy; intractable or chronic migraines complicated with PFO, as well as moderate to extensive RLS; platypnea-orthodeoxia syndrome (POS) complicated with PFO and moderate to extensive RLS; PFO along with an atrial septal aneurysm (ASA), extensive interatrial septum activity, a large PFO, or a PFO complicated with RLS at rest. Patients who were pregnant or diagnosed with intracardiac thrombosis, pulmonary hypertension, rheumatic heart disease, or valvular heart disease were excluded from this study.

### 2.2. Transthoracic echocardiography

GE-ViVid7 color Doppler ultrasound system (GE Healthcare, Horten, Norway) equipped with a 2 to 4 MHz transducer was used to perform transthoracic echocardiography (TTE), and a 4 to 7 MHz transducer was used to conduct transesophageal echocardiography (TEE). A parasternal long-axis view, parasternal short-axis view of the great arteries and substernal view of the left atrium and right atrium were used to confirm the presence or absence of PFO. If no PFO was observed or the image quality was unsatisfactory, additional TEE was conducted to understand the PFO morphology, to measure its size, and to determine whether it was complicated by ASA. TEE was also carried out to rule out other diseases of the left heart system. ASA was defined as mobile septum excursion  $>10$  mm into the left atrium or the right atrium and a base width of the aneurysm of at least 15 mm.<sup>[12]</sup>

Contrast-transthoracic echocardiography (c-TTE) was utilized to identify RLS. The apical four-chamber view was used for most

cases. We prepared a contrast agent with 8 mL of saline solution, 1 mL of air, and 1 mL of blood from the patients. We mixed the contrast agent, using 2 10-mL syringes that were connected by a 3-way stopcock, at least 10 to 20 times before being injected into the left cubital vein as a bolus. The RLS volume was determined by measuring the maximum micro-bubbles detected in the left chamber on a single frame image after contrast agent was injected both under basal conditions and during the Valsalva maneuver. The widely accepted echocardiographic standard currently that is used for differentiating a PFO from pulmonary arteriovenous malformation was applied. Briefly, for a developing time between 3 and 5 cardiac cycles, most RLSs are from PFOs, while for a developing time of more than 5 cardiac cycles, RLSs are considered to be due to pulmonary arteriovenous malformations.<sup>[13]</sup> The effective Valsalva maneuver was performed while having patients blow into a manometer device to maintain a pressure of 40 mmHg for 5 seconds. The above operation was performed and observed by the same skilled operator.

The degree of RLS severity was divided into 4 grades, depending upon the number of micro-bubbles detected in the left atrium on a still frame.<sup>[14,15]</sup> When no, 1 to 10 bubbles, 11 to 30 bubbles, and  $>30$  bubbles (or left atrial opacity) were detected in the left atrium, the RLS was considered as negative, "small," "moderate," or "large," respectively.

### 2.3. The occluder and closure methods

All patients or their relatives had previously provided written informed consent. Depending on the preference of patients, either the Cardi-O-fix PFO occluder or Amplatzer PFO occluder were used. The Amplatzer PFO occluder is constructed from nitinol wires and consists of a double-disc (right atrial and a slightly smaller left atrial disk) connected by a narrow and short central waist. It is presently available in 4 sizes: 18/18, 18/25, 30/30, and 25/35 mm for the left and right atrial disc size, respectively. The Cardi-O-fix PFO occluder is a self-expandable double-disc device made from nitinol wire-mesh, which is similar, but less costly, than the Amplatzer PFO occluder, however, in addition to the 4 sizes of the Amplatzer occluder, the Cardi-O-fix PFO occluder has a unique size of 25/25 mm. Generally, the Cardi-O-fix PFO occluder costs only half the price of the Amplatzer occluder. Implantation of all devices was performed by the same skilled operator. The choice of device size was based on the structural characteristics of the foramen oval. All patients received aspirin 3 to 5 mg/kg per day and clopidogrel 75 mg/d up to 48 hours before the procedure. Prophylactic antibiotics could be administered 1 hour prior to surgery. Common femoral vein needle puncture was conducted under local anesthesia. After the delivery sheath was inserted into the right femoral vein, 100 IU/kg heparin was administered intravenously, with an additional quarter to a third loading dose being administered every hour. We routinely performed right-heart catheterization and right atrium or fossa oval angiography. Right heart catheterization can be used to cross the PFO and was then positioned in the left upper pulmonary vein under fluoroscopy guidance. The closure device was deployed and released under angiographic guidance to observe the shunt. Procedures were conducted under local anesthesia and fluoroscopy guidance. After the procedure, all patients were prescribed low molecular-weight heparin of 10 U/(kg h) or subcutaneous injection of 4000 to 5000 U (twice per day) for 48 hours. Aspirin 3 mg/(kg h) is recommended to be used for 6 months after the procedure and clopidogrel (50 to 75 mg/d) is recommended to be used for 3 months after foramen ovale closure.

### 2.4. Postoperative follow-up

Effective indicators included the incidence of recurrent TIA and CS, death as well as the rate of complete and effective closure during the follow-up periods. Safety indicators included the incidence of various complications. All patients were followed up for 12 months after device implantation. Dynamic electrocardiograph and TEE were performed to confirm the presence or absence of atrial fibrillation and device embolization. C-TTE was performed at 1, 3, 6, and 12 months after the procedure to detect the presence of a residual shunt. Effective closure was described as closure without a shunt or using a small shunt. All patients were followed-up through phone calls and questionnaires or office visits. If patients exhibited symptoms of palpitation and chest pain, a dynamic electrocardiogram was obtained immediately. Patients who were suspected of recurrent embolism events were assessed by 2 neurological specialists using computed tomography or magnetic resonance imaging.

### 2.5. Statistical analysis

A nonparametric rank sum test was used to compare residual shunting between the 2 groups and Mann-Whitney *U* test was performed to compare the ordinal data between the 2 groups. *P* < 0.05 indicated statistical significance. Statistical analyses were conducted using SPSS Version 18.0 (SPSS, Chicago, IL).

## 3. Results

### 3.1. Baseline characteristics

Cardi-O-fix PFO occluders were used in 180 patients and Amplatzer occluders were used in 66 patients. Complications included CS (80 cases), TIA (95 cases), migraine (86 cases), and recurrent shunting (15 cases), and there was no significant difference between the 2 groups in the development of these events. There were no significant differences in baseline characteristics between the 2 groups (Table 1). The procedural success rate (i.e., device implantation success without serious complications during hospitalization) was 100% in both groups.

**Table 1**  
Baseline characteristics of the 246 patients with patent foramen ovale (PFO).

	Cardi-O-fix (n=180)	Amplatzer (n=66)	<i>P</i>
Male	76 (42.2%)	29 (43.9%)	0.809
Female	104 (57.8%)	37 (56.1%)	
Age (y)	41.8	39.2	0.152
Risk factors			
Diabetic mellitus	7 (3.9%)	5 (7.6%)	0.392
Arterial hypertension	37 (20.6%)	12 (18.2%)	0.680
Hyperlipidemia	22 (12.2%)	5 (7.6%)	0.302
Smoking	49 (27.2%)	12 (18.2%)	0.146
Coronary artery disease	3 (1.7%)	1 (1.5%)	1
Arrhythmia	11 (6.1%)	4 (6.1%)	1
Migraine	98 (54.46%)	27 (40.9%)	0.060
Closure objects			
Stroke	58 (32.2%)	22 (33.3%)	0.869
TIA	64 (35.6%)	31 (47.0%)	0.103
Migraine alone	69 (38.3%)	17 (25.8%)	0.067
Recurrent events	11 (6.1%)	4 (6.1%)	1

PFO=patent foramen ovale, TIA=transient ischemic attack.

The mean procedure time was 40.0 ± 6.36 minutes in the Cardio-O-fix group and 40.6 ± 6.57 minutes in the Amplatzer group. The mean fluoroscopy time was 9.6 ± 2.26 minutes in the Cardio-O-fix group and 9.7 ± 2.11 minutes in the Amplatzer group. The mean hospital stay was 5.5 ± 2.58 days in the Cardio-O-fix group and 5.4 ± 2.59 days in the Amplatzer group. There was no significant difference in procedure, fluoroscopy time, and mean hospital stay between the 2 groups (Table 2).

### 3.2. Clinical follow-up

All 246 patients were followed-up for a period of 12 months, and no recurrent stroke and death occurred. Two patients experienced TIA in the Cardi-O-fix occluder group at 1 month and 6 months after the procedure. One incidence of TIA occurred in the Amplatzer occluder group 3 months after the procedure. Among the 3 cases of TIA, 1 patient had small RLS. Another 2 patients had no RLS. There were no significant differences in recurrent cerebral ischemic events.

Procedure-related adverse events included 3 patients in the Cardi-O-fix PFO occlude group who developed paroxysmal atrial fibrillation at 1 week, 1 month, and 3 months after the procedure. Of these events, 1 patient reverted spontaneously to sinus rhythm, while the other 2 cases experienced pharmacologic conversion to sinus rhythm. One patient in the Amplatzer PFO occluder group developed paroxysmal atrial fibrillation and was able to undergo pharmacologic conversion to sinus rhythm. There were no significant differences between the 2 groups in development of arrhythmia. No occluder translocation, erosion, pericardial effusion, or puncture site bleeding was observed in the 2 groups within 12 months of follow-up. One case of occluder replacement was reported in the Cardi-O-fix occluder group. The size of the PFO, as measured intraoperatively, was 3.5 mm, and the length was 14 mm. The poor morphology PFO occluder of 18/25 mm was first implanted and then replaced by a 30/30 mm occluder.

### 3.3. Echocardiographical follow-up

C-TTE was performed to detect residual shunting at 1 month, 3 months, 6 months, and 12 months after device implantation. There were no significant differences in closure rate of each follow-up period. The complete closure rate following use of the Cardi-O-fix and Amplatzer PFO occluder devices at 12 months after the procedure was 73.9% and 63.6%, respectively, and the

**Table 2**  
Implantation procedure.

	Cardi-O-fix (n=180)	Amplatzer PFO (n=66)
Procedural success (%)	100	100
Procedural time (min)	40.0 ± 6.36	40.6 ± 6.57
Fluoroscopy time (min)	9.6 ± 2.26	9.7 ± 2.11
Hospital stay (d)	5.5 ± 2.58	5.4 ± 2.59
Mean sheath size	9	9
Device size (mm)	18:0	18:2
	25:129	25:41
	25/25:1	30:12
	30:20	35:11
	35:30	
>1 placement attempt	1	0

PFO=patent foramen ovale.

**Table 3**  
**Echocardiography findings and follow-up.**

	Cardi-O-fix (n=180)	Amplatzer PFO (n=66)	P
Baseline characteristics			
Atrial septal aneurysm	34 (18.9%)	8 (12.1%)	0.211
PFO diameter (mm)	3.3±1.29	3.1±1.09	0.385
c-TTE before procedure			
	n (%)	n (%)	
Moderate RLS	9 (5.0)	2 (3.0)	0.509
Large RLS	171 (95.0)	64 (97.0)	
30-day follow-up			
No RLS	22 (12.2)	6 (9.1)	0.371
Small RLS	62 (34.4)	25 (37.9)	
Moderate RLS	42 (23.3)	8 (12.1)	
Large RLS	54 (30)	27 (40.9)	
3 months follow-up			
No RLS	52 (28.9)	17 (25.8)	0.111
Small RLS	66 (36.7)	20 (30.3)	
Moderate RLS	46 (25.6)	14 (21.2)	
Large RLS	16 (8.9)	15 (22.7)	
6 months follow-up			
No RLS	87 (48.3)	25 (37.9)	0.124
Small RLS	59 (32.8)	22 (33.3)	
Moderate RLS	20 (11.1)	17 (25.8)	
Large RLS	14 (7.8)	2 (3.0)	
12 months follow-up			
No RLS	133 (73.9)	42 (63.6)	0.120
Small RLS	30 (16.7)	15 (22.7)	
Moderate RLS	14 (7.8)	8 (12.1)	
Large RLS	3 (1.7)	1 (1.5)	
Effective closure 12 months after procedure	163 (90.6)	57 (86.4)	0.343

c-TTE=contrast transthoracic echocardiography, PFO=patent foramen ovale, RLS=right to left shunt.

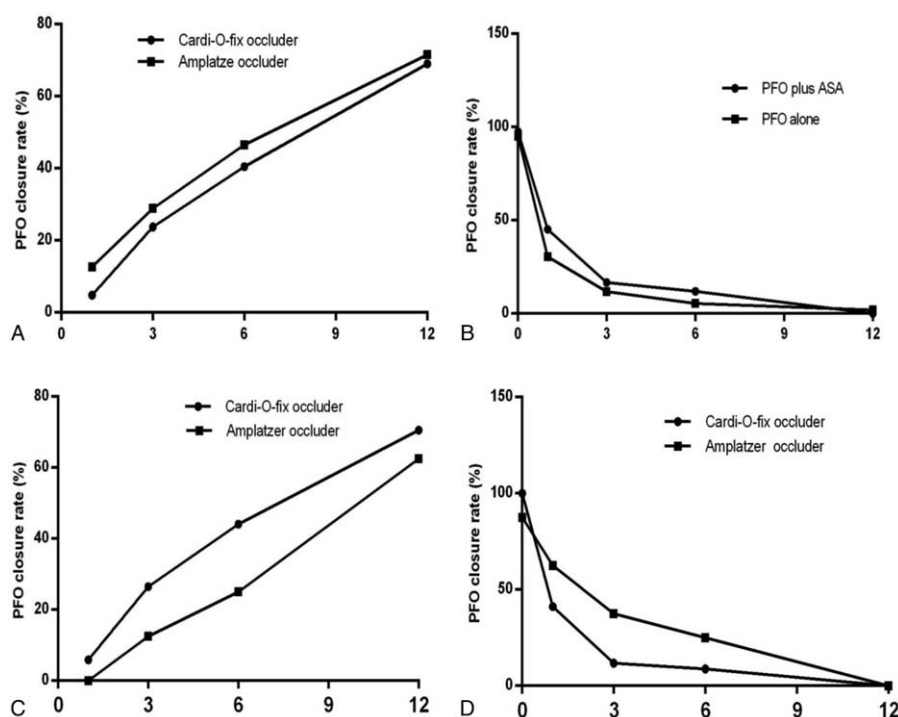
effective closure rate was 90.6% and 86.4%, respectively (Table 3). There were 42 patients with PFO who developed complication with ASA and 34 patients who developed complications with ASA in the Cardi-O-fix group and 8 patients in the Amplatzer group. PFO alone had a higher complete closure rate compared with PFO plus ASA; however, there were no significant differences ( $P>0.05$ ). The complete closure rate of PFO plus ASA at 12 months after the procedure was 69.0%, and the complete closure rate of PFO alone was 71.6% ( $P>0.05$ ) (Fig. 1A). Similarly, there was no significant difference in large RLS between PFO plus ASA and PFO alone (Fig. 1B). For PFO patients who developed ASA, we compared the complete closure rate (Fig. 1C) and incidence of extensive large RLS (Fig. 1D) between the 2 groups; however, the findings did not reveal a significant difference.

#### 4. Discussion

The Cardi-O-fix PFO occluder is a China-made closure device that is approved by China the FDA and whose characteristics are similar to those Amplatzer PFO occluder. The Amplatzer PFO occluder is widely used in clinical practice for percutaneous PFO closure. However, whether the clinical application of the Cardi-O-fix PFO occluder is similar to the Amplatzer PFO occluder, there is still a lack of research reports. Previously, conventional echocardiography has only been used to assess occluder location and the presence or absence of a residual left to right shunt; however, it fails to document RLS by contrast echocardiography in paradoxical embolism formation theory. In this study, we

compared the Cardi-O-fix occluder with the Amplatzer occluder, however, there was no significant difference ( $P>0.05$ ) with respect to procedural success rate, fluoroscopy time, or duration of hospital stay. The complete closure rate of the Cardi-O-fix and Amplatzer PFO occluder devices at 12 months after the procedure was 73.9% and 63.6%, respectively, and the effective closure rate was 90.6% and 86.4%, respectively ( $P>0.05$ ). There were no cases of recurrent stroke nor death during the follow-up period. TIA was observed in 2 patients (1.1%) in the Cardi-O-fix PFO occluder group, and 1 patient (1.5%) occurred in the Amplatzer PFO occluder group. There were no significant differences between the 2 groups with respect to arrhythmia development ( $P>0.05$ ). No patients experienced occluder translocation, erosion, pericardial effusion, or puncture site bleeding in the 2 groups during the follow-up period. Thus, there was no significant difference with respect to the effectiveness and safety of the Cardi-O-fix occluder compared with the Amplatzer occluder during PFO closure.

Evaluation of the STARFlex septal closure system in patients with a stroke and/or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale (CLOSURE I), randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment (RESPECT) from the United States, and the patent foramen ovale and cryptogenic embolism (PC trials) from European published in 2012 and 2013. These studies sought to confirm the superiority of PFO closure over medical therapy alone to reduce the recurrence of stroke.<sup>[8–10]</sup> However, the CLOSURE I and PC trials indicated that the PFO closure device did not offer more benefits than medical management alone in the prevention of TIA or recurrent stroke. Meanwhile, in the RESPECT study, PFO closure was shown to reduce the recurrence risk of stroke by 63.4% according to the prespecified per-protocol analysis and by 72.7% by the as-treated analysis ( $P<0.05$ ), but the reduction did not reach statistical significance in the intention-to-treat (ITT) analysis. Thus, whether PFO closure is beneficial in preventing cryptogenic stroke remains controversial. In addition to differences in study design, the clinical studies may have differed in the type of closure device used. Hence, whether this is related to the type of closure devices has become the focus of concern. Hornung et al<sup>[16]</sup> reported 5-year follow-up results of a randomized trial and compared the 3 different devices for PFO closure to prevent stroke in 2013. In doing so, they demonstrated that the incidence of device-associated thrombus formation and atrial fibrillation was significantly higher in the Cardio SEAL-STARflex than in the Helex and Amplatzer occluders. Meanwhile, the Amplatzer occluder was superior to the STARFlex and Helex occluders in preventing the primary endpoint event incidence rate. It further showed that the risk of recurrence of stroke and TIA after undergoing the procedure was related to the different type of occluders. A meta-analysis concluded that different occluders differed in their ability to prevent recurrent CS events. The probability of preventing strokes was 77.1% after using the Amplatzer occluder, 20.9% after using the Helex occlude, and 1.7% after using the STARFlex occluder.<sup>[11]</sup> The long-term (more than 10 years) RESPECT extended follow-up results<sup>[17]</sup> revealed that, in the intention-to-treat (ITT) population, the CS recurrence risk was 54% lower in comparison to drug therapy ( $P=0.042$ ). While, in the device in place population, the risk was decreased by 70% ( $P=0.004$ ). By subgroup analysis, in patients experiencing complications with ASA and extensive RLS, the CS rate for occlusion of PFO decreased by 75% ( $P=0.007$ ). After long-term use of the Amplatzer PFO occluder, no patient presented with



**Figure 1.** The relationship between patent foramen ovale (PFO) closure rate and follow-up. (A) Comparison of complete closure rate between PFO plus atrial septal aneurysm (ASA) and PFO alone; (B) comparison of extensive right to left shunt (RLS) between PFO plus ASA and PFO alone; (C) comparison of complete closure rate in patients with PFO plus ASA between the 2 groups; (D) comparison of extensive RLS in patients with PFO plus ASA between the 2 groups. The x axis represents months after PFO closure, with 0 indicating before PFO procedure.

occluder-related thrombus, migration, or erosion. The major vascular complication rate was 0.9%, while the complication rate of occluder implantation was 0.4%. Overall, the Amplatzer PFO occluder was superior to drug treatment in reducing recurrent cryptogenic ischemic stroke, and was the most effective and safely implanted device.

A comparative study of transcatheter closure of PFO with the Amplatzer occluder versus the Cardio-O-fix occluder concluded that extensive RLS at 6 months after the procedure occurred in 21% of patients in the Amplatzer group and 24% of patients in the Cardio-O-fix group when continuous transcranial Doppler examination (c-TCD) was used. The incidence of extensive RLS 6 months follow-up was higher than we observed (7.8% of patients in the Amplatzer group and 3% of patients in the Cardio-O-fix group) when c-TTE was utilized. It is possible that the incidence of residual RLS was overestimated in the c-TCD test owing to pulmonary arterio-venous fistula development.<sup>[18]</sup> PFO complicated with ASA and extensive RLS were regarded as a high risk of PFO. ASA could increase the risk of recurrent stroke.<sup>[19,20]</sup> The short- and long-term results of the RESPECT study suggested that patients with large RLS and ASA benefited more from PFO closure rather than from medical management, with the incidence of CS after PFO closure having decreased by 75% ( $P=0.007$ ).<sup>[17]</sup> In this study, 95% of patients were enrolled experienced PFO that was complicated with extensive RLS. Furthermore, there were no significant differences between the Cardio-O-fix occluder and the Amplatzer occluder in developing to RLS during the follow-up periods. However, this incidence of RLS was higher than that in previous studies<sup>[8-10]</sup> during the follow-up period. There are several possible reasons for these outcomes. First, in this study, follow-up was performed using the cTTE, which often prevents

patients from completing the Valsalva maneuver, thereby underestimating the residual shunt severity. Second, the patients who were enrolled in this study had different characteristics. In the CLOSURE I, RESPECT, and PC trials, the proportion of patients with small to moderate RLS was 82%, 39%, and 77%, respectively, while 95% of patients in our study experienced PFO with extensive RLS. There was no significant difference in the complete closure rate and incidence of residual RLS in patients with PFO and ASA following treatment with the Cardio-O-fix occluder and the Amplatzer occluder. We found that the effective closure rate of PFO combined with ASA was generally lower tendency than that of PFO alone. This indicated that, for patients with PFO complicated with ASA, occluders should be carefully chosen. It is best to perform TEE to better understand the structure of the PFO before performing the procedure.

This study has the following limitations. First, the price of the Amplatzer device is relatively high, therefore, few patients can afford it. The large difference in the number of patients treated with the Cardio-O-fix occluder and the Amplatzer occluder may have affected the final results. Second, this study is a small sample of non-randomized controlled trials. Therefore, extrapolation of the results is limited. Third, the follow-up time was only 1 year; however, embolization recurs earlier and the results may have been affected.

## 5. Conclusion

Regardless of the controversy behind the mechanism of PFO in patients with CS, TIA, and migraines, our study indicates that PFO closure is a safe and effective form of treatment. However, there are differences in outcomes between various occluders. Our

preliminary study demonstrated that there were no significant differences with respect to closure rate, recurrent cerebral ischemic events, and complications between the 2 occluder types. We demonstrated that the efficacy and safety of the Cardio-fix occluder were comparable to those of the Amplatzer PFO occluder. However, further randomized controlled trials are required to confirm this finding.

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