ORIGINAL ARTICLE

Long-term follow-up outcomes in a real-world study cohort after percutaneous patent foramen ovale closure

Perkütan perkütan patent foramen ovale kapamanın gerçek yaşam verisi ışığında uzun dönem takip sonuçları

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ABSTRACT

Objective: In recent years, percutaneous closure of a patent foramen ovale (PFO) has gained widespread use. This study is an evaluation of the safety and efficacy of the Figulla and Amplatzer devices for PFO closure, including long-term follow-up results.

Methods: A total of 305 patients (43.6% male; mean age: 43.25±10.98 years) who underwent percutaneous PFO closure between 2003 and 2019 were enrolled. The Risk of Paradoxical Embolism (RoPE) score was calculated to predict the recurrence risk of cerebrovascular events due to PFO. Transthoracic echocardiography was used during the procedure.

Results: The devices were successfully implanted in all patients. The in-hospital periprocedural complications recorded were atrial fibrillation in 1 patient (0.3%), supraventricular tachycardia in 1 patient (0.3%), and femoral hematoma in 3 patients (1%). The procedure time and fluoroscopy time was 21.92±2.93 minutes and 2.19±0.24 minutes, respectively. Recurrent ischemic stroke or transient ischemic attack (TIA) was observed in 7 (2.2%) patients during the median 85.77 months (25th-75th percentile: 10.21–108.00 months) follow-up. The RoPE score was significantly lower in patients with recurrent ischemic cerebral event (stroke or TIA) compared with asymptomatic patients (p<0.001). Kaplan-Meier curve analysis revealed that there was no significant difference between PFO device types (Amplatzer: 2.4% vs. Figulla: 3.3%) in terms of recurrent ischemic cerebral events during follow-up (log-rank; p=0.642).

Conclusion: Percutaneous PFO closure was safe, feasible, and effective. Our study confirmed the efficacy and safety of transthoracic echocardiogram guidance during percutaneous closure of PFO, which shortens the procedure time. A lower RoPE score was related to the recurrence risk of ischemic cerebrovascular events.

ÖZET

Amaç: Patent foramen ovale'nin (PFO) perkütan kapatılması, son yıllarda sıkça uygulanan bir işlemdir. Bu çalışmamızda, Occlutech Figulla ve Amplatzer cihazları ile PFO kapama işleminin uzun dönem güvenliliği ve etkinliğini araştırdık.

Yöntemler: Çalışmaya 2003–2019 yılları arasında perkütan PFO kapama işlemi yapılan 305 hasta (%43.6 erkek, ortalama yaş: 43.25±10.98 yıl) dahil edildi. Nükseden serebrovasküler olayı (SVO) tahmin eden RoPE (Risk of Paradoxical Embolism) skoru hesaplandı. İşlemler sırasında transtorasik ekokardiyografi kullanıldı.

Bulgular: Tüm hastalara cihazlar başarı ile implante edildi. Hastane içi komplikasyon 5 hastada (1 hastada supraventriküler taşikardi, 1 hastada atriyal fibrilasyon ve 3 hastada femoral hematom) gelişti. Ortalama işlem süresi sırasıyla 21.92±2.93 dakika, floroskopi süresi 2.19±0.24 dakika saptandı. Nükseden iskemik inme ya da geçici iskemik atak 85.77 (25.-75. yüzdelik dilim: 10.21–108.00 ay) aylık takip süresince 7 (%2.2) hastada gelişti. RoPE skoru nükslü serebrovasküler olayı olan hastalarda asemptomatik vakalara göre belirgin olarak daha düşüktü (p<0.001). Kaplan-Meier analizinde nükseden iskemik inme açısından cihazlar arasında fark tespit edilemedi (Amplatzer cihazı kolunda %2.4; Occlutech Figulla cihazı kolunda %3.3, log rank, p=0.642).

Sonuç: Perkütan PFO kapama işlemi güvenli, makul ve efektif bir işlemdir. Çalışmamız, transözofajiyal ekokardiyografiye göre işlem süresini kısaltan transtorasik ekokardiyografinin PFO kapama işleminde güvenli ve etkili olduğunu göstermiştir. RoPE skoru nükseden iskemik serebrovasküler olay ile ilişkilidir.

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Abbreviations:

ASA	*Atrial septal aneurysm*
CS	*Cryptogenic stroke*
ICE	*Intracardiac echocardiography*
PFO	*Patent foramen ovale*
RoPE	*Risk of Paradoxical Embolism*
TEE	*Transesophageal echocardiography*
TIA	*Transient ischemic attack*
TTE	*Transthoracic echocardiography*
US	*Ultrasonography*

Stroke accounts for approximately 1 of every 20 deaths worldwide and ischemic stroke is among the leading causes of disability and death, especially in adults. Nearly 87% of all strokes are ischemic.[1] An ischemic stroke may be cardioembolic, atherosclerotic, or lacunar (small vessel occlusion).[2] The etiology remains unexplained in approximately 20% to 40% of patients despite extensive vascular, cardiac, serological, and hematological evaluation, and these are classified as cryptogenic stroke (CS).[3,4] CS is most commonly seen in younger patients (<55 years) and is frequently due to cardiac embolism. Paradoxical embolism through the patent foramen ovale (PFO) is an important cause of cardiac embolism, especially in younger patients without any accompanying cardiovascular disorder.[1,5]

A PFO is a normal interatrial communication or opening present during fetal life that does not close after birth. The prevalence of PFO ranges from 25% to 35%, and increases in size over time.[6] A paradoxical embolism via a PFO was first reported in 1880 by Cohnheim and Litten,[7] who demonstrated simultaneous systemic and venous embolism through large PFOs. Treatment of CS via paradoxical embolism through a PFO includes medical treatment (oral antiplatelet agents, warfarin) and interventional approaches (surgical or percutaneous closure). Open-heart surgery is no longer recommended due to perioperative complications and a long hospital stay. Medical treatment has limited effectiveness and necessitates long-term drug usage and possible side effects include bleeding and gastrointestinal complications.[8] The CLOSURE I (Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale), PC (PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism), and RESPECT (Patent Foramen Ovale Closure or Medical Therapy After Stroke) trials failed to show a benefit to percutaneous PFO closure versus medical therapy alone in the prevention of recurrent CS; however, results from the CLOSE (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) and Gore REDUCE (GORE® Septal Occluder Device for Patent Foramen Ovale Closure in Stroke Patients) trials, and the long-term follow-up of the RESPECT trial demonstrated effectiveness of PFO closure with combined antiplatelet therapy.[9] Therefore, percutaneous closure of symptomatic PFOs with occluder devices is currently recommended as it generally produces less trauma and a quicker recovery.[10,11]

The objective of this study was to assess the acute efficacy and safety of percutaneous PFO closure with Amplatzer (St. Jude Medical, Inc., St. Paul, MN, USA) and Figulla (Occlutech GmbH, Jena, Germany) devices, and to present long-term follow-up results of PFO closure experience at a single center.

METHODS

Consecutive patients who underwent transcatheter PFO closure under echocardiographic guidance with the diagnosis of CS, migraines, recurrent transient ischemic attack (TIA), or peripheral embolism between January 2003 and July 2019 were screened. In all, 305 patients (43.6% male; mean age: 43.25±10.98 years) with accessible, retrospective data were included. All of the patients had signed a hospitalization form which includes permission to use clinical data for future clinical studies according to appropriate guidelines. Due to the retrospective design of the study, no additional informed consent was requested from the patients.

A complete blood count, blood biochemistry, electrocardiography, and chest X-ray were performed at the initial clinical visit. A neurological examination, transcranial Doppler ultrasonography (US) and hypercoagulability screening were also performed (Fig. 1). The exclusion criteria were atrial fibrillation; significant stenosis of the carotid arteries; presence of thrombophilic disorder; pregnancy; acute infection; allergic reaction to clopidogrel, aspirin, or nickel; and age <18 years. The decision to perform a PFO closure in the CS patients was made in collaboration with the hospital neurology clinic. Before the intervention, all of the CS patients with an indication for closure underwent a routine transthoracic echocardiography (TTE) and a contrast study with agitated saline with transesophageal echocardiography (TEE) applied to confirm a right-to-left shunt as well as to assess the

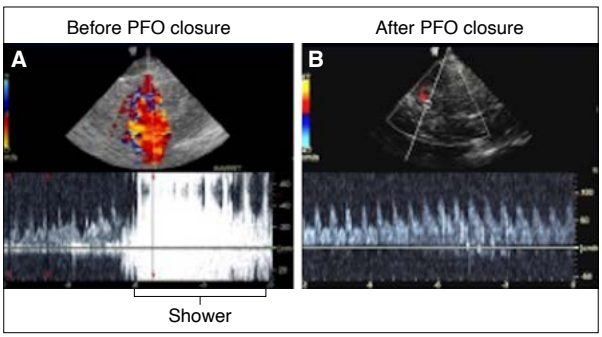

Figure 1. Transcranial doppler ultrasonography images before and after patent foramen ovale (PFO) closure. Color-mode and Doppler images of the middle cerebral artery illustrate **(A)** significant microbubble passage, indicating the presence of a large left-to-right shunt in a high-volume PFO, and **(B)** no recordable microbubbles after the PFO closure.

cardiac structures and left atrial thrombus. The Risk of Paradoxical Embolism score (RoPE Score) was calculated for each patient to predict the recurrence risk of cerebrovascular events due to PFO.[12] Data about complications and outcomes, including recurrent cerebrovascular event, pericardial effusion, inguinal complications, arrhythmias, etc. were obtained retrospectively from follow-up visit information. The study was approved by the Hacettepe University Faculty of Medicine Ethics Committee (July 9, 2019; no: GO 19/750).

Echocardiographic evaluation

All of the echocardiographic examinations were performed by an experienced cardiology specialist using a Vivid FiVe Vingmed cardiac ultrasound machine (GE Healthcare, Inc. Chicago, IL, USA). TTE was performed initially and TEE was used to further diagnose and assess the anatomy and right-to-left shunt. A PFO was defined as the abnormal persistence of a flat-like opening in the interatrial septum due to inappropriate sealing of septum secundum and a superior apical remnant of septum primum, in which septum primum serves as a one-way valve allowing the right-to-left shunt. The diagnosis of PFO was made after an agitated saline contrast study showing a spontaneous or Valsalva maneuver-induced interatrial right-to-left shunt or a flow visible with a Doppler color study.[13,14] The diagnosis of an atrial septal aneurysm (ASA) was made based on the presence of the atrial septum protruding at least 1.5 cm beyond the plane of the interatrial septum or phasic excursion exceeding 1.5 cm, and an aneurysm base greater than 1.5 cm in diameter. A positive bubble study was defined as the passage of at least 3 bubbles through the interatrial septum within 3 beats of right atrial filling with agitated saline.[15,16] A severe shunt was defined as ≥20 bubbles crossing the interatrial septum.[17]

The choice to use a closure device for PFO was made before the intervention according to the TEE findings. The length of the PFO tunnel, mobility of the interatrial septum, and the presence or absence of ASA or multiple fenestrations are the main factors to determine the appropriate device size. Two PFO closure devices (Amplatzer and Figulla) were used during the study period and the device selection was made according to device availability at the hospital at the time of procedure. The passage of a 0.035-in exchange wire was best controlled with TTE from the apical 4-chamber or subcostal view. After documentation of the correct position under fluoroscopic guidance, the location of the device was also checked with TTE and the relationship to neighboring structures was evaluated. Special effort was made to detect possible impingement on the atrioventricular valves or any obstruction of the caval or pulmonary veins.

Patent foramen ovale closure protocol

All of the patients underwent percutaneous PFO closure under local anesthesia with 10 mL of 2% xylocaine applied to the venous access site. The patients received 2 g cefazolin as a prophylactic antibiotic during the procedure. Venous access was obtained from the right femoral vein in all patients. The closure device was prepared before the intervention to minimize the total procedure time, which was defined as the time between the venous puncture and device deployment. An 18-mm or 25-mm device was usually selected. An 8-F sheath was introduced into the same vein and 5000 IU of intravenous heparin was administered to all of the patients. At the same time, an experienced echocardiography practitioner performed the TTE with multiple subxiphoid (frontal and caval position) and precordial windows (modified parasternal 4-chamber and short-axis aortic position), and the best-quality image plane was selected for guidance. Procedural guidance was chiefly fluoroscopic throughout the intervention (crossing the PFO with the exchange wire, deployment of the left atrial disk, deployment of the right atrial disk), with assistance from TTE to shorten fluoroscopy time and visualize any complications. Under fluoroscopic guidance in the anteroposterior position,

the PFO was crossed either with a 0.035-in guidewire or a 6-F multipurpose catheter, with the catheter positioned in the left upper pulmonary vein. In cases of challenging anatomical situations, such as a long PFO tunnel, significant ASA, or lipomatous hypertrophy that could not be crossed with the wire, a cardiac electrophysiology ablation catheter was used to core the septum or a transseptal puncture with a Brockenbrough needle was performed under both fluoroscopic and echocardiographic guidance. Measurement of the maximal PFO opening to determine the device size is not a predictor of procedural success; therefore, we did not perform balloon sizing in our study. The catheter was typically exchanged for an 8-F Amplatzer or Occlutech Figulla delivery sheath over a super-stiff 0.035-in exchange wire. After ensuring that the sheath was air-free, the occluder device was attached to the end of the delivery wire and introduced through the sheath. After the left atrial disk was unfolded it was pulled back against the left side of the interatrial septum until tilting of the disk was observed. This phase was also confirmed with echocardiography. The right atrial disk was then deployed to confirm the correct position of the deployed device, and a fluoroscopic view was obtained, generally in left anterior oblique 45° projection, to see the position of the left and right atrial disks of the device and ensure that the cranial halves of the parallel discs appeared like open jaws biting into the thick septum secundum, known as the Pacman sign.[18] Before the device was unscrewed from the cable, control echocardiography was also performed to confirm the proper placement of the device, making sure that one disk was deployed in each chamber (Fig. 2).

Postprocedural care and follow-up

All of the patients were monitored for 6 hours and discharged on the same day after an evaluation with electrocardiogram and TTE. Clinical evaluation (including a detailed neurological examination) and TTE were performed at the 1st, 6th, and 12th month, and annually thereafter. Additional clinical and echocardiographic evaluations were performed earlier in the event of patient complaints compatible with TIA/stroke, peripheral embolization, or device-related complications. A combination of 100 mg aspirin and 75 mg clopidogrel was prescribed to all of the patients for the first 6 months and 100 mg ASA thereafter. Prophylaxis for infective endocarditis was given for the first 6 months when needed.

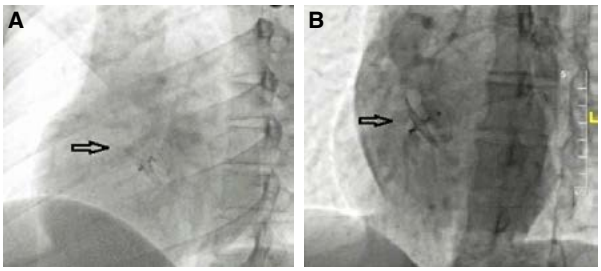

Figure 2. Left anterior oblique 45° fluoroscopic images of each device. **(A)** Occlutech Figulla occlude device, and **(A)** Amplatzer occluder device.

Statistical analysis

Continuous variables were expressed as a mean±SD or median (25th-75th percentile) and categorical variables were expressed as a number (%). The Shapiro-Wilks criterion was used to assess normality. Comparisons of categorical and continuous variables between 2 groups were performed using a chi-squared test or an independent samples t-test, respectively. All tests for significance were 2-sided and used a threshold of $p<0.05$ for significance. Survival analysis was performed using Kaplan-Meier curves and log-rank tests. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 statistical software (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 305 patients (43.6% male, mean age: 43.25±10.98 years) underwent successful transcatheter PFO closure. The mean procedure time and fluoroscopy time was 21.92±2.93 minutes and 2.19±0.24 minutes, respectively. The baseline demographic and echocardiographic characteristics of the study population are illustrated in Tables 1 and 2. A Figulla PFO occluder was used in 206 patients (67.5%) and an Amplatzer PFO occluder device was used in 99 patients (32.4%). A comparison of the 2 devices is presented in Table 3.

The indication for PFO closure was an ischemic stroke in 172 (56.4%), recurrent TIA in 108 (35.4%), and peripheral embolism in 4 (1.3%) of the patients. A PFO was closed due to migraine attacks with aura in 21 (6.9%) patients. In 66 patients (21.6%), ASA was detected in addition to PFO. A severe shunt was detected in 111 (36.3%) patients. A Eustachian ridge was detected in 27 (5.4%) patients. Procedural char-

Table 1. Baseline characteristics of the study population (n=305)

	n	%
Male gender	133	43.6
Age, years, mean±SD	43.25±10.98	
Coronary artery disease	12	3.9
Diabetes mellitus	18	5.9
Hypertension	67	21.9
Smoking	61	20.0
PFO closure indication		
Transient ischemic attack	108	35.4
Stroke	172	56.3
Migraine	21	6.8
Peripheral embolism	4	1.3
RoPE score	6 (5–7)	

Data are shown as mean±SD, median (25^{th}-75^{th} percentile), or n (%). PFO: Patent foramen ovale; RoPE: Risk of paradoxical embolism; SD: Standard deviation.

Table 2. Echocardiographic characteristics of the patients (n=305)

	n	%	Mean±SD
LVEF, %			64.34±3.99
LV end-diastolic diameter, mm			45.56±3.68
Left atrium diameter, mm			31.84±4.16
Shunt through IAS			
Mild	51	16.7	
Moderate	143	46.8	
Severe	111	36.3	
IAS aneurysm	66	21.6	
Eustachian valve	27	5.4	
Lipomatous IAS hypertrophy	42	13.7	
Chiari network	20	6.5	

Data are shown as mean±SD, median (25^{th}-75^{th} percentile), or n (%). IAS: Interatrial septum; LV: Left ventricle; LVEF: Left ventricular ejection fraction; SD: Standard deviation.

acteristics and periprocedural and follow-up data are shown in Tables 4 and 5, respectively. Transseptal puncture was required in 21 (6.8%) patients and no device-related complications, such as embolization, fracture, or migration, were observed in any of the study patients.

In all, 280 patients with an indication for PFO closure of ischemic stroke or TIA were included in further analysis. Recurrent ischemic stroke or TIA was observed in 7 (2.2%) patients during long-term follow-up. The RoPE score was significantly lower in patients with a recurrent ischemic cerebral event (a stroke or TIA) as compared with asymptomatic patients (median 4 [2–4] vs. 6 [2–9], p<0.001) (Fig. 3). Kaplan-Meier curve analysis revealed that there was no significant difference between PFO device types (Amplatzer: 2.4% vs. Figulla: 3.3%) regarding recurrent ischemic cerebral events during follow-up (log-rank; p=0.642) (Fig. 4). In follow-up, 9 patients (2.9%) had ongoing migraine attacks with aura despite percutaneous PFO closure.

Periprocedural complications

The acute procedural success was 100%. There was no thrombus formation in any patient during the peri-procedural period. Groin hematoma developed in 3 (1%) patients, but required no further intervention. Atrial fibrillation was observed in 1 (0.3%) patient. Sinus rhythm was achieved after an intravenous propafenone infusion. Supraventricular tachycardia developed in 1 patient just after the closure procedure and resolved with medical therapy. Pericardial effusion developed in 2 (0.6%) patients, which resolved spontaneously without any further intervention.

Follow-up

The median length of follow-up was 85.77 months (25^{th}-75^{th} percentile: 10.21–108.00 months). During the follow-up period, atrial arrhythmia developed in 5 (1.5%) patients (3 atrial fibrillation and 2 supraventricular tachycardia). In the entire study group, 5 (1.5%) patients had recurrent TIA and 2 (0.6%) patients had recurrent ischemic stroke. However, there was no residual shunt or thrombus formation detected in these patients. In 1 patient who received a Figulla device, thrombosis was found at 12^{th}-month follow-up, which required surgical intervention. This late thrombus formation appeared to be due to cessation of antiplatelet therapy for gynecological surgery.

DISCUSSION

The major findings of our study were that *(i)* percutaneous closure of PFO proved to be an effective method to prevent the recurrence of TIA and ischemic strokes, *(ii)* a lower RoPE score was an important predictor of recurrent cerebral events, *(iii)* both the Amplatzer and Figulla occluder devices were effective

Table 3. Comparison of the baseline demographic, clinical, and echocardiographic characteristics of the study population according to occluder device type

Parameters	Figulla (n=206)	Amplatzer (n=99)	*p*-value
Age, years, mean±SD	43.31±11.76	43.13±9.20	0.894
Male gender, n (%)	86 (41.7)	47 (47.5)	0.412
Hypertension, n (%)	44 (21.4)	23 (23.2)	0.824
Diabetes mellitus , n (%)	13 (6.3)	5 (5.1)	0.859
Coronary artery disease, n (%)	11 (5.3)	1 (1)	0.112
Smoking, n (%)	40 (19.4)	21 (21.2)	0.831
Left ventricular ejection fraction, %	64.57±4.47	63.85±2.67	0.149
Eustachian valve, n (%)	12 (5.8)	15 (15.2)	0.014**
Chiari network, n (%)	14 (6.8)	6 (6.1)	1.000
IAS aneurysm, n (%)	43 (20.9)	23 (23.2)	0.749
Lipomatous IAS hypertrophy, n (%)	27 (13.1)	15 (15.2)	0.758
RoPE Score	6 (5–7)	6 (5–7)	0.445
Shunt through IAS, n (%)			
Mild	30 (14.6)	21 (21.2)	0.249
Moderate	96 (46.6)	47 (47.5)	
Severe	80 (38.8)	31 (31.3)	
PFO closure indications, n (%)			
Migraine	14 (6.8)	7 (7.1)	0.734
TIA	77 (37.4)	31(31.3)	
Stroke	112 (54.4)	60 (60.6)	
Peripheral embolism	3 (1.5)	1 (1)	
Procedure details			
Device size, mm	25.33±2.54	25.16±2.54	0.578
Procedure time, min	21.92±2.96	21.91±2.89	0.982
Fluoroscopy time, min	2.19±0.22	2.19±0.29	0.828
Transseptal puncture, n (%)	15 (7.2)	6 (6)	=0.879
Follow-up, n (%)			
Recurrent TIA/ stroke	4 (2.1)	3 (3.2)	0.686
Ongoing migraine attacks	6 (42.8)	3 (42.8)	1.000

Data are shown as mean±SD, median (25^{th}-75^{th} percentile), or n (%).
IAS: Interatrial septum; PFO: Patent Foramen Ovale; RoPE: Risk of Paradoxical Embolism; TIA: Transient ischemic attack; SD: Standard deviation.

and safe methods to close a PFO, and (iv) the efficacy of PFO closure to control migraine attacks was inconclusive due to the small patient group. The results of our study are consistent with previous data regarding the role of percutaneous PFO closure in reducing the risk of recurrent stroke and TIA compared with medical therapy alone. To the best of our knowledge, our study is one of the largest series of percutaneous PFO closure that includes long-term follow-up results (median follow-up: 85.77 months (25^{th}-75^{th} percentile: 10.21–108.00 months).

Approximately 40% of ischemic strokes have an unknown etiology and are classified as CS. Although it normally closes at birth, 25% of foramen ovale remain patent during adulthood.[19] Patients with PFO and cryptogenic ischemic stroke are at risk for cerebrovascular events, with an average recurrence rate of 3.8% after the first cerebrovascular event.[20,21] Therefore, these patients should be treated and followed up to prevent a recurrence. The important role of PFO in the pathogenesis of CS as a source and passage for paradoxical embolism increased the attempts regard-

Table 4. Procedural characteristics of the study population (n=305)

Device size, mm	25.27±2.54
Device type, n (%)	
Figulla	206 (67.5)
Amplatzer	99 (32.4)
Procedure time, min	21.92±2.93
Fluoroscopy time, min	2.19±0.24
Anesthetic approach, n (%)	
General anesthesia	30 (9.8)
Sedation	275 (90.2)
Medications after closure, n (%)	
Aspirin	302 (99.0)
Clopidogrel	280 (91.8)
Anticoagulants	4 (1.3)
Duration of follow-up, months	85.77 (10.21–108.00)

Data are shown as mean±standard deviation, median (25th-75th percentile), or n (%).

Table 5. Immediate and long-term follow-up safety outcomes of the patent foramen ovale closure in all patients (n=305)

	n	%
Periprocedural complications		
Device embolization	–	–
Device dislodgement	–	–
Thrombus formation	–	–
Pericardial effusion	2	0.61
Vascular access complications	3	0.92
Atrial fibrillation	1	0.30
Supraventricular tachycardia	1	0.30
Follow-up results		
Thrombus formation	1	0.30
Atrial fibrillation	3	0.92
Recurrent TIA	5	1.5
Recurrent ischemic stroke	2	0.61
Other thromboembolic events	–	–
Cardiac death	–	–
Subsequent migraine attacks	9	2.7
Supraventricular tachycardia	2	0.6

TIA: Transient ischemic attack.

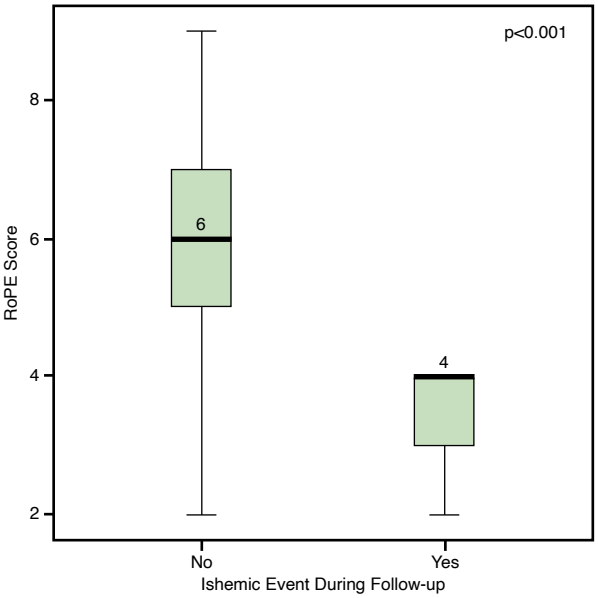

Figure 3. Comparison of Risk of Paradoxical Embolism (RoPE) scores between patients with and without recurrent ischemic events during follow-up.

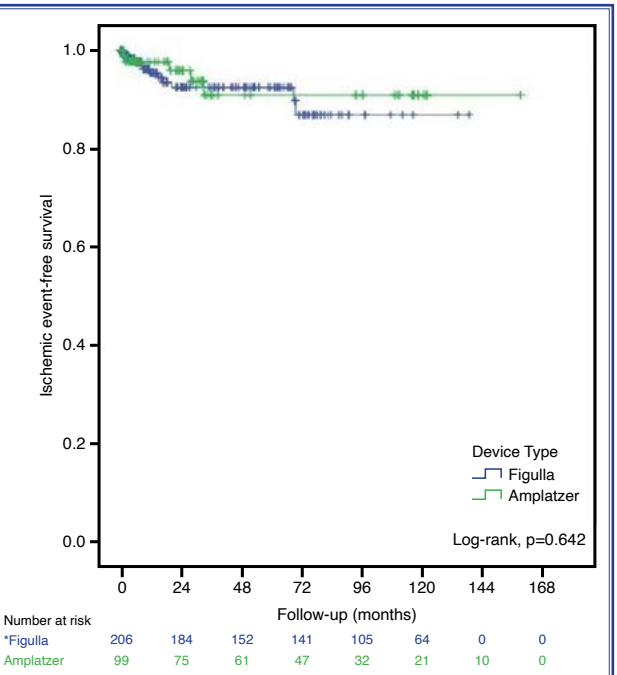

Figure 4. Kaplan-Meier curve illustrating ischemic event-free survival during follow-up according to patent foramen ovale closure device type (log-rank, p=0.642).

ing the role of percutaneous intervention.[22]

For years, transcatheter closure of a PFO was considered an invasive therapy that could prevent recurrent stroke or TIA. However, randomized trials with long-term follow-up had conflicting results regarding PFO closure and the prevention of recurrent stroke.

[9] The CLOSURE study was a multicenter trial that compared the CardioSeal STARFlex device (NMT Medical Inc., Boston, MA, USA) with medical therapy in 909 subjects who presented with CS or TIA and a PFO with a follow-up period of 2 years. The findings revealed no significant benefit to the STARFlex device, a low closure success rate (86%), and a high rate of complications.[23] In the PC and RESPECT trials, the Amplatzer PFO occluder device was used and the results of these studies also showed no reduced risk compared with medical therapy.[24,25] In 2013, Khan et al.[26] presented a meta-analysis of these 3 randomized trials (CLOSURE, PC, and RESPECT) and reported that device closure of PFO was beneficial, with a reduction of 33% to 39% in the hazard for a recurrent cerebral ischemic event. However, when only the RESPECT and PC trials were analyzed (using the Amplatzer PFO occluder), the reduction in recurrence was 46% to 58%.[26] These 3 trials may have failed to find significant efficacy of percutaneous PFO closure due to insufficient patient numbers, short follow-up, and selection of low-risk patients.

Despite the conflicting results of the abovementioned studies, 2 recently published randomized controlled trials (CLOSE and REDUCE trials) and the long-term results of the RESPECT trial have demonstrated that PFO closure was beneficial in a specific patient population with CS. The RESPECT trial was the largest, enrolling 980 patients, and had a mean follow-up duration of 5.9 years. The long-term results of the RESPECT trial confirmed that PFO closure was associated with a lower rate of recurrent ischemic strokes than optimal medical therapy alone.[9] The REDUCE trial compared percutaneous PFO closure combined with antiplatelet therapy to an antiplatelet-only group. Among 664 patients with a median follow-up period of 3.2 years (interquartile range: 2.2 to 4.8 years), the incidence of recurrent ischemic stroke was significantly lower in the PFO closure group compared with the antiplatelet-only group (p=0.002). In the PFO closure group, the technical success rate was 98.8% and atrial fibrillation occurred in 6.6% of patients.[27] In the CLOSE trial, the investigators enrolled 664 patients in 3 arms of 238 patients in the device arm, 235 patients in the antiplatelet arm, and 187 in the anticoagulation arm, and found a technical success of 99.6%. At a mean follow-up of 5.3±2.0 years, the incidence of recurrent stroke was significantly lower (p<0.001) while the rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group.[28]

To the best of our knowledge, although a single-center study, our study has one of the longest follow-up periods and our procedural success was 100%. Based on the experience of the operators at our institution, TTE guidance is used during the closure procedure as the main technique, which is less invasive than TEE guidance, and there is no necessity for general anesthesia. In some studies, periprocedural TEE guidance is advocated for appropriate sizing of the PFO occluder and confirmation of the correct position of the device, however, complications due to general anesthesia and endotracheal intubation are major limitations of TEE, which cause a longer hospital stay. To overcome these disadvantages of TEE, ultrasound intracardiac echocardiography (ICE) guidance has been assessed in several studies.[29,30] Hijazi et al.[31] concluded that ICE potentially could replace TEE as a guiding imaging tool for secundum type atrial septal defect and PFO closure, although additional venous access sites are needed for the insertion of an ICE catheter. Koenig et al.[32] reported that ICE provided good image quality and shortened the procedure time by eliminating the need for general anesthesia. Nonetheless, the use of a femoral sheath, the cost of an ICE catheter, and the need for experienced staff to evaluate ICE images are important limitations preventing wider use of this technology. Bijl et al.[33] and Fateh-Moghadam et al.[34] demonstrated that fluoroscopic guidance alone was safe and effective during percutaneous closure of PFO. Although fluoroscopic and angiographic guidance offers excellent visualization, exposure to radiation and contrast agents might pose a greater risk to the operator and patients. In a comparison of techniques, TTE as the imaging tool causes less trauma; avoids general anesthesia and endotracheal intubation, as well as its complications; and requires no radiation exposure. In our hospital, intraprocedural guidance of transcatheter PFO closure was primarily fluoroscopic throughout the intervention (crossing the PFO with the guidewire, advancing the sheath system, deployment of stiff wire to the left upper pulmonary vein, deployment of left and right atrial discs) with the assistance of TTE. This technique shortens the fluoroscopy time compared with TEE guidance.[35]

Transseptal puncture is not a routine procedure during transcatheter PFO closure; however, especially

in patients with long-tunnel PFO, a transseptal puncture is required in order to prevent device deformity and inadequate closure. Pericardial effusion, cardiac tamponade, and cardiac rupture are well-defined complications of transseptal puncture, with reported complication rates of between 1.3% and 4.8%.[36] In our study, a transseptal puncture was necessary in 21 (6.8%) patients. There were no complications in these cases. The main determinant of the complication rate after interventional procedures is institutional experience. Our hospital is experienced in cardiac interventional procedures and several interventional treatments have been performed for several years. The lower complication rate in our study is probably due to our experience performing transseptal puncture and interventional procedures.

The Amplatzer and Figulla are the most commonly used of several occluder devices. An observational study from Italy with 406 patients who were treated with either an Amplatzer device or a Figulla device found that there was no statistically significant difference between the devices in terms of procedural time, fluoroscopy time, or periprocedural complication rate.[37] Although both devices are made of a nitinol wire mesh, the nitinol content in the Occlutech Figulla device is half that of the Amplatzer device.[35] The device flexibility, which can allow for better deployment of the device in the interatrial septum, is better in the Figulla device as a result of the reduced nitinol content.[38] In our study, most patients were fitted with a Figulla occluder device. Kaplan-Meier analysis showed an insignificant difference between the device groups (Amplatzer: 2.4% vs. Figulla: 3.3%) in terms of recurrent ischemic cerebral events in the follow-up period. Our data indicated that both the Amplatzer and the Figulla devices were safe and effective for the prevention of recurrent ischemic cerebral events.

A relationship between CS and PFO has long been known. To identify patients who are most likely to benefit from PFO closure, Kent et al.[39] developed the RoPE score, consisting of a history of hypertension, diabetes mellitus, stroke and TIA, smoking status, cortical infarct on imaging, and age, to predict the risk of recurrent ischemic stroke. Morais et al.[12] observed that during a mean follow-up period of 6.4±3.7 years, the RoPE score was an independent predictor of recurrent ischemic cerebrovascular events. A score of ≤6 was shown to identify patients with a significantly higher risk of recurrent ischemic events. In our study, recurrent ischemic stroke or TIA was observed in 7 (2.2%) patients during long-term follow-up. The RoPE score was significantly lower in patients who experienced a recurrent ischemic cerebral event (stroke or TIA) compared with asymptomatic patients [median: 4 (25^{th}-75^{th} percentile: 2–4) vs. 6 (25^{th}-75^{th} percentile: 2–9); $p<0.001$)]. This score primarily depends on a consistent empirical relationship between easily obtained clinical variables and the prevalence of a PFO in CS patients. In short, younger patients without classic risk factors for atherosclerotic disease (i.e., hypertension, diabetes, smoking) or a prior cerebrovascular attack are more likely to have a PFO-related CS. A PFO detected in older patients with traditional cardiovascular risk factors for ischemic stroke and without an infarct on cerebral imaging is more likely to be an incidental finding.[12,39]

The MIST (Migraine Intervention with STARFlex Technology) trial was the first prospective, randomized study to investigate the effects of PFO closure for migraines. No significant difference was observed in the primary endpoint of migraine headache cessation between STARFlex device implant and sham groups during 6 months follow-up.[40] The PRIMA study (Percutaneous Closure of the Patent Foramen Ovale in Migraine with Aura) also compared the effectiveness of percutaneous PFO closure in patients who suffered migraines with aura that were refractory to medical treatment. Although the PFO closure group experienced fewer migraine attacks than the control group, the difference was not significant.[41] In our study, among 21 patients with migraines who underwent percutaneous PFO closure, 9 (42.8%) had migraine attacks during the follow-up period. Although the recurrent migraine attack rate seems very high, there were too few patients to properly assess its efficacy in such a specific group. Large-scale, randomized, controlled studies are needed to evaluate the effectiveness of PFO closure on migraine attacks.

Although uncommon, arrhythmias after PFO device implantation have been observed in previous studies.[42,43] In our study, after device implantation in the acute phase, we observed atrial fibrillation in 1 patient. Sinus rhythm was achieved with intravenous propafenone. Supraventricular tachycardia developed in 1 patient just after the closure of the PFO and recovery was seen after medical cardioversion. Atrial

arrhythmias developed during the follow-up period in 5 patients (3 atrial fibrillation and 2 supraventricular tachycardia). Medical treatment successfully controlled the symptoms in all of these cases.

Limitations

A small number of patients were enrolled in this study, and our research was a retrospective, single-center study with no comparison to medical therapy alone without percutaneous PFO closure. Multi-center studies are needed to further validate the benefits of device closure and to formulate clear guidelines for patients of CS with PFO.

Conclusion

The long-term results of our single-center study revealed that transcatheter interventions to treat CS-related PFO were safe and effective. Our findings not only confirm previous reports, but add to the literature regarding long-term results with Occlutech Figulla and Amplatzer devices. Large-scale studies with long-term follow-up are needed to further examine potential advantages and disadvantages relevant to technical aspects and device profile, as well as future complications.

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