

## Transcatheter Amplatzer Device Closure of Atrial Septal Defect and Patent Foramen Ovale in Patients With Presumed Paradoxical Embolism

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- **Objective:** To review our experience with, and profile the safety and efficacy of, the Amplatzer PFO (patent foramen ovale) occluder (APO) and Amplatzer septal occluder (ASO) used to close PFO and/or atrial septal defect (ASD) in patients with paradoxical embolism (PE).

- **Patients and Methods:** Between April 1998 and November 2002, 103 patients at the Mayo Clinic in Rochester, Minn, and Scottsdale, Ariz, mean age 52.4 years, with presumed PE (transient ischemic attack [n=22], stroke [n=77], or peripheral emboli [n=4]) underwent transcatheter device closure of PFO (n=81), ASD (n=12), and ASD/PFO (n=10) with 106 devices (APO [n=22] or ASO [n=84]).

- **Results:** All devices deployed successfully, and no patients died. Procedural complications included atrial fibrillation (n=2), vessel injury (n=3), profound sinus node dysfunction (n=1), and device embolization with successful retrieval (n=1). At 3 months, 7 of 95 monitored patients had trivial residual shunt; at 12 months, 2 of 28 monitored patients had trivial residual shunt. Three patients had recurrent events—2 transient ischemic attacks and 1 reti-

nal artery occlusion—at a mean  $\pm$  SD follow-up of 8.3 $\pm$ 8.1 months (range, 1-34 months). None of these 3 patients had residual shunt or evidence of intracardiac thrombus. The average annual recurrence of all events was 3.6% at 23 months. The overall mean  $\pm$  SD freedom from recurrence of all events was 98.9% $\pm$ 1.2% and 83.8% $\pm$ 10.2% at 12 and 29 months of follow-up, respectively.

- **Conclusions:** Transcatheter device closure of PFO and/or ASD with use of APO/ASO in patients with presumed PE is effective and safe. Recurrent events may occur in the absence of a residual shunt.

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AF = atrial fibrillation; APO = Amplatzer PFO (patent foramen ovale) occluder; ASA = atrial septal aneurysm; ASD = atrial septal defect; ASO = Amplatzer septal occluder; ICE = intracardiac echocardiography; PE = paradoxical embolism; PFO = patent foramen ovale; TEE = transesophageal echocardiography; TIA = transient ischemic attack; TTE = transthoracic echocardiography

The foramen ovale remains patent in approximately 27% of individuals at postmortem examination,<sup>1</sup> and transesophageal echocardiography (TEE) reveals a 9% to 19% incidence of patent foramen ovale (PFO) in the healthy population.<sup>2</sup> Use of contrast TEE with a Valsalva maneuver is the most sensitive method for detecting PFO with right-to-left shunt.<sup>3</sup> The importance of PFO as a mechanism for cryptogenic stroke is now gaining acceptance. Presumed paradoxical embolism (PE) has been a suspected mechanism with PFO; this has been rarely observed in patients with a “thrombus in transit.” Studies have established a strong association between the presence of PFO with or without atrial septal aneurysm (ASA) and cryptogenic stroke.<sup>4,5</sup> The incidence of PFO in a patient

with cryptogenic stroke is much higher than in the healthy population (40%-70% vs 10%-23%).<sup>2,6,7</sup> To prevent further transient ischemic attack (TIA), stroke, and embolic events, lifelong anticoagulation treatment with warfarin is standard. Both anticoagulation and surgical closure of PFO have been used to prevent recurrent stroke.<sup>8-10</sup>

Transcatheter closure of PFO has been used successfully to treat patients with presumed PE. Various devices have been used: atrial septal defect occlusion system (ASDOS) devices (Sulzer Osypka, Rheinfelden, Germany); Das Angel Wings occluders (Microvena Corp, White Bear Lake, Minn); CardioSEAL/STARFlex occluders (NMT Medical, Boston, Mass); and Amplatzer PFO occluders (APO) and Amplatzer septal occluders (ASO) (AGA Medical Corp, Minneapolis, Minn).<sup>11-13</sup>

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The ASO, designed for closure of atrial septal defect (ASD), is now approved by the US Food and Drug Administration. Although PFO and ASD are anatomically and hemodynamically different, the ASO technically can be used to close both PFO and ASD.

Table 1. Patient Population (N=103)\*

Defect	Device		No. of patients
	ASO	APO	
ASD	15†		12
ASD/PFO	10		10
PFO	59	22	81

\*ASD = atrial septal defect; APO = Amplatzer PFO (patent foramen ovale) occluder; ASO = Amplatzer septal occluder.

† Three patients with multiple defects needed 2 ASO devices.

This study was performed to systematically review the records of patients with severe right-to-left shunt across the atrial septum and presumed PE who underwent PFO and/or ASD closure with use of either ASO or APO. Our objectives were to review our experience with, and to profile the safety and efficacy of, the APOs and ASOs used to close PFO and/or ASD associated with PE. To our knowledge, no randomized trials have proven that device closure of PFO is superior to medical therapy.

## PATIENTS AND METHODS

### Study Population

Between April 1998 and November 2002, 104 patients at the Mayo Clinic in Rochester, Minn, and Scottsdale, Ariz, with presumed PE underwent PFO and/or ASD closure by catheter-based device; 1 patient with a CardioSEAL device was excluded, resulting in a total study population of 103 patients. Our study was approved by the Mayo Foundation Institutional Review Board, and patients gave authorization consent.

We participated in the early clinical trial for ASO closure of ASD and APO closure of PFO in patients with a history of stroke. The Food and Drug Administration approved the ASO for clinical use in December 2001. Since then, we elected to use this device in all patients with a septal defect and PE, regardless of septal anatomy. All patients had evidence of PFO and/or ASD with right-to-left shunt revealed by color flow or contrast echocardiography (transthoracic echocardiography [TTE] or TEE) and had a history of documented TIA, stroke, or peripheral embolism. Seven patients had a hypercoagulable state including heterozygous factor V Leiden mutation (n=3), heterozygous prothrombin 20210 A mutation (n=3), and the presence of anticardiolipin antibodies (n=1).

### Methods

A total of 103 patients (57 males), mean  $\pm$  SD age 52.4 $\pm$ 13.6 years (range, 21-82 years), were included in this study. The indications for device closure included TIA (n=22), stroke (n=77), and peripheral emboli (n=4). Multiple thromboembolic events occurred before device closure in 32 patients (31%), yielding a mean  $\pm$  SD of

1.5 $\pm$ 0.9 events per patient. Seventy-one patients had 1 event, 24 had 2 events, 5 had 3 events, 2 had 4 events, and 1 had 8 events.

Transesophageal echocardiography was performed during the procedure in 41 patients (40%), and intracardiac echocardiography (ICE) was performed in 62 patients (60%). Eighty-one patients had PFO, 12 had ASD, and 10 had PFO with ASD (2 defects in 8 patients and 3 defects in 2 patients). Of 103 patients, 23 (22%) had ASA and 17 (17%) had atrial septal redundancy. All had at least small right-to-left shunt at the atrial level on contrast echocardiography and/or color flow Doppler echocardiography. Of 103 patients, 23 had a moderate degree of right-to-left shunt. Also, 74 patients (72%) had small left-to-right shunt that was evident with color flow Doppler echocardiography.

Twenty-two APO devices, 25 mm (n=10) and 35 mm (n=12) were used to close PFO in 22 patients, whereas 84 ASO devices were used to close PFO (n=59), ASD (n=12), and PFO with ASD (n=10); 3 patients with multiple defects needed 2 ASO devices (Table 1). The stretched mean  $\pm$  SD diameter for the defects when ASO devices were used was 11.7 $\pm$ 4.3 mm (range, 4-28 mm). The mean  $\pm$  SD size of ASO devices was 14 $\pm$ 4 mm (range, 8-30 mm). The largest ASO device used for PFO was 22 mm. The mean  $\pm$  SD procedure time was 112 $\pm$ 41 min, and fluoroscopy time was 31 $\pm$ 17 min.

### Procedure

Under general anesthesia for TEE or local anesthesia for ICE, prograde right heart catheterization and left heart catheterization via the existing atrial communication were performed with hemodynamic and oxygen saturation measurements. Intravenous heparin, 50 to 100 U/kg (maximum, 8000 U), was given after all sheaths were placed to achieve an activated clotting time of 250 to 300 seconds. Intravenous antibiotic prophylaxis was given. For the APO device, balloon sizing was not performed; either a 25-mm or 35-mm device was selected, depending on the size of the PFO determined by TEE or ICE. In the PFO study protocol, patients with PFO and ASA received a 35-mm APO device. Balloon sizing of the stretched diameter of the PFO or ASD by Amplatzer sizing balloon was performed in other patients to select the size of ASO device. All devices were deployed in a typical fashion using venous access via the femoral vein with a 7F to 10F Amplatzer long sheath through which the Amplatzer detachable delivery system was advanced. Careful evaluation of the device position was made by ICE or TEE and fluoroscopy, and subsequently the device was deployed. Device position, stability, and the presence of residual shunt were evaluated by ICE or TEE (with use of color flow Doppler echocardiography

Table 2. Peri-interventional Complications\*

Complication	No. of complications	APO	ASO	Intervention
Atrial fibrillation	2	1	1	Cardioversion in 1 patient
Femoral arteriovenous fistula	2	1	1	Surgical repair in 1 patient
Small aneurysm of femoral artery	1		1	None
Profound sinus node dysfunction	1		1	Pacemaker implantation
Device embolization dislodgement	1		1	Device retrieval
Total	7	2	5	4

\*APO = Amplatzer PFO (patent foramen ovale) occluder; ASO = Amplatzer septal occluder.

and contrast echocardiography) and angiography at the inferior vena cava.

All patients received maintenance doses of warfarin plus aspirin or clopidogrel for the initial 3 months after device closure and then aspirin or clopidogrel for an additional 3 months. Patients with a hypercoagulable state were maintained on warfarin plus aspirin or clopidogrel for 6 months after device closure.

We performed a saline echocardiographic contrast study at 3 months to determine shunt occlusion as a decision point for discontinuing warfarin therapy. All patients had a follow-up examination at 3 months and 1 year after device closure, at which time chest x-ray films, electrocardiograms, and TTEs were obtained for all patients. At 3 months after device closure, a contrast study was performed with agitated saline injections at rest and after Valsalva maneuver. If study results were abnormal, a repeated contrast study was performed at the next visit 12 months after device closure.

### Statistical Analyses

All continuous variables were expressed as mean  $\pm$  SD. Nominal variables were compared with use of Fisher exact tests; paired continuous variables were analyzed with use of 2-sided, paired *t* tests.  $P < .05$  was considered statistically significant. Actuarial analysis of freedom from recurrent thromboembolic events was calculated according to the Kaplan-Meier method. Average annual event rates were calculated according to the formula  $1 - [(1 - P)^{1/n}]$ , in which *P* equals the cumulative event rate at *n* years of follow-up. The log-rank test was used for univariate analysis of independent variables (age, sex, procedural complications, postprocedural shunt, or device type) on the rate of recurrence.

## RESULTS

### Immediate Results

All devices deployed successfully. Of the 103 patients, 39 had complete occlusion, 44 had a trivial to small left-to-right residual shunt through a central part of the device, 11 had a small right-to-left shunt on contrast echocardiography, and 9 had a small bidirectional shunt immedi-

ately after the device closure. Although 1 patient had embolization of the ASO device during the first procedure, he underwent successful device closure 9 days later. During the first procedure, the device was partially deployed in the left atrium, prematurely separated from the delivery cable, embolized into the left atrium, and finally lodged at the descending aorta. This device was subsequently snared and removed successfully through the right femoral artery.

### Peri-interventional Complications

There were no procedural deaths; however, there were procedural complications in 7 patients (6.8%) (Table 2). The patient with profound sinus node dysfunction had similar symptoms predating the PFO closure but did not require earlier intervention.

### Postprocedural Follow-up

The mean  $\pm$  SD follow-up period was 8.3 $\pm$ 8.1 months (range, 1-34 months). Follow-up echocardiography showed a progressive increase in the percentage of patients with full occlusion during the first year after the procedure (Figure 1). Ninety-five patients (92%) were monitored for at least 3 months, of whom 88 patients (93%) had no residual shunt, 2 had a tiny left-to-right shunt, 3 had a tiny right-to-left shunt, and 2 had a bidirectional shunt across the atrial septum on TTE and/or TEE with contrast echocardiography. Twenty-eight patients (27%) were monitored for at least 12 months, of whom 26 (93%) had no residual shunt, 1 had a tiny right-to-left shunt, and 1 had a small left-to-right shunt and a tiny right-to-left shunt across the atrial septum.

Ten patients (10%) had a relatively long PFO tunnel (Figure 2, left). We placed somewhat oversized (3-4 mm larger) devices to accommodate the long tunnel, which often resulted in a longer and more bulbous-appearing device (Figure 2, middle). At 3-month follow-up, a stable device position with flattened disks and lower profile was noted (Figure 2, right). No patients had a residual shunt.

At 3-month follow-up, there was no significant correlation between residual shunt and sex, age, ASA, atrial septal

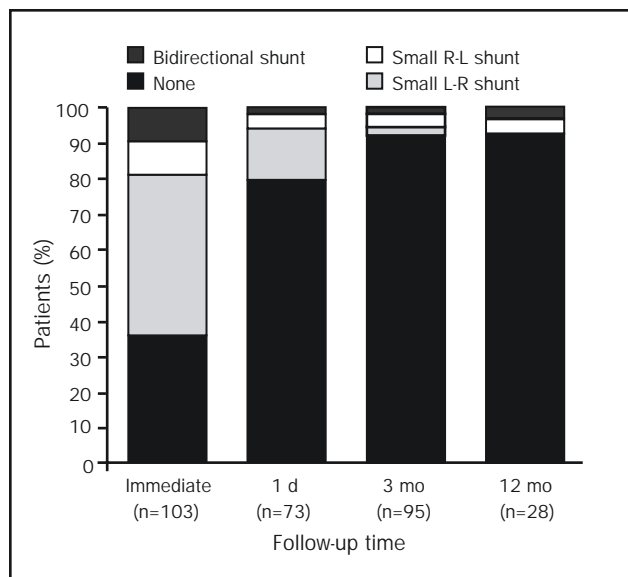


Figure 1. After device deployment, residual shunt was assessed by transthoracic echocardiography and/or transesophageal color flow Doppler echocardiography with agitated normal saline injected into the right atrium via the peripheral vein. The number of patients in each time frame is shown in parentheses. R-L = right-to-left; L-R = left-to-right.

redundancy, tunnel PFO, type of defect, type of device, or type of echocardiography used during closure. Two patients had an APO device, and 5 had ASO devices.

### Late Complications

No evidence of thrombus on the device was revealed at any time on follow-up TTE and/or TEE. No reintervention was required, and no late deaths were recorded. Four patients (1 with an APO, 3 with an ASO) developed arrhythmias during follow-up: 3 developed atrial fibrillation (AF) at 3 weeks, 2.5 months, and 5 months after device implantation, respectively; 2 of the 3 patients with AF had a history of AF before the procedure. The fourth patient had some palpitations with negative Holter monitoring.

### Recurrent PE Events

Three patients had recurrent neurologic events (Table 3). The first patient developed transient numbness of his right arm, and a computed tomographic scan of the brain revealed no new lesion. The second patient developed transient numbness of the left arm and hand with a speech abnormality. Magnetic resonance imaging of the brain showed no new lesion. The third patient developed right retinal artery occlusion (different side from the previous episode, 6 weeks after discontinuation of aspirin therapy). Interestingly, none of these patients with recurrent events had residual intracardiac or pulmonary shunt, evidence of

thrombus on the device, or other intracardiac thrombus. Right-to-left shunt was excluded by contrast TEE done with and without Valsalva.

Because of the small number of patients with recurrent events, there were no statistical correlations between the recurrent events and sex, age, number of prior cardiac events, ASA, atrial redundancy, or residual shunt at 3 or 12 months. The average annual recurrence of all combined events was 3.6% at 23 months. The overall mean  $\pm$  SD freedom from recurrence of the combined events of TIA, stroke, and peripheral embolism was  $98.9\% \pm 1.2\%$  and  $83.8\% \pm 10.2\%$  at 12 and 29 months of follow-up, respectively (Figure 3).

### DISCUSSION

Transcatheter device closure of PFO for PE presenting with TIA, stroke, or peripheral embolism has been reported to have a high technical success rate.<sup>11,12,14-17</sup> Amplatzer occlusion devices (APO and ASO) are self-expanding and repositionable and are made from nitinol wires tightly woven into 2 interconnected disks.<sup>18</sup> The ASO was developed to occlude secundum ASD with left-to-right shunts, and the APO was developed to occlude PFO. The ASO has a smaller right atrial side compared with the APO; the ASO also has been used to close PFO. Walsh et al<sup>19</sup> first reported that the ASO can close the flap-like PFO in patients with neurologic decompression illness. Du et al<sup>17</sup> described 6 of 18 patients for whom the ASO was used successfully to close PFO. In our series, the ASO closed PFO in 69 patients as effectively as APO (n=22).

Embolization of a device has been reported with Amplatzer, Sideris, and STARFlex devices.<sup>16,20,21</sup> In our series, 1 embolization occurred during partial deployment of the device in the left atrium when the device prematurely separated from the delivery cable. A manufacturing intolerance between the cable and device was the subject of a subsequent product recall, and the delivery cable was modified to correct this problem. No further inadvertent device separations have occurred in this series.

The overall peri-interventional complication rate was comparable to, or lower than, the rate noted in other studies.<sup>12,16,22</sup> The profound sinus node dysfunction may not have been related to device closure because the patient had a history of a similar event. Previously reported complications, including air embolism, retroperitoneal hematoma, device fracture, device-adherent thrombus formation, need for surgical removal, and device-induced pericardial effusion, were not found in this study. Type of device (APO vs ASO) or type of echocardiography (TEE vs ICE) used was not associated with the occurrence of complication. No recurrent events or complications occurred in any of the 7 patients with a hypercoagulable state.

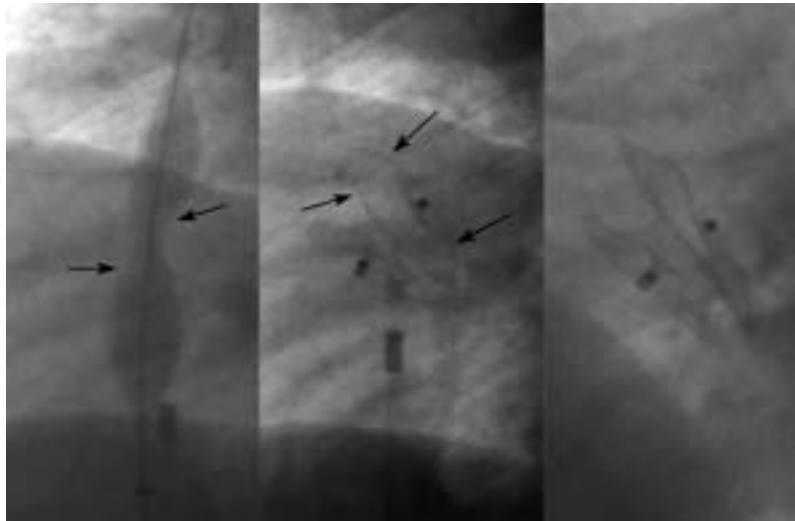


Figure 2. Angiographic features of long-tunnel patent foramen ovale. Left, Inflation of balloon sizing shows 2 waists and a long-tunnel patent foramen ovale (arrows). Middle, Immediately after deployment of atrial septal occluder device, longer and more bulbous-appearing device is seen at the left atrial side (arrows). Right, At 3-month follow-up, a stable device position with flattened disks and lower profile is seen.

Concern has been expressed about the use of the ASO device in a long-tunnel PFO; however, 3-month follow-up has shown a flattened device now incorporated into the septum (Figure 2).

**Residual Shunts After the Procedure**

Although it is common to see trivial left-to-right shunt through a central portion of the device soon after the device is placed, this begins to disappear as soon as 1 day after implantation and completely disappears in most patients by 3-month follow-up. The incidence of residual shunt after device placement decreased steadily during the follow-up period. Although 2 of 28 patients (7%) still had a residual shunt at 1-year follow-up, the degree of residual shunt was tiny to small and did not appear to have clinical significance in terms of reintervention or recurrence events. One patient, with a tiny residual right-to-left shunt and small left-to-right shunt at 30-month follow-up, was the first in

this series to have an ASO device implanted. The other patient, who had an APO device, had a tiny right-to-left shunt and 1 to 2 bubbles in the left atrium on TEE with Valsalva contrast injection. The incidence of the residual shunt in our series was comparable to the reports from different device types.<sup>14,23-25</sup>

**Recurrent Events After the Procedure**

Interestingly, no patients with recurrent PE had a residual intracardiac or pulmonary shunt or evidence of intracardiac thrombus detected by contrast TEE. Similar results were reported by many studies and showed that recurrent neurologic ischemic events may occur despite successful percutaneous PFO closure without evidence of residual shunt.<sup>12,16,22-24</sup> These findings revealed that PFO and neurologic events may coexist without true causal relationship, and in such cases, even with confirmed PFO closure, recurrent events may happen.

Table 3. Patients With Recurrent Neurologic Events During Follow-up\*

Patient No./age (y)/sex	Type of defect	Type of device	Prior events	No. of events	Recurrent events	No. of recurrent events	Onset of event (mo)
1/74/M	PFO	ASO	Stroke	8	TIA	2	1
2/71/F	PFO	APO	Stroke	4	TIA	4	16
3/44/F	ASD	ASO	RAO	1	RAO	1	24

\* None of these patients had residual shunt. APO = Amplatzer PFO (patent foramen ovale) occluder; ASD = atrial septal defect; ASO = Amplatzer septal occluder; RAO = right retinal artery occlusion; TIA = transient ischemic attack.

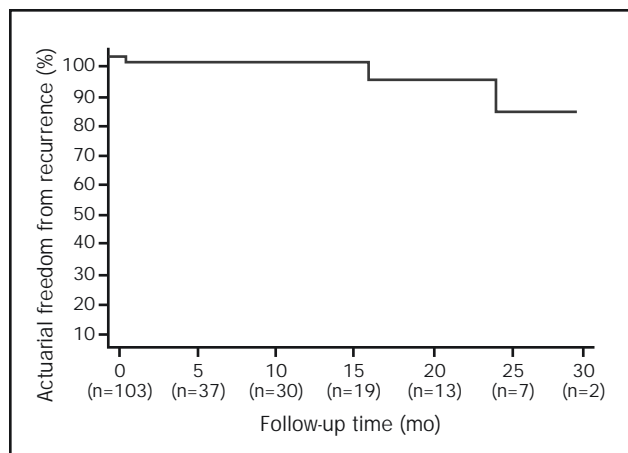


Figure 3. The actuarial mean  $\pm$  SD freedom from recurrence of the combined events of transient ischemic attack, stroke, and peripheral embolism by Kaplan-Meier curve was  $98.9\% \pm 1.2\%$  and  $83.8\% \pm 10.2\%$  at 12 and 29 months of follow-up, respectively. The number of patients in each time frame is shown in parentheses.

Numerous studies have estimated the recurrence risk of cryptogenic cerebral ischemia after an initial event in patients with PFO.<sup>26-28</sup> In the Lausanne Study,<sup>28</sup> the annual recurrence rate was 1.9% for stroke, 1.9% for TIA, and 3.8% for stroke and/or TIA despite treatment. In the French study,<sup>27</sup> the average annual recurrence rate was 1.2% for stroke and 3.4% for TIA.

Mas et al<sup>29</sup> concluded that PFO associated with ASA had a higher risk for recurrent stroke (15.2% in 4 years) than with PFO alone (2.3%). In this study, we could find no clinical or procedural factor (age, sex, type of device, type of defect, number of prior events, ASA, or residual shunt) related to the recurrent events; however, this analysis may be limited because of the small numbers of patients involved (22% with ASA). Surgical closure of PFO in patients with PE reportedly has varying success rates for reducing the incidence of recurrent stroke or TIA.<sup>30-32</sup> Homma et al<sup>31</sup> reported a recurrence rate of stroke or TIA of 19.5% within 13 months. Dearani et al<sup>30</sup> found the risk for recurrence of TIA was 7.5% within the first year and 16.6% within 4 years, whereas Ruchat et al<sup>32</sup> found no recurrences at 1.5 years after surgical closure. However, surgery-related complications of AF and pericardial effusion still existed.<sup>30</sup>

Recurrent rates after various types of device closure for PFO have been reported to vary from no recurrence to 3.2%.<sup>14,15,22-25</sup> Our results were comparable to those obtained with use of long-term oral anticoagulation, surgical closure, or percutaneous closure of PFO for patients with PE. We achieved successful device implantation without mortality and with minimal morbidity.

## CONCLUSIONS

Transcatheter device closure of PFO and/or ASD with use of APO/ASO in patients with presumed PE is a safe and effective procedure resulting in elimination of interatrial shunt in 93% of our patients. The average annual neurologic recurrence rate was 3.6% in the absence of a residual shunt, suggesting that more than 1 mechanism may have been responsible.

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