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## ***PATENT FORAMEN OVALE AND STROKE***

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### **EXECUTIVE SUMMARY**

The association between the patent foramen ovale (PFO) and ischemic stroke of undetermined cause (cryptogenic stroke) in young adults remains controversial. First, data regarding the relative risk of primary or secondary cryptogenic stroke among patients with PFO are conflicting. Second, the role of the size of the PFO and/or shunt, and the role of other cardiac abnormalities such as an atrial septal aneurysm (ASA) and a persistent eustachian valve are unclear, and have confounded the determination of an etiologic role of PFO in cryptogenic stroke. Despite these obstacles, the development of reasonably safe and easily implemented transcatheter PFO closure devices has spurred interest in closing the PFO for secondary stroke prevention. Non-randomized studies have documented a relatively lower stroke recurrence rate after transcatheter PFO closure versus medical therapy, despite a relatively higher-risk population. Although randomized trials comparing PFO closure to medical therapy are underway, the current lack of randomized, controlled data has led to variable practice patterns, necessitating publication of practice guidelines formulated by relevant professional societies.

## Introduction

The purported pathogenic mechanism of the association between the patent foramen ovale (PFO) and stroke is a right-to-left shunt across the septum through the PFO of thromboemboli that subsequently enter the cerebral circulation and cause ischemic stroke, termed “paradoxical embolism.” Although thromboemboli have been seen in transit across the interatrial septum (1), documentation of paradoxical embolism is rare, and suggestive evidence is uncommon in these patients, with deep venous thrombosis, hypercoagulable state and/or Valsalva maneuver at the time of stroke occurring in the minority of patients (2).

## The Association Between PFO and Stroke Remains Controversial

In the late 1980s, a case-control study first reported that PFO is twice as common in young cryptogenic stroke patients (54%) as in normal controls (21%) (3). These findings were confirmed by other case-control studies, culminating in a meta-analysis to show an increased prevalence of PFO in 194 young cryptogenic stroke patients compared to 272 normal controls (odds ratio (OR): 5.01, 95% confidence interval (CI): 3.24-7.75) (4). A number of studies have documented supporting physiological evidence, indicating that the size of the PFO and the degree of shunt, as well as shunting at rest, are also correlated with increased stroke risk.

While the combined retrospectively collected evidence generally favors an etiological role for PFO in cryptogenic stroke, a recent population-based case-control study of 133 patients with cryptogenic stroke and 519 randomly selected controls showed no association between PFO and cryptogenic stroke after adjustment for age, sex, and vascular risk factors (OR: 1.29, 95% CI: 0.078-2.14) (5). Results from additional recent prospective studies have also called the association of stroke and PFO into question. The SPARC (Stroke Prevention: Assessment of Risk in a Community) study consisted of a random sample of 585 subjects from Olmsted County, Minnesota (6); baseline and follow-up data were collected with respect to atherosclerosis risk factors, cardiac or cerebrovascular disease, and venous thromboembolism. Transesophageal echocardiography with provocative testing and blinded assessment was performed to detect the presence of PFO. There were 41 cerebrovascular events in follow-up, with 12 events occurring in the 140 patients with PFO. It was not reported whether the events that occurred were considered cryptogenic or of identifiable cause. The Kaplan-Meier estimate of survival free of cerebrovascular disease did not differ between subjects with PFO (91%) and those without PFO (93%). A multivariable model adjusting for age, gender, prior myocardial infarction, and atrial fibrillation/flutter failed to find an association between PFO and cerebrovascular events (hazard ratio (HR): 1.46, 95% CI: 0.74-2.88;  $p = 0.28$ ). Another prospective population-based cohort of patients who had a transthoracic echocardiogram to evaluate for atrial septal abnormalities has been reported only in abstract form (7). Incidence of ischemic stroke was 1.10/100 person-years in subjects with PFO and 0.97/100 person-years in those without PFO.

While these results appear to discount an association of PFO and stroke, there are mitigating factors that lessen the strength of these conclusions. Principally, these studies may be underpowered to detect a statistically small but important association. In fact, the 95% CI's were wide, with the potential for a HR greater than 2. Additionally, the mean age of patients in the

prospective study was about 67 years. It has been stated previously in retrospective studies that PFO is not a risk factor for cryptogenic stroke in older patients (age >55 years) or in patients with stroke of known etiology (3,4,8). The conclusion most consistent with the SPARC data is that the mere presence of any PFO in asymptomatic patients without cerebrovascular events does not carry a significant stroke risk. Correlating with this, there are currently no treatment recommendations for the primary prevention of stroke in patients with a PFO.

### **Risk of Recurrent Stroke with PFO**

The data for recurrent stroke risk among patients with a PFO are also difficult to interpret. The most frequently cited study was performed by Mas et al. (PFO-ASA study; 9). A total of 581 patients with cryptogenic stroke were enrolled consecutively after their index event and followed for 4 years; all patients were treated medically with aspirin alone. After 4 years there was no increased risk for recurrent events among patients with a PFO alone, although a significant risk was found among patients with both a PFO and an atrial septal aneurysm (ASA). There was no difference between patients with a small, medium, or large shunt with respect to stroke recurrence. The conclusion of this study was that isolated PFO, regardless of size, is not a risk factor for stroke recurrence on aspirin therapy.

The only other prospective study to evaluate this question was the PICSS (PFO in Cryptogenic Stroke Study) substudy of the larger WARSS (Warfarin-Aspirin Recurrent Stroke Study) study, evaluating the use of warfarin or aspirin for recurrent stroke prevention (10). PICSS included patients with cryptogenic stroke who were recruited from the WARSS study to undergo transesophageal echocardiography, as well as any patients who underwent the procedure for clinical indications. Similar to the PFO-ASA study, this study failed to document an association between isolated PFO and recurrent stroke, although it did include older patients and non-cryptogenic stroke subtypes. Because this study failed to find a difference between patients treated with warfarin and those treated with aspirin with respect to stroke recurrence, it has been interpreted as evidence that either therapy is effective to prevent stroke recurrence. Subsequent analysis of PICSS showed that PFO was associated with recurrent stroke only in patients >65 years (11), though the generalizability of this finding is questionable.

### **PFO-associated Cardiac Anomalies and Cryptogenic Stroke**

While 25% of the population has a PFO (approximately 30 million people), only 0.1% will have a cryptogenic stroke, clearly indicating that the majority of PFOs remain benign. Certain factors, some of which have already been discussed, must be important in determining which PFOs are at higher risk for stroke pathogenesis. Atrial anomalies associated with PFO have been considered as possible mediators of increased stroke risk. The ASA, a protrusion of the interatrial septum, although uncommon in the general population (2%), is found in 19-58% of cryptogenic stroke patients with PFO (12). When an ASA is found with a PFO, the risk of cryptogenic stroke appears to be significantly higher (OR: 33.3, 95% CI: 4.1-270;13), as does the risk for stroke recurrence (HR 15.2 at 4 years, 95% CI: 1.8-28.6; 9). This increased stroke risk is speculated to relate to an increased interatrial shunt across the PFO, development of thrombus within the ASA, or associated atrial arrhythmias.

### **Non-randomized Data for Transcatheter PFO Closure**

Data regarding transcatheter PFO closure consists of largely retrospective, single-center case series. These reports have generally supported the use of transcatheter closure devices to reduce the risk for recurrent stroke. Most notably, a meta-analysis of transcatheter therapy versus medical therapy concluded that the 1-year rate of recurrent stroke or transient ischemic attack (TIA) after transcatheter intervention ranges from 0% to 4.9%, whereas the 1-year recurrence rate with medical therapy alone ranges from 3.8% to 12% (14). While this suggests that transcatheter closure may prevent a substantial proportion of cryptogenic strokes, the interpretation of this body of literature is limited by variable patient populations, lack of controlled data, and non-standardized definitions. Further, inclusion of TIA as an endpoint is problematic due to difficulties with validation and adjudication of suspected events, particularly when assessment of these events is not blinded to treatment.

A recent prospective, non-randomized study supported the finding of the above meta-analysis. Schuchlenz et al. (15) reported the recurrent event rate in 280 consecutive patients with cryptogenic stroke who either underwent transcatheter closure (N = 167) or medical therapy with platelet inhibitors (N = 66) or medical therapy with anticoagulation (N = 47). Despite having a larger PFO size and more commonly stroke as the index event (versus TIA), device therapy patients had a lower recurrent stroke or TIA rate than medical therapy patients (0.6% annual recurrence rate with device closure, 13% with aspirin, and 5.6% with warfarin). Independent predictors of recurrent events included a large PFO.

### **Randomized, Controlled Trials for Transcatheter PFO Closure**

The first randomized, controlled trials are underway to evaluate the safety and efficacy of transcatheter device closure. These include CLOSURE 1 using the STARFlex® septal closure system (NMT Medical, Inc., Boston, MA), and RESPECT using the Amplatzer® PFO occluder (AGA Medical, Minneapolis, MN). There is no indication these trials will be completed anytime soon due to slow enrollment, and they run the risk of remaining underpowered if enrollment is terminated too soon or the follow-up interval is not adequate. Another potential criticism of these trials is the lack of specificity in terms of inclusion criteria for PFO size or associated atrial anomalies such as ASA. If indeed PFO alone is not associated with increased risk, as suggested in the prospective studies by Mas et al. (9) and Homma et al. (10), inclusion of “small” PFOs or those without ASA may lead to a false negative result.

### **Current Guidelines for Secondary Stroke Prevention**

As a natural result of the conflicting data regarding the role of PFO and ASA in cryptogenic stroke, practice patterns with respect to treatment are not uniform. The enthusiasm for device closure of physicians (particularly interventional cardiologists) and patients who have suffered a cryptogenic stroke, has led to widespread utilization of these devices under Humanitarian Device Exemptions (HDE) and “off-label” use, despite the lack of randomized, controlled trials. In fact, slow enrollment in randomized trials may be due to physician and patient reluctance to be randomized to medical therapy.

In order to provide specific guidance to physicians and patients with respect to treatment, the Quality Standards Subcommittee of the American Academy of Neurology recently formulated a set of clinical guidelines (16). This committee concluded that PFO is not associated with an increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke, but that both PFO and ASA possibly increase the risk of subsequent stroke in younger patients (less than 55 years old). They also concluded that there is no clear benefit to any specific therapy and encouraged clinicians encountering patients with cryptogenic stroke and PFO – with or without ASA – to enroll such patients in research protocols. The American Stroke Association, in conjunction with the American Heart Association, recently published a new set of guidelines for secondary stroke prevention. Consistent with the guidelines published by the American Academy of Neurology, this committee concluded that transcatheter PFO closure may be considered in patients with recurrent cryptogenic stroke despite medical therapy (Class IIb, level of evidence C), but that insufficient data exists to make a recommendation about PFO closure in patients with a first stroke and PFO (17).

### **Clinically Available Transcatheter PFO Closure Devices**

Currently available transcatheter PFO closure devices were originally designed for percutaneous closure of atrial septal defects. The first septal defect closure devices were based on a button-like design, but due to early failures (device embolization) a “double-disk” configuration, with a left atrial and right atrial disk, respectively, came into vogue. Currently, two PFO closure devices are available on the market, both based on the “double-disk” configuration. At least ten PFO closure devices with variable design characteristics have been reported in the literature but failed to reach widespread use.

Aside from clinical research trials, only two devices in the United States have FDA approval for use under HDE. The CardioSEAL® septal occlusion system (NMT Medical, Boston, MA) and the Amplatzer® PFO occluder (AGA Medical, Minneapolis, MN, USA) are approved under HDE for PFO closure in patients with recurrent cryptogenic stroke due to a presumed paradoxical embolism while on conventional drug therapy. Many physicians are reluctant to wait for a second, potentially devastating stroke in a young patient, and therefore these devices have been implanted “off-label.” The CardioSEAL device has a clamshell design with four nitinol struts on each half of the shell which are draped with biocompatible knitted polyester fabric (Figure 1). The Amplatzer PFO occluder is a self-expandable, double disc device composed of flexible nitinol wire mesh lined with thin polyester fabric sewn into each disc (Figure 2). The next generation of NMT devices, the STARFlex® PFO closure device, is currently in use only in the CLOSURE I trial (Figure 3).

### **Innovations in Transcatheter Device Designs**

Understanding the procedural and device characteristics of current PFO closure devices has aided in the development of new devices. Potential complications with current devices include incomplete closure, device arm fracture, thrombus formation, nickel allergy, late cardiac perforation, and atrial arrhythmias. The overall incidence of such complications is low, but significant if the benefit of the devices is not entirely clear. Improved PFO closure device designs are attempting to eliminate the issues associated with a permanent metal implant by

using creative means such as radiofrequency coaptation of the septum, bioabsorbable devices, and suture-based devices. Table 1 lists currently available and investigational PFO closure devices.

### **The Role of PFO in Other Neurological and Pulmonary Conditions**

As the interest in PFO and right-to-left shunt has increased, so has the number of potential conditions in which PFO may play an etiologic role. Although most commonly considered important in cryptogenic stroke etiology, PFO is also suspected to play a significant role in decompression illness, platypnea-orthodeoxia, migraine headaches, fat-embolism syndrome, intraoperative cerebral air embolism, and more recently, obstructive sleep apnea. As the list of potential pathogenic roles for PFO grows, it may seem at times that PFO is an anomaly in search of a disease. However, interest in studying PFO in other conditions is likely to provide increased understanding to the topic of paradoxical embolism, and perhaps aid in our understanding of cryptogenic stroke evaluation and treatment.

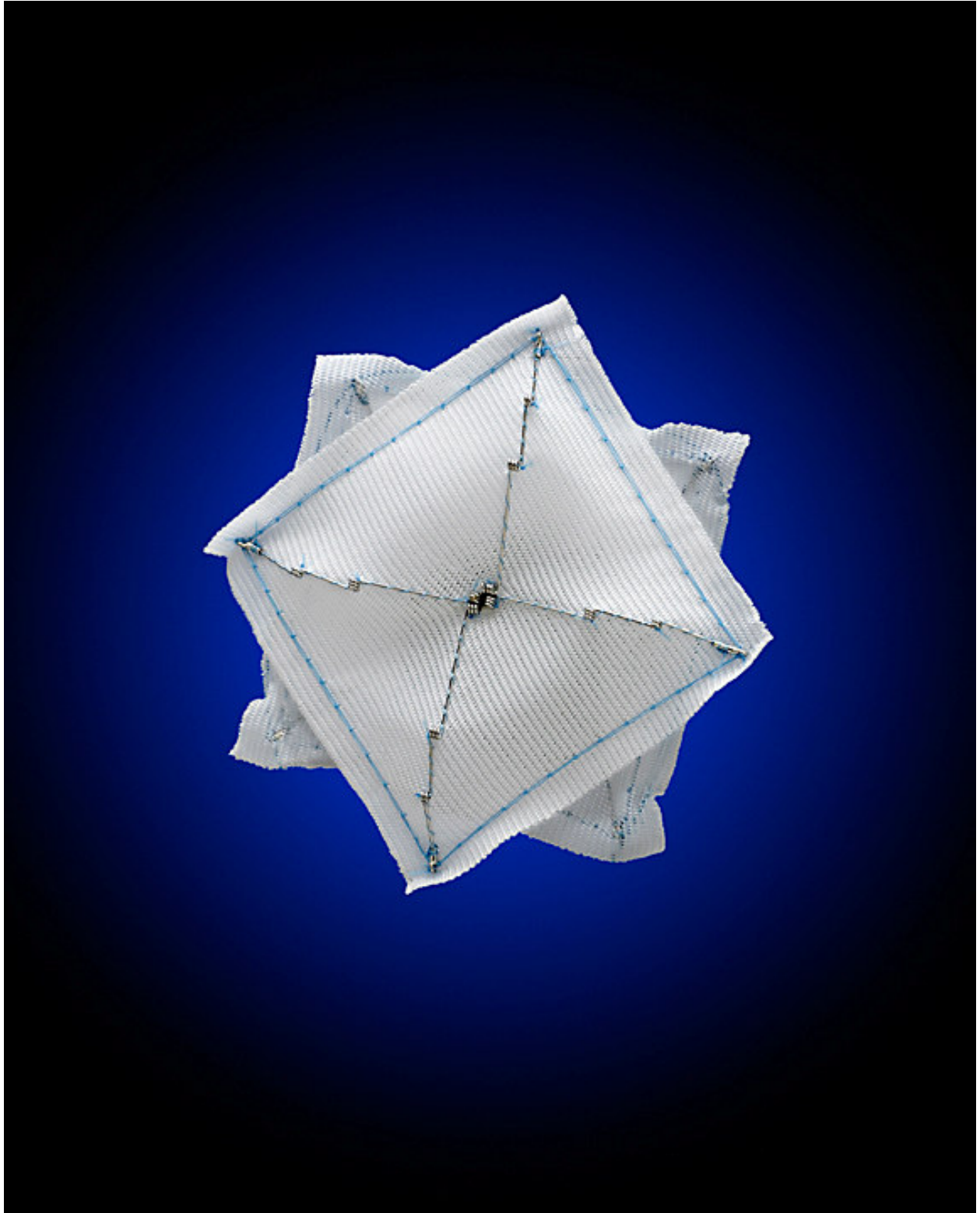
### **Conclusions**

The relationship between PFO, paradoxical thromboembolism, and cryptogenic stroke remains enigmatic. The current enthusiasm for device closure may be premature, as adoption of this procedure has perhaps outpaced the scientific data to support its widespread use. The recommendations of the relevant professional societies in neurology and cardiology, regarding device PFO closure, encourage enrollment in clinical trials and restraint when facing patients who have had only a single cryptogenic stroke. In the meantime, knowledge is increasing with respect to current device complications and new device development. Cryptogenic stroke patients are most likely to benefit when we are better able to identify high-risk patients, and can close the PFO successfully and safely, and with no permanent cardiac implant.

**Table 1.** PFO Closure Devices.

Device	Mechanism of closure	Device regulatory status	Device company website
Amplatzer® PFO occluder (AGA)	Double-disk, nitinol implant	HDE	www.aga.com
CardioSeal® PFO occluder (NMT Medical, Boston, MA)	Umbrella, nitinol implant	HDE	www.nmtmedical.com
STARFlex® (NMT Medical, Boston, MA)	Umbrella, nitinol implant	IDE	www.nmtmedical.com
BioSTAR™ (NMT Medical, Boston, MA)	Resorbable double-disc	IDE	www.nmtmedical.com
HELEX™ Septal Occluder (W.L. Gore & Assoc., Newark, DE)	Collapsing helical design	IDE	www.goremedical.com
SeptRx (NDC Inc., Fremont, CA)	Intrapocket occlusion	Awaits clinical evaluation	www.nitinol.com
PFX™ Closure System (Cierra Inc, Redwood City, CA)	Radiofrequency coaptation	Evaluated in Europe only	www.cierrainc.com
Coaptus RF (CoAptus Medical Corporation, Redmond, WA)	Radiofrequency coaptation	Awaits clinical evaluation	www.coaptus.com
Sutura (Sutura, Inc., Fountain Valley, CA)	Suture-based device	Awaits clinical evaluation	www.suturaus.com

**Figure 1.** The CardioSEAL® Septal Occlusion System



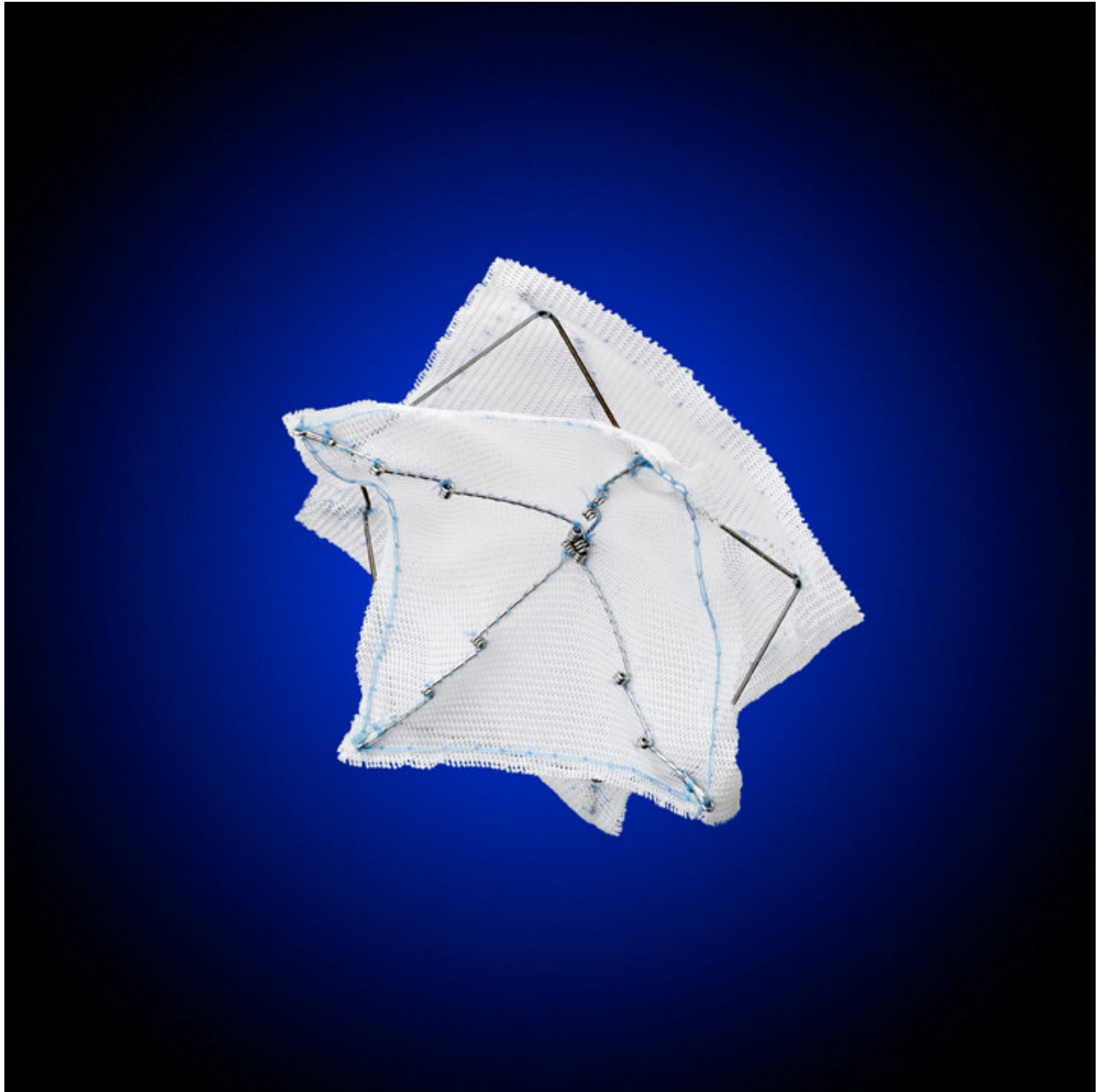
Photograph courtesy of and reproduced with permission from NMT Medical, Inc., Boston, MA, USA

**Figure 2.** The Amplatzer® PFO Occluder



Image courtesy of and reproduced with permission from AGA Medical, Minneapolis, MN, USA

**Figure 3.** The STARFlex® PFO Closure Device



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