Transcatheter patent foramen ovale closure: review and choice of devices

The foramen ovale is an essential part of the fetal circulation, allowing right-to-left shunt of oxygenated blood bypassing the nonfunctional lungs *in utero*. In approximately 20% of individuals, the foramen ovale remains patent after birth. Several conditions, such as cryptogenic stroke or transient ischemic attack, decompression sickness in divers, platypnea–orthodeoxia, high altitude pulmonary edema and migraine headaches have been found to be associated with a patent foramen ovale (PFO). Closure of a PFO may allow attenuation of symptoms of hypoxemia or recurrence of strokes or migraine headaches. This article briefly reviews the data supporting transcatheter PFO closure in a variety of clinical scenarios. We also provide an overview of the different devices available for PFO closure with a focus on device specifics that are important to the interventional cardiologist.

KEYWORD: cryptogenic stroke ■ device ■ migraine ■ percutaneous patent foramen ovale closure

Christian Spies[1],
Qi-Ling Cao[2]
& Ziyad M Hijazi[†2]

[1]*Department of Cardiovascular Diseases, The Queen's Medical Center; Department of Medicine, University of Hawaii, Honolulu, HI, USA*
[2]*Rush Center for Congenital & Structural Heart Disease, Section Chief, Pediatric Cardiology, 1653 W Congress Parkway, Jones 770, Chicago, IL 60612, USA*
[†]*Author for correspondence: Tel.: +1 312 942 6800 Fax: +1 312 942 8979 zhijazi@rush.edu*

The foramen ovale is an essential part of the fetal circulation, allowing right-to-left shunt of oxygenated blood derived from the umbilical vein to bypass the nonfunctional lungs *in utero*. It is formed by the septum primum and septum secundum. After birth, owing to an increase in the left atrial pressure and a decrease in the right atrial pressure, the septum primum is pushed against the thicker septum secundum from the left atrial side, resulting in closure of this foramen ovale. However, in a significant proportion of individuals, the foramen ovale remains patent. On autopsy studies, a patent foramen ovale (PFO) has been identified in 27% of individuals [1,2]. Such post-mortem 'probe patency' may be an overestimate of the prevalence of a PFO under physiologic conditions in the general population, as transesophageal echocardiographic studies have found a PFO to be present in approximately 10–15% of individuals [3,4].

Owing to its high prevalence, a PFO is mostly considered to be a benign, incidental finding. However, several conditions have been found to be associated with a PFO. Those conditions include cryptogenic stroke or transient ischemic attack (TIA), decompression sickness in divers, platypnea–orthodeoxia syndrome, high altitude pulmonary edema and migraine headaches [5–11]. The mechanism by which a PFO is believed to be related to those disease states is secondary to the resulting right-to-left shunt. This shunting allows passage of blood low in oxygen content, vasoactive substances or corpuscular material such as thrombi into the systemic circulation, potentially causing hypoxemia, migraine or strokes. Closure of a PFO in the right context may allow attenuation of symptoms of hypoxemia or recurrence of strokes or migraine headaches.

This article briefly reviews the data supporting transcatheter PFO closure in a variety of clinical scenarios, understanding that the majority of data are available in patients with cryptogenic stroke or TIA. We will then provide an overview of the different devices available for PFO closure with a focus on device specifics that are important to the interventionalist when choosing a device for transcatheter PFO closure.

Evidence for transcatheter closure in PFO-associated conditions
■ Cryptogenic stroke & transient ischemic attack

In approximately 30–40% of ischemic strokes, evaluation does not reveal an obvious cause, referred to as stroke of undetermined etiology, or cryptogenic stroke [12–14]. Triggered by two reports describing a higher prevalence of PFO in patients with cryptogenic stroke, several case–control studies have confirmed a positive association between those two conditions [15–17]. Irrespective of age, PFO is approximately three- to five-times more prevalent in patients with cryptogenic stroke compared with age-matched controls [17,18]. A variety of prospective studies have evaluated the risk of recurrence in medically treated patients following cryptogenic strokes or nonselected patients with ischemic strokes and coexisting PFO [19–22]. Data are

part of future medicine fsg

conflicting, with a wide range of estimated recurrence rates of ischemic strokes [19,21,23]. However, a recurrent theme is that patients with PFO and atrial septal aneurysms compared with patients with PFO alone have a higher risk of stroke recurrence [20,24].

Several case series of transcatheter PFO closure using a variety of different devices have been published [25–34]. With improvement in device design and deliverability, the procedure has become exceptionally successful and safe with technical success rates of 100%, total closure rates of over 90% and major complication rates of 1–2% [28,35,36]. Recurrence rates of stroke or TIA after successful closure ranges between 0 and 5%, averaging approximately 2% [23]. Khairy et al. summarized recurrence rates of stroke and TIA in patients with cryptogenic stroke and PFO treated medically or with transcatheter closure prior to 2003 [23]. Acknowledging the nonrandomized nature and probable patient selection bias, the authors found a lower risk of recurrent neurologic events in patients undergoing transcatheter PFO closure versus medically treated patients (0–4.9 vs 3.8–12.0%, respectively).

A nonrandomized study compared treatment modalities in 308 patients treated with transcatheter PFO closure versus medical management. The study demonstrated a strong trend towards a lower recurrence rate of stroke or TIA at 4-year follow-up in the PFO closure group (7.8 vs 22.2%; p = 0.08) [30]. In a subgroup analysis of patients with more than one cryptogenic thromboembolic event at the time of closure, transcatheter closure outperformed medical therapy (4-year recurrent rate of stroke/TIA: 7.3 vs 33.2%; p = 0.01). Similarly, in the group of patients who had complete PFO closure, recurrence rates of stroke and TIA were significantly lower compared with medically managed patients (4-year recurrence rate of stroke/TIA: 6.5 vs 22.2%; p = 0.04). A comparable nonrandomized study was published by Schuchlenz et al., who reported results of 280 patients treated with either aspirin or warfarin versus transcatheter closure [32]. Annual recurrence rates of stroke and TIA were lowest in patients following closure (0.6%), followed by participants treated with warfarin (5.6%). Patients treated with aspirin (13%) had the highest recurrence rates. A finding shared with all nonrandomized comparisons of transcatheter PFO closure with medical therapy is that the medically treated group of patients has more competing risk factors for stroke, such as higher age and traditional cardiovascular risk factors, potentially leading to a higher recurrence rate of stroke or TIA.

Several ongoing randomized controlled trials are being conducted evaluating medical therapy versus transcatheter closure in patients with cryptogenic stroke and PFO. Enrollment and completion of trials in this field has been difficult for a variety of reasons. First, transcatheter PFO closure can easily be accomplished outside of randomized controlled trials, as devices are approved for this indication outside the USA. Within the USA, PFO closure can be carried out 'off–label' using devices approved for atrial septal defect (ASD) closure [37]. If patients have the option to undergo PFO closure without the 'risk' of being randomized to the medical management arm of a randomized trial, the vast majority will elect to have their PFO closed directly, outside of a trial. Furthermore, given the relatively low rate of stroke recurrence, a fairly large number of participants is needed, requiring a long follow-up period for those trials. Among the currently ongoing trials are the Randomized Evaluation of Recurrent Stroke Comparing Patent Foramen Ovale Closure to Established Current Standard of Care Treatment (RESPECT) trial, the Gore HELEX™ Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (REDUCE) trial, the Patent Foramen Ovale and Cryptogenic Embolism (PC) trial and the investigator-initiated Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial. The Evaluation of the STARFlex Septal Occluder System in Patients With Stroke or TIA Due To the Possible Passage of a Clot of Unknown Origin Through a PFO (CLOSURE) 1 trial has finished enrolling its 900 patients and completed its 2-year follow-up period. The long-awaited results are expected to be available by the end of 2010.

■ Decompression sickness
Patent foramen ovale is approximately five-times more prevalent in patients suffering from decompression sickness during diving compared with age-matched controls [38,39]. Caused by a decrease in pressure during ascent after a dive, dissolved nitrogen may form bubbles, usually absorbed and exhaled via the lung circulation. However, a PFO allows those bubbles to enter the systemic circulation, leading to decompression sickness. It is unclear whether PFO closure

.

prevents recurrent episodes, as decompression sickness is a rare event occurring in approximately one in 10,000 dives [39]. Nevertheless, since no prophylactic therapy is available, transcatheter PFO closure is being performed, particularly in professional divers. Obviously, no randomized trials have been and are unlikely to ever be conducted, given the rare occurrence of this disease.

■ Hypoxemia or platypnea–orthodeoxia syndrome

Platypnea–orthodeoxia, dyspnea and desaturation occurring in the upright posture and improvement in the recumbent position is a rare condition leading to systemic hypoxemia caused by a PFO and right-to-left shunt [40–42]. There are other conditions that can cause hypoxemia by the same mechanisms. These conditions share an increased right ventricular afterload in common, leading to preferential shunting via a PFO at the atrial level. Among those situations are pulmonary hypertension, pulmonary valve stenosis and right ventricular infarction. Although PFO closure is an effective means of therapy, the indication and ability to safely close an interatrial shunt in those conditions needs to be decided on an individual basis.

Platypnea–orthodeoxia usually results in unacceptable lifestyle limitations warranting therapy. Transcatheter PFO closure in that setting has been proven to be very effective [8,43,44]. Medical therapy is of limited value, as significant right-to-left shunt persists at the atrial level, even after aggressive reduction in right ventricular afterload, given the very low pressure gradient at the atrial level.

■ Migraine headaches

Similarly to patients with cryptogenic stroke, PFO has been shown to be two- to three-times more prevalent in patients with migraine headaches, in particular in the subgroup of patients with aura [10,38,45–47]. By contrast, a recent case–control study including 288 patients with and without migraine headache documented an equal prevalence of PFO in approximately a quarter of the participants in each group [48]. In patients undergoing PFO closure for cryptogenic strokes and coexisting migraine headaches, it was observed that transcatheter PFO closure resulted in resolution or improvement of migraine. Triggered by the first report by Wilmshurst *et al.* in 2000, several case series and small case–control studies have confirmed those initial findings (65–91% reported either

improvement or resolution of migraine) [49–54]. Possible explanations for the relationship between PFO and migraine headaches may stem from the ability to shunt vasoactive substances, such as serotonin or substance P [55]. Otherwise filtered in the lung vasculature, those substances may cause vasospasm followed by vasodilation of arteries if circulating to the cerebrovascular system, resulting in migraine headaches. The topic of PFO and migraine headaches is heavily debated among the different subspecialists involved. The discussion is complicated by cross-links with other conditions such as white matter lesions observed on brain MRI as well as ischemic strokes, found to be more prevalent in patients with migraine, suggesting a possible common denominator, such as the PFO for certain migraine types and strokes [56–58].

The only completed randomized controlled trial comparing PFO closure with a sham procedure in patients with migraine headaches and PFO is the Migraine Intervention with Starflex Therapy (MIST) 1 study. This 147 patient trial failed to reach its primary end point, defined as complete freedom from migraine during 3–6-month follow-up [59]. The trial's failure was probably related to an overambitious end point, as complete resolution of migraine headaches in patients with prior refractory migraine headaches used as inclusion criteria seems unlikely [60]. At present, ongoing trials comparing PFO closure with medical management include the Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder Compared To Medical Management (PREMIUM) trial in North America and the PFO Repair In Migraine with Aura (PRIMA) trial in Europe. Other trials designed to evaluate the role of PFO closure in migraine patients, such as MIST 2 and the Effect of Septal Closure of Atrial PFO on Events of Migraine With Premere (ESCAPE) trial have failed to enroll patients and were terminated.

Overview & comparison of PFO closure devices
### ■ Background of transcatheter PFO closure

Prior to the availability of percutaneous techniques, PFOs were closed surgically [61]. At present, with the development of closure devices, isolated surgical PFO closure is rarely, if ever, performed. The first-in-man percutaneous closure of an interatrial communication was performed in the 1970s by King and colleagues [62].

The defect closed was a secundum ASD. Over the course of the following years, a variety of different devices were designed for percutaneous ASD closure. Owing to safety concerns or to their cumbersome deployment techniques [63,64], the vast majority of these devices are no longer in use. However, until now, some devices initially designed for closure of ASDs have been used to close PFOs. The first transcatheter PFO closure was reported in 1992 by Bridges *et al.* [65]. More recently, devices specifically designed for PFO closure have been introduced into clinical practice, owing to the anatomical differences between PFO and a secundum ASD.

Procedural technique, outcome & safety

Although there are minor differences in the deployment techniques, the vast majoriy of devices used for PFO closure are deployed in a similar fashion. Following administration of conscious sedation, femoral venous access and placement of a delivery sheath across the PFO, the left atrial component (disk, umbrella or retention hook) of the device is placed in the left atrium. Then, the right atrial component is deployed, wedging the interatrial septum (septum primum and septum secundum) inbetween. Deployment of the device is carried out either under fluoroscopic guidance (FIGURE 1) with concurrent intracardiac (FIGURES 2 & 3) or transesophageal echocardiographic guidance or under fluoroscopic guidance alone [31,35,66]. In experienced hands, the procedure should not take longer than 30–60 min. Acetylsalicylic acid is administered a day prior to the procedure. Following PFO closure, antiplatelet therapy is continued for 6 months with acetylsalicylic acid 81–325 mg daily. Frequently, clopidogrel 75 mg daily is administered for 1–3 months, mainly to reduce potentially transiently occurring migraine headache following closure of interatrial shunts [67]. Technical success rates approach 100% [68,69]. Major periprocedural complications such as device embolization, tamponade, a need for emergency surgery or death are rare, occuring in less than 1% of cases [36,70,71]. Early postprocedurally, transient atrial fibrillation may occur [72,73]. Long-term complications are rare, with erosion
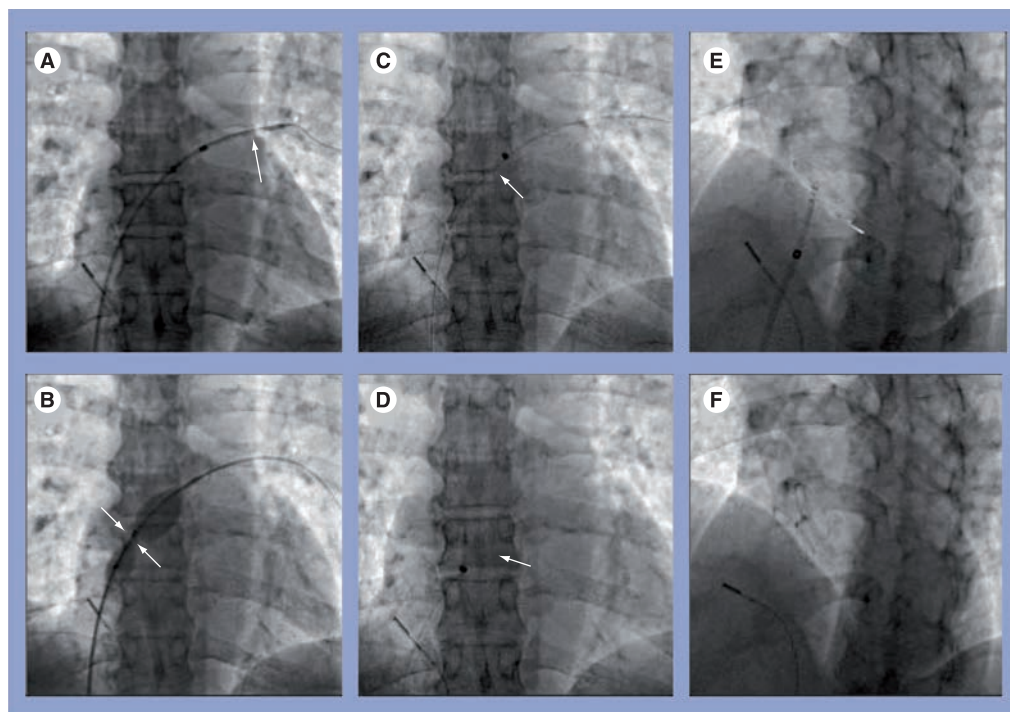
Figure 1. Cine fluoroscopic images of a patient with patent foramen ovale who sustained cryptogenic stroke demonstrating closure steps. Images **(A–D)** were taken in straight frontal projection and images **(E & F)** were taken in four-chamber view (35° left anterior oblique/35° cranial). **(A)** Cine fluoroscopy in straight frontal projection demonstrating passage of a catheter through the patent foramen ovale (PFO) into the left upper pulmonary vein (arrow). **(B)** Balloon sizing of the PFO shows the waist of the balloon (arrows). **(C)** Passage of the Gore Helex™ delivery catheter over a wire (arrow) through the PFO into the left atrium. **(D)** Deployment of the left atrial disk (arrow) of a 30-mm Gore Helex device in the left atrium. **(E)** Deployment of the right atrial disk (arrow) in the right atrium and **(F)** demonstrates the effectiveness of the device after final release.
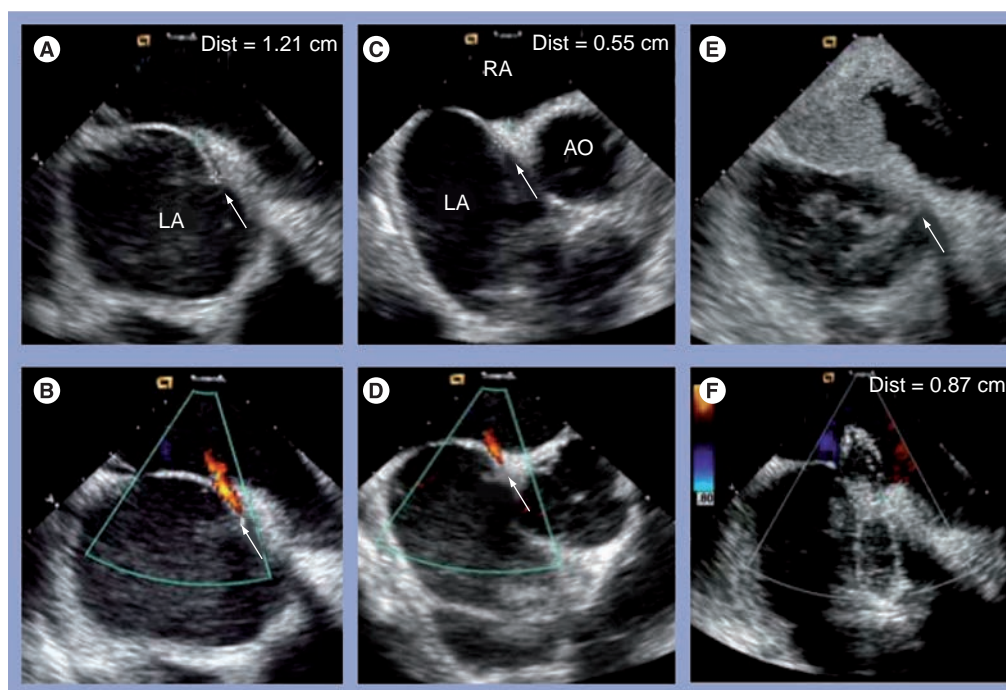
Figure 2. Intracardiac echocardigraphic images in a patient with patent foramen ovale who underwent device closure demonstrating closure steps. (A & B) Long-axis view without and with color Doppler demonstrating the patent foramen ovale (PFO) tunnel and left-to-right shunt (arrow). **(C & D)** Short-axis view without and with color Doppler demonstrating the PFO tunnel and left to right shunt (arrow). **(E)** Contrast bubble study at rest demonstrating passage of bubbles from right to left atrium. **(F)** Balloon sizing of the PFO.
AO: Aorta; LA: Left atrium; RA: Right atrium.

of the device into surrounding structures being the most serious complication. The exact incidence of this feared complication is difficult to determine, but is probably well below 0.1% [74]. Thrombus formation on the closure device **(Figure 4)**, if occurring on the left atrial side, can have catastrophic consequences [75]. Occurrence of device-related thrombus formation may be device design-related, as further discussed later. Possible complications of transcatheter PFO closure need to be weighed up against potential benefits of the procedure, which in turn depend on the indication for PFO closure. Published complication rates are largely derived from case series of experienced operators. Improved outcome and lower complication rates have been documented to depend on experience and number of cases performed by the operator and center in other settings of interventional cardiology, such as primary percutaneous coronary interventions for acute myocardial infarctions [76]. Although the same may hold true in the area of PFO closure, low complication rates have been documented in 'low-volume centers' performing less than 15 transcatheter PFO closure procedures per year [77].

Types of PFO closure device
■ Double disk devices
CardioSEAL/STARFlex/Biostar
The first device to be used in clinical practice consisting of two opposing, self-expanding umbrellas was the clamshell. The closure mechanism of a PFO by these umbrella devices is by clamping the interatrial septum inbetween. The clamshell occluder was first implanted in 1988 and was designed for closure of secundum ASDs [78]. Several modifications of this original device have resulted in the CardioSEAL® septal occluder (NMT Medical, MA, USA). The CardioSEAL septal occluder consists of two squared dacron patches mounted onto wire spring arms. The successor of the CardioSEAL was the STARFlex® (NMT Medical Inc.) occluder. The added feature of this next-generation device is a self-centering mechanism, provided by a nitinol microspring, attached in between the umbrella arm tips, allowing an automatic, central alignment of implant within the defect [79]. The most recent development in this family of occluders is the BioSTAR® device (NMT Medical Inc.) [80]. It is similar in design to the STARFlex, except for the umbrella material that consists of bioabsorbable collagen material made of the
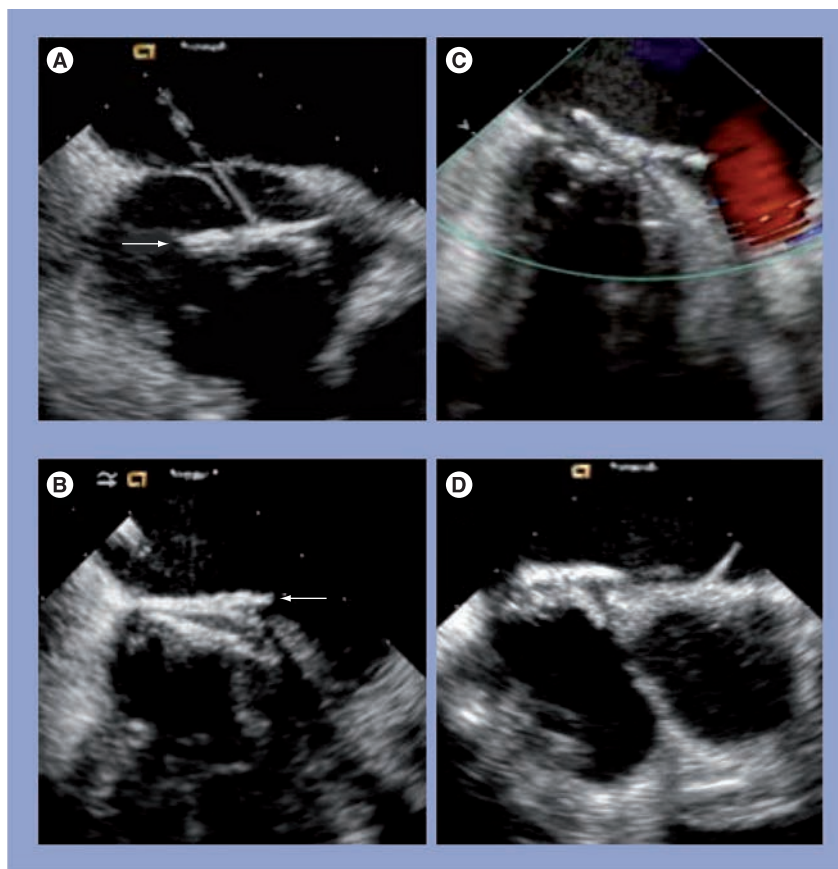
Figure 3. Intracardiac echocardiographic images of final steps of patent foramen ovale closure. (A) Deployment of the left atrial desk of a 30-mm Gore Helex™ device (arrow). **(B)** Deployment of the right atrial desk of the device (arrow). **(C)** Image in long-axis view with color Doppler after the device has been released demonstrating good device position and no shunt at rest. **(D)** Image in short-axis view demonstrating good device position.

submucosal layer of porcine small intestine. This collagen matrix is incorporated into the atrial septum following implant and leaves only the metallic framework behind.

Atriasept PFO occluder

The Atriasept PFO occluder is the most recent development of prior generations of devices, including the Intrasept and PFO-Star (Cardia, MN, USA) [31,81]. This device is made of two Ivalon® (polyvinyl alcohol; Fabco, CT, USA) umbrellas mounted onto nitinol arms. Unlike the Atriasept ASD occluder, the PFO occluder is purposefully not self-centering. The centerpost has a joint, allowing the umbrellas to align to the interatrial septum independently of each other.

Amplatzer® family of devices

Various Amplatzer® devices (AGA Medical, MN, USA) can be used for PFO closure [5,71,82]. All devices consist of two self-expanding disks made of a thin nitinol wire mesh. Inside these disks are polyester patches sewn to the wires to allow more rapid, controlled thrombosis of the device, followed by endothelialization. In the Amplatzer septal occluder, the two disks are connected by a 3–4-mm connecting waist. The device is available in a wide range of diameters (4–40 mm). This connecting waist is designed to stent the hole of an ASD [83]. The Amplatzer PFO device only has a 3-mm diameter connecting waist, irrespective of the size of the occluder disk diameter. In the PFO occluder, the right atrial disk is larger than the left atrial disk. The Amplatzer Cribriform (multifenestrated) occluder, designed for closure of multifenestrated ASDs, is similar in design to the PFO occluder, except that the two disks are equal in diameter.

The Gore Helex™ device

Designed for closure of secundum ASDs, the Helex™ septal occluder (WL Gore & Associates, AZ, USA) is made of a single spiral-shaped nitinol wire attached to a polytetrafluoroethylene membrane [84]. Upon exit out of the delivery sheath of the stretched occluder, the wire assumes the double disk shape. After placement, the two disks are locked and the system is released. The locking system fixes the two discs in place and stabilizes the occluder within the defect.

Figulla–Occlutech®

This is a double disc device (Occlutec AB, Sweden), similar in design to the Amplatzer PFO device without the hub in the left atrial disc. There are two different PFO devices available: a single- and double-layered device. On the single-layer device, the left atrial disk is single layered, which forms a very flat disk, reducing the amount of metal needed. The double-layered device is available for the so-called long-track PFO defects. This device consists of a double-layered disk on the left atrial side.

Premere™ occluder

The Premere™ occluder (St Jude Medical, MN, USA) is specifically designed for PFO closure [85]. It consists of a right-sided 'anchor' made of a cross-shaped frame of nitinol. Mounted onto this anchor are two layers of polyester. The left atrial disk consists of a similar cross-shaped frame, but without the polyester mount. The two disks are connected by a flexible tether. The length of this tether can be adjusted, allowing individualization of device placement based on the PFO morphology.

Solysafe® septal occluder

The Solysafe® occluder (Swissimplant, Switzerland) consists of two polyester patches attached to wires made of a memory metal termed phynox [86]. It is designed for ASD and PFO closure. The device is low-profile, self-centering and fully retrievable, even after release. It is delivered over a guidewire without the need for a delivery sheath, theoretically reducing the risk of air embolization during placement.

■ In tunnel devices
Coherex FlatStent™

The most recent development in PFO closure technology is the FlatStent™ PFO occluder system (Coherex, UT, USA) [87]. The occluder is made of nitinol with its central portion wrapped into polyurethane foam. This device sits inside the PFO. The polyurethane foam is intended to stimulate tissue in-growth leading to closure of the tunnel. The FlatStent is anchored with two small arms each in the left and right atrium, leaving minimal foreign material exposed to the blood stream.

■ Radiofrequency-generated devices

The idea of radiofrequency-generated devices consists of a suction cup that approximates septum primim to the septum secundum, the radiofrequency is then applied to weld the two septae together. The initial application of the PFX™ system (Cierra, CA, USA) resulted in closure rates of approximately 60% in patients with suitable anatomy. Therefore, with such low closure rates, the manufacturer decided to withhold further development.

■ Suture-based techniques

Similar in concept to vessel closure devices, suture-based techniques use similar technology in order to suture septum primum with septum secundum to achieve closure. The advantage of this technique is the lack of any metal insertion in the heart. Limited clinical trials are being conducted outside of the USA.

Comparison of devices & techniques

Most contemporary case series of PFO closure report results predominantly derived from one device, while early case series commonly described results based on the use of a variety of largely out-dated different occluders. The Premere and Solysafe occluders have not been included in case series comparing results of various devices. A small number of publications are available specifically comparing performance characteristics of the different occluders available.

The largest and probably methodologically most sound series is from Sievert *et al.* [69]. This trial compared three different devices: Amplatzer occluders, Helex and CardioSEAL/STARFlex. Patients were randomized to PFO closure with one of the three occluders, with 220 patients in each group. Baseline characteristics revealed the Helex group to include the oldest patients and most commonly had an atrial septal aneurysm, while patients in the CardioSEAL/STARFlex group more commonly had diabetes and arrhythmias prior to PFO closure. Procedural success was 100% in all three groups and periprocedural complications were similar. However, most placement attempts were necessary with the Helex device (17 vs two with Amplatzer and CardioSEAL/STARFlex). The longest procedural and fluoroscopy times were noted in the Helex group. Further embolizations only occurred with the Helex, further underscoring the more complex deployment technique of this device, compared with the other occluders. However, the authors point out that in case of embolization, retrieval and replacement of the Helex occluder were considerably simpler than with the other occluders. Furthermore, the most common technical problem leading to repeat placement attempts with the Helex were caused by difficulties in locking the right atrial disk. This problem was addressed by the manufacturer as the Helex now has a modified locking system.

Immediate complete closure of the PFO was most frequently accomplished with the Amplatzer devices (52.3 vs 41.8% Helex vs 44.1% CardioSEAL/STARFlex). Similarly, at 30-day
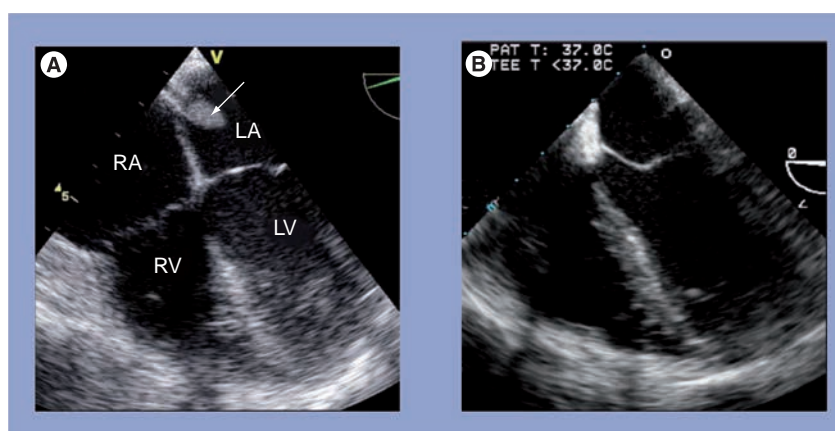
Figure 4. Transesophageal echocardiographic images of a 22-year-old female who underwent patent foramen ovale closure with a 30 mm Amplatzer® Cribriform device 2 years prior. (A) Four-chamber view demonstrates the presence of a thrombus (arrow) on the left atrial disc. **(B)** Repeat transesophageal echocardiography 3 months later after treatment with anticoagulation, demonstrating resolution of the clot. Notably, this patient presented with hematuria and nephrotic syndrome.
LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle.
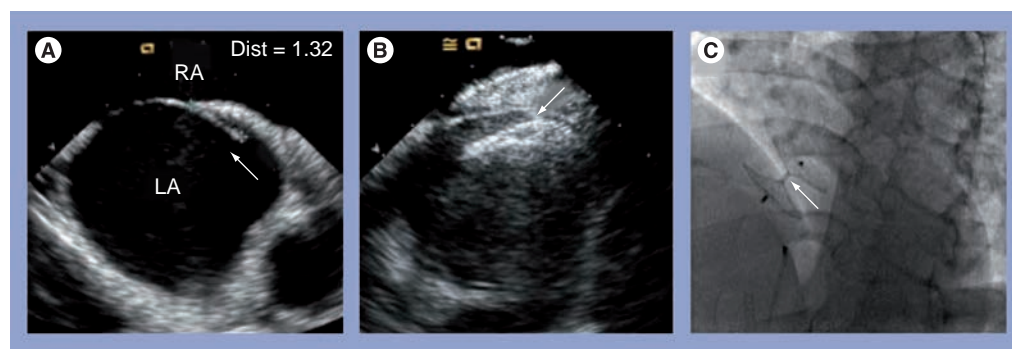
Figure 5. Patient with a long tunnel patent foramen ovale. (A) An intracardiac echocardiographic image demonstrating long tunnel patent foramen ovale measuring 13 mm (arrow). **(B)** An intracardiac echocardiographic image after placement of a 30-mm Amplatzer Cribriform device, demonstrating the separation of the two disks of the device. **(C)** Corresponding cine fluoroscopic image showing the separation of the disks (arrow).
LA: Left atrium; RA: Right atrium.

follow-up, residual shunt was observed to be the least with the Amplatzer (65% complete closure) and the lowest with the Helex occluder (52.7% complete closure). The CardioSEAL/STARFlex had a complete closure rate of 62.3%. An explanation for the lower closure rates with the Helex is its soft construction and the fact that this group had more atrial septal aneurysms at baseline. Although the soft nature of the Helex device may result in less complete closure rates immediately after closure, it is probably the least traumatic of all devices available.

During the 30-day follow-up period, thrombus was not observed on the Amplatzer or Helex occluders. However, in eight patients (3.6%), thrombus on the CardioSEAL/STARFlex was documented. This finding is consistent with results of the largest case series evaluating the incidence of thrombus formation on atrial septal occluders, although the patient population of the two publications overlaps [75]. Krumsdorf *et al.* reported on 1000 consecutive patients undergoing PFO or ASD closure using nine different devices. At 1-month follow-up, thrombus was seen on seven of 119 implanted CardioSEAL/STARFlex devices (5.9%). A high thrombus formation rate was observed with the early generation of Cardia device (6.6%). As the majority of thrombi were noted on uncoated metal arms of the umbrellas, the Cardia devices were modified by placing the nitinol arms at the inner side of the left atrial umbrella, not exposing it to the bloodstream. The lowest rate of thrombus formation within 1 month was observed with the Amplatzer devices (0%), followed by the Helex, with one event of thrombus formation documented (0.8%).

In the randomized trial comparing the three different devices for PFO closure, atrial fibrillation following device placement was most commonly documented in the CardioSEAL/STARFlex group, where ten patients developed atrial fibrillation (4.5%), compared with only two in the Helex group (0.9%) and three in the Amplatzer group (1.4%). However, at baseline, the CardioSEAL/STARFlex group more commonly had atrial arrhythmias. Our series evaluating the incidence of atrial fibrillation in more than 1000 patients undergoing PFO or ASD closure showed no impact of the occluder type or size on the occurrence of atrial fibrillation [72]. Despite the periprocedural differences identified among the three different occluders in the randomized trial by Sievert *et al.*, no clinical differences in terms of stroke or TIA recurrence were noted. However, the trial was designed to provide only 30-day follow-up information, a time period too short to truly identify clinical differences.

Braun *et al.* described results of the non-randomized comparison of the early-generation Cardia device, Amplatzer PFO occluder and CardioSEAL/STARFlex [33]. All 307 implants were successful and no relevant differences with respect to periprocedural complications, echocardiography and clinical midterm follow-up results were observed. Annual recurrence rate of thromboembolic events ranged between 0.7 and 1.0%. Complete closure was documented in 53% of patients closed with the Cardia device, 59% in the Amplatzer PFO group and 61% in patients receiving the CardioSEAL/STARFlex (p = not significant). There was no difference in the prevalence of atrial or ventricular arrhythmias among the three groups as noted by 24-h Holter monitoring 6 months after device implantation.

Findings by Schwerzmann *et al.*, comparing the results of 100 patients either undergoing PFO closure with the early-generation Cardia device or the Amplatzer PFO occluder, differed from

Braun's findings [88]. The authors found that although placement of all devices were successful, more placement attempts were necessary with the Cardia occluder (more placement attempts: five vs one). They also found a higher periprocedural complication rate with the Cardia device, with two device embolizations and four air embolizations compared with no device embolization and one air embolism with the Amplatzer PFO occluder. At 6-month follow-up, more patients were found to have complete PFO closure with the Amplatzer (94%) than the Cardia (66%) device. Although not statistically significant, the authors found a trend for higher event-free survival with the Amplatzer device than with the Cardia occluder.

Comparing the Amplatzer PFO occluder with the early-generation (first and second) Cardia and the third-generation Cardia device (Intrasept), we were not able to reproduce the findings by Schwerzmann *et al.* [36]. In a comparison of almost 800 patients, periprocedural complications were similar among the three devices. Complete closure rate accomplished with the different devices was identical. In addition, recurrence rates of thromboembolic events during follow-up were independent of the device used in a stratified Kaplan–Meier analysis. With the orientation of the nitinol arms on the inner surface of the third-generation umbrellas, device-related thrombus formation was no longer detected.

A few smaller case series have compared PFO closure devices. Meier *et al.* compared a total of 40 patients undergoing closure with either the early-generation Cardia device or the STARFlex [89]. At 6-month follow-up, the authors found a significantly higher complete closure rate with the STARFlex (90%) compared with the Cardia occluder (50%). In another study comprising 100 patients with an interatrial communication treated with either the CardioSEAL or Amplatzer device revealed a higher complete occlusion rate at 6 months with the Amplatzer device (71%) compared with the CardioSEAL (48%) [90].
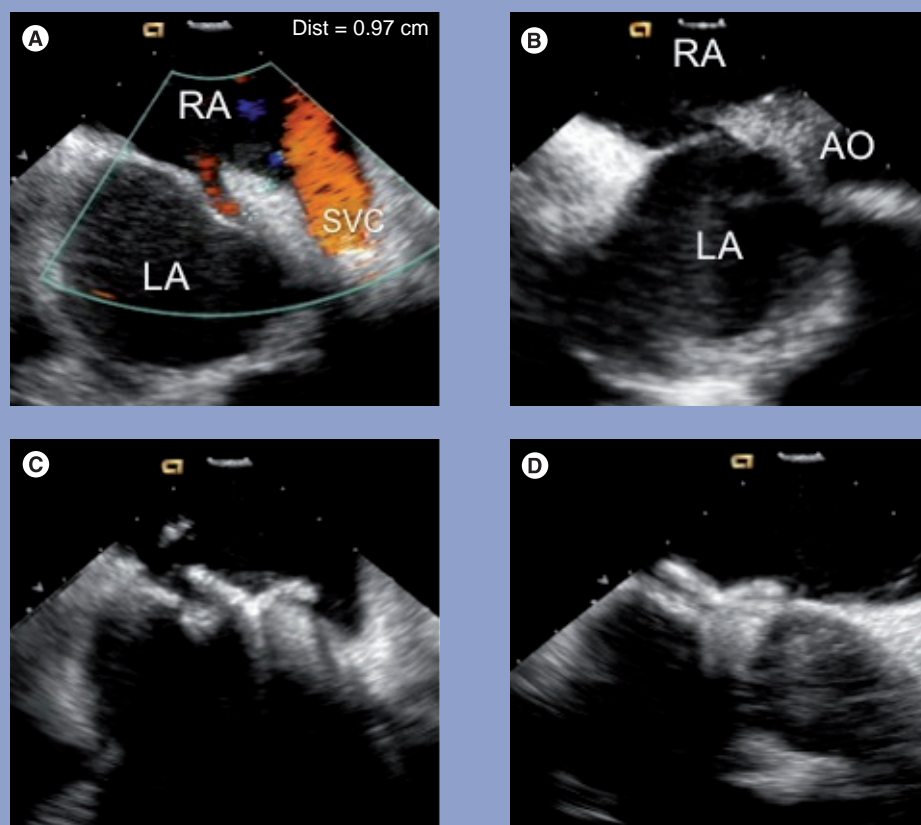
Figure 6. Intracardiac echocardiographic images in a patient with patent foramen ovale and lipomatous septum secundum. (A) Long-axis view with color Doppler demonstrating thick septum secundum. **(B)** Short-axis view showing the thick septum secundum. **(C & D)** Images in long- and short-axis view after placement of a 30-mm Helex device showing good device position.
AO: Aorta; LA: Left atrium; RA: Right atrium; SVC: Superior vena cava.

Device-specific PFO closure considerations

■ Overview of device selection

Device selection for PFO closure in clinical practice is largely operator-dependent and also depends on geographical location, as approval of some devices is country-dependent. Several devices are unavailable in the US market due to lack of US FDA approval. Among those are the Occlutech, Premere, Amplatzer PFO occluder, Solysafe and FlatStent. Only the Amplatzer PFO occluder and the Gore Helex devices are currently being evaluated in the setting of randomized trials in the USA and are theoretically available if the individual operator is an investigator participating in the RESPECT or REDUCE clinical trials.

Assuming availability of all devices and no operator preference, certain devices have specific advantages. These advantages are either theoretical, being based on the device's design, or practical, being based on operators' experience. However, it is important to realize that only the very basic characteristics of a small number of devices have been compared with each other, as previously summarized. Choosing a device in a specific clinical setting is rather subjective and, for the most part, based on theoretical considerations and not firm evidence. Nevertheless, we attempt to summarize treatment options based on PFO morphology and patient characteristics.

Long PFO tunnel

The length of the PFO is variable. The average length is approximately 10–12 mm [91]. There is no standardized methodology to measure the PFO tunnel length. Transesophageal or intracardiac echocardiography can estimate the total length of the tunnel in two distinct views, the short-axis and the long-axis (bicaval) views, while balloon sizing of the PFO provides information about both PFO tunnel length and diameter. The problem with particularly long tunnels is that double disk or double umbrella devices may not align to the interatrial septum as their connecting centerpost is tilted, due to the long tunnel (Figure 5). In an attempt to overcome this problem, trans-septal puncture in the fossa ovalis and placement of the occluder through the puncture, rather than the PFO itself, has been described [92]. This technique has not found broad acceptance among interventional cardiologists. The Premere occluder has a theoretical advantage in this setting, since the length of the tether connecting the two disks of the occluder can be adjusted. Especially in

patients with a large diameter PFO as estimated by balloon sizing, most operators would agree that an Amplatzer septal occluder is preferable over use of the dedicated PFO or Cribriform occluder from AGA Medical. The benefit of the Amplatzer septal occluder is that the PFO tunnel is stented by the waist of the occluder, rather than relying on PFO closure by tight alignment of the two disks to the interatrial septum as needed in the case of the Amplatzer PFO or Cribriform occluders. The CardioSEAL or STARFlex devices are deemed suboptimal in patients with long tunnel; owing to the softness of the devices, the disk may be pulled inside the PFO tunnel leading to protrusion off the umbrella into the left or right atrium and poor alignment to the interatrial septum. Owing to its soft nature, the Helex device often does not result in good alignment of the disks to the septum in the setting of long PFOs, since the stiffer centerpost inside the tunnel tilts the device.

Atrial septal aneurysm

Being present in up to 10% of patients with PFOs, the atrial septal aneurysm may also represent a challenge if PFO closure is considered. An aneurysmal or floppy septum may not allow stable positioning of an occluder. For this reason, operators commonly choose a slightly oversized device. Alternatively, an Amplatzer septal occluder may allow more stable positioning as it wedges the device inside a slightly stretched PFO. In addition, the CardioSEAL/STARFlex occluder may be a good choice as the umbrella's tips are overlapping and comparably stiff, theoretically allowing better stabilization of an aneurysmal septum. In comparison, devices such as the Amplatzer PFO or Cribriform occluder may be suboptimal, as they potentially allow the aneurysmal septum to move in between the two parallel disks, potentially leading to higher rates of residual shunt.

Lipomatous septum

A very thickened or lipomatous septum secundum may lead to misalignment and protrusion of the device. The two disks or umbrellas of the occluder placed within the PFO are normally more separated on the aortic and inferior aspect of the PFO, caused by the thicker septum secundum, compared with the thin septum primum, wedged inbetween the device. However, in case of a lipomatous septum (Figure 6), this asymmetry becomes more prominent. All double disk or double umbrella devices have the potential to protrude into the left and right atrium in this

setting. Devices should neither be too large, as this may potentially result in device protrusion, nor too small, or this may lead to incomplete closure or unstable positioning. Occasionally, the centerpost may be too short, leading to deformation of the disks or umbrellas as they are not able to entirely expand. Theoretically, the Coherex FlatStent may have an advantage in closure of PFOs with a lipomatous septum, if the morphology and overlap of septum primum and secundum allows.

Thrombophilia

Patients with thrombophilia and PFO are at a particularly high risk for stroke. In patients with prior stroke and documented thrombophilia, PFO closure has been performed [93]. Although clinicians may elect to continue oral anticoagulation despite PFO closure in this setting, it is desirable to use devices with the least thrombogenic potential in this setting. As previously noted, the occluders with the most solid data documenting the lowest rate of thrombus formation are the Amplatzer devices. In addition, the Helex appears to only rarely cause device-related thrombosis. Limited data are available for the FlatStent; however, given the design of the device, thrombus formation on the surface of the FlatStent appears unlikely.

Atrial fibrillation

Placement of a PFO occluder may trigger atrial fibrillation. Whether the type of device influences the likelihood of recurrence of atrial fibrillation, following PFO closure is still unclear. Sievert *et al.* found the highest incidence of atrial fibrillation occurring after placement of the STARFlex devices [73], while our analysis showed no impact of the choice of device on the incidence of atrial fibrillation [72]. The mechanism by which the occluders cause atrial fibrillation is speculative. If local inflammatory response is the cause for atrial fibrillation, then the smallest possible device may be beneficial as it may theoretically result in less inflammation, given its smaller contact area with myocardial tissue.

Future perspective

Results of one randomized controlled trial, the CLOSURE I trial, comparing medical management with transcatheter closure of PFO in 900 patients with cryptogenic stroke will be available soon. If the trial turns out to be in favor of transcatheter closure, catheter-based PFO interventions for patients with stroke will probably increase significantly, since possibly as many as 100,000 North Americans with a PFO suffer a cryptogenic stroke each year [94]. If the trial results are in favor of medical therapy, it seems likely that transcatheter PFO closure will continue to be practiced in selected patients, as the argument will be made that the trials conducted are limited by inclusion criteria that are too broad. The third possible and most likely scenario is that only high-risk subgroups, such as patients with atrial septal aneurysm, will be found to benefit from transcatheter PFO closure, leading to a selected strategy of PFO closure.

Executive summary

Epidemiology
- The prevalence of patent foramen ovale (PFO) is 27% at autopsy studies and 10–15% under physiologic conditions based on echocardiographic studies.

Evidence for transcatheter closure in PFO-associated conditions
- The prevalence of PFO appears to be higher in patients with certain conditions such as cryptogenic stroke, migraine headache and decompression sickness.
- PFO closure has been successfully performed in a variety of PFO-associated conditions.

Overview & comparison of PFO closure devices
- PFO closure can be accomplished safely and effectively with different occluders.

Types of PFO closure devices
- The majority of occluders used for PFO closure are double disk/umbrella devices.
- A newer technique used for PFO closure utilize 'in-tunnel' devices.

Comparison of devices/techniques
- Limited data are available that directly compare different occluders.
- Differences regarding complete closure rates and incidence of device-related thrombus formation between different devices have been documented.

Device-specific PFO closure considerations
- Device selection for PFO closure is largely operator- and country-dependent, as several devices are unavailable on the US market.
- Based on theoretical considerations and operator experience, some devices may be preferred in specific settings depending on the morphology of the PFO and patient characteristics.

Furthermore, indications for PFO closure may expand if planned randomized controlled trials evaluating PFO closure in patients with migraine headaches are found to be in favor of closure. With the number of patients suffering from migraine headache compared with cryptogenic stroke, the impact of potentially beneficial therapy is much larger from a socioeconomic point of view.

Bibliography

Papers of special note have been highlighted as:
- of interest
- of considerable interest

1   Hagen PT, Scholz DG, Edwards WD: Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin. Proc.* 59(1), 17–20 (1984).

2   Krishnan SC, Salazar M: Septal pouch in the left atrium: a new anatomical entity with potential for embolic complications. *JACC Cardiovasc. Interv.* 3(1), 98–104 (2010).

3   Konstadt SN, Louie EK, Black S, Rao Tl, Scanlon P: Intraoperative detection of patent foramen ovale by transesophageal echocardiography. *Anesthesiology* 74(2), 212–216 (1991).

4   Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME: The incidence of patent foramen ovale in 1,000 consecutive patients. A contrast transesophageal echocardiography study. *Chest* 107(6), 1504–1509 (1995).

5   Hong TE, Thaler D, Brorson J, Heitschmidt M, Hijazi ZM: Transcatheter closure of patent foramen ovale associated with paradoxical embolism using the Amplatzer pfo occluder: initial and intermediate-term results of the U.S. multicenter clinical trial. *Catheter. Cardiovasc. Interv.* 60(4), 524–528 (2003).

6   Spies C, Wong M: Patent foramen ovale and cryptogenic stroke: a complex neuro-cardio-vascular problem. *Expert Rev. Cardiovasc. Ther.* 7(11), 1455–1467 (2009).

7   Germonpre P, Hastir F, Dendale P, Marroni A, Nguyen AF, Balestra C: Evidence for increasing patency of the foramen ovale in divers. *Am. J. Cardiol.* 95(7), 912–915 (2005).

8   Waight DJ, Cao QL, Hijazi ZM: Closure of patent foramen ovale in patients with orthodeoxia-platypnea using the Amplatzer devices. *Catheter. Cardiovasc. Interv.* 50(2), 195–198 (2000).

9   Allemann Y, Hutter D, Lipp E *et al.*: Patent foramen ovale and high-altitude pulmonary edema. *JAMA* 296(24), 2954–2958 (2006).

10   Del Sette M, Angeli S, Leandri M *et al.*: Migraine with aura and right-to-left shunt on transcranial doppler: a case–control study. *Cerebrovasc. Dis.* 8(6), 327–330 (1998).

11   Schwerzmann M, Nedeltchev K, Lagger F *et al.*: Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* 65(9), 1415–1418 (2005).

12   Sacco RL, Ellenberg JH, Mohr JP *et al.*: Infarcts of undetermined cause: the NINCDS stroke data bank. *Ann. Neurol.* 25(4), 382–390 (1989).

13   Adams HP Jr, Bendixen BH, Kappelle LJ *et al.*: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 24(1), 35–41 (1993).

14   Grau AJ, Weimar C, Buggle F *et al.*: Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke* 32(11), 2559–2566 (2001).

15   Lechat P, Mas JL, Lascault G *et al.*: Prevalence of patent foramen ovale in patients with stroke. *N. Engl. J. Med.* 318(18), 1148–1152 (1988).

16   Webster MW, Chancellor AM, Smith HJ *et al.*: Patent foramen ovale in young stroke patients. *Lancet* 2(8601), 11–12 (1988).

17   Overell JR, Bone I, Lees KR: Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 55(8), 1172–1179 (2000).

- **Meta-analysis of case–control studies defining the association of patent foramen ovale (PFO) with cryptogenic strokes.**

18   Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A: Patent foramen ovale and cryptogenic stroke in older patients. *N. Engl. J. Med.* 357(22), 2262–2268 (2007).

19   Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G: Stroke recurrence in patients with patent foramen ovale: the Lausanne study. Lausanne Stroke with Paradoxal Embolism Study Group. *Neurology* 46(5), 1301–1305 (1996).

20   Mas Jl, Arquizan C, Lamy C *et al.*: Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N. Engl. J. Med.* 345(24), 1740–1746 (2001).

- **Landmark prospective study evaluating the risk of stroke recurrence of patients with PFO and/or atrial septal aneurysm.**

21   Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP: Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 105(22), 2625–2631 (2002).

22   Almekhlafi MA, Wilton SB, Rabi DM, Ghali WA, Lorenzetti DL, Hill MD: Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis. *Neurology* 73(2), 89–97 (2009).

23   Khairy P, O'Donnell CP, Landzberg MJ: Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann. Intern. Med.* 139(9), 753–760 (2003).

- - **Review comparing medical therapy with transcatheter PFO closure in patients with cryptogenic stroke.**

24   Wohrle J: Closure of patent foramen ovale after cryptogenic stroke. *Lancet* 368(9533), 350–352 (2006).

25   Onorato E, Melzi G, Casilli F *et al.*: Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J. Interv. Cardiol.* 16(1), 43–50 (2003).

26   Martin F, Sanchez PL, Doherty E *et al.*: Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 106(9), 1121–1126 (2002).

27   Wahl A, Krumsdorf U, Meier B *et al.*: Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J. Am. Coll. Cardiol.* 45(3), 377–380 (2005).

28   Ford MA, Reeder GS, Lennon RJ *et al.*: Percutaneous device closure of patent foramen ovale in patients with presumed cryptogenic stroke or transient ischemic attack: the Mayo clinic experience. *JACC Cardiovasc. Interv.* 2(5), 404–411 (2009).

29   Post MC, Van Deyk K, Budts W: Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol.* 60(5), 515–519 (2005).

30 Windecker S, Wahl A, Nedeltchev K *et al.*: Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J. Am. Coll. Cardiol.* 44(4), 750–758 (2004).

▪ **Nonrandomized comparison of PFO closure with medical management of a large single-center cohort.**

31 Spies C, Strasheim R, Timmermanns I, Schraeder R: Patent foramen ovale closure in patients with cryptogenic thrombo-embolic events using the cardia PFO occluder. *Eur. Heart J.* 27(3), 365–371 (2006).

32 Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R: Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int. J. Cardiol.* 101(1), 77–82 (2005).

33 Braun M, Gliech V, Boscheri A *et al.*: Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur. Heart J.* 25(5), 424–430 (2004).

34 Du ZD, Cao Ql, Joseph A *et al.*: Transcatheter closure of patent foramen ovale in patients with paradoxical embolism: intermediate-term risk of recurrent neurological events. *Catheter. Cardiovasc. Interv.* 55(2), 189–194 (2002).

35 Wahl A, Tai T, Praz F *et al.*: Late results after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism using the Amplatzer PFO occluder without intraprocedural echocardiography: effect of device size. *JACC Cardiovasc. Interv.* 2(2), 116–123 (2009).

36 Spies C, Reissmann U, Timmermanns I, Schrader R: Comparison of contemporary devices used for transcatheter patent foramen ovale closure. *J. Invasive Cardiol.* 20(9), 442–447 (2008).

37 O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC; American Heart Association; American Stroke Association; American College of Cardiology Foundation: Percutaneous device closure of patent foramen ovale for secondary stroke prevention: a call for completion of randomized clinical trials. A science advisory from the American Heart Association/American Stroke Association and the American College of Cardiology Foundation. *J. Am. Coll. Cardiol.* 53(21), 2014–2018 (2009).

38 Wilmshurst P, Pearson M, Nightingale S: Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts. *Clin. Sci. (Lond.)* 108(4), 365–367 (2005).

39 Torti SR, Billinger M, Schwerzmann M *et al.*: Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur. Heart J.* 25(12), 1014–1020 (2004).

40 Adolph EA, Lacy WO, Hermoni YI, Wexler LF, Javaheri S: Reversible orthodeoxia and platypnea due to right-to-left intracardiac shunting related to pericardial effusion. *Ann. Intern. Med.* 116(2), 138–139 (1992).

41 Godart F, Rey C, Prat A *et al.*: Atrial right-to-left shunting causing severe hypoxaemia despite normal right-sided pressures. Report of 11 consecutive cases corrected by percutaneous closure. *Eur. Heart J.* 21(6), 483–489 (2000).

42 Nagayoshi Y, Toyama K, Kawano H *et al.*: Platypnea–orthodeoxia syndrome combined with multiple congenital heart anomalies. *Intern. Med.* 44(5), 453–457 (2005).

43 Landzberg MJ, Sloss LJ, Faherty CE *et al.*: Orthodeoxia-platypnea due to intracardiac shunting – relief with transcatheter double umbrella closure. *Cathet. Cardiovasc. Diagn.* 36(3), 247–250 (1995).

44 Ilkhanoff L, Naidu SS, Rohatgi S, Ross MJ, Silvestry FE, Herrmann HC: Transcatheter device closure of interatrial septal defects in patients with hypoxia. *J. Interv. Cardiol.* 18(4), 227–232 (2005).

45 Sztajzel R, Genoud D, Roth S, Mermillod B, Le Floch-Rohr J: Patent foramen ovale, a possible cause of symptomatic migraine: a study of 74 patients with acute ischemic stroke. *Cerebrovasc. Dis.* 13(2), 102–106 (2002).

46 Lamy C, Giannesini C, Zuber M *et al.*: Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA study. Atrial septal aneurysm. *Stroke* 33(3), 706–711 (2002).

47 Wilmshurst PT: The persistent foramen ovale and migraine. *Rev. Neurol. (Paris)* 161(6–7), 671–674 (2005).

48 Garg P, Servoss SJ, Wu JC *et al.*: Lack of association between migraine headache and patent foramen ovale. *Circulation* 121, 1406–1412 (2010)

49 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL: Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 356(9242), 1648–1651 (2000).

▪ **Initial report of a positive treatment effect of PFO closure on migraine headache.**

50 Azarbal B, Tobis J, Suh W, Chan V, Dao C, Gaster R: Association of interatrial shunts and migraine headaches: impact of transcatheter closure. *J. Am. Coll. Cardiol.* 45(4), 489–492 (2005).

51 Morandi E, Anzola GP, Angeli S, Melzi G, Onorato E: Transcatheter closure of patent foramen ovale: a new migraine treatment? *J. Interv. Cardiol.* 16(1), 39–42 (2003).

52 Post MC, Thijs V, Herroelen L, Budts WI: Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. *Neurology* 62(8), 1439–1440 (2004).

53 Reisman M, Christofferson RD, Jesurum J *et al.*: Migraine headache relief after transcatheter closure of patent foramen ovale. *J. Am. Coll. Cardiol.* 45(4), 493–495 (2005).

54 Anzola GP, Frisoni GB, Morandi E, Casilli F, Onorato E: Shunt-associated migraine responds favorably to atrial septal repair. *Stroke* 37, 430–434 (2006)

55 Spies C, Schrader R: Transcatheter closure of patent foramen ovale in patients with migraine headache. *J. Interv. Cardiol.* 19(6), 552–557 (2006).

56 Kruit MC, Van Buchem MA, Hofman PA *et al.*: Migraine as a risk factor for subclinical brain lesions. *JAMA* 291(4), 427–434 (2004).

57 Etminan M, Takkouche B, Isorna FC, Samii A: Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 330(7482), 63 (2005).

58 Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G: Potential source of cerebral embolism in migraine with aura: a transcranial doppler study. *Neurology* 52(8), 1622–1625 (1999).

59 Dowson A, Mullen MJ, Peatfield R *et al.*: Migraine Intervention with StarFLEX Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with starflex septal repair implant to resolve refractory migraine headache. *Circulation* 117(11), 1397–1404 (2008).

60 Carroll JD: Migraine intervention with starflex technology trial: a controversial trial of migraine and patent foramen ovale closure. *Circulation* 117(11), 1358–1360 (2008).

61 Dearani JA, Ugurlu BS, Danielson GK *et al.*: Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 100(Suppl. 19), II171–II175 (1999).

62 King TD, Thompson SL, Steiner C, Mills NL: Secundum atrial septal defect. Nonoperative closure during cardiac catheterization. *JAMA* 235(23), 2506–2509 (1976).

63 Schrader R: Catheter closure of secundum ASD using 'other' devices. *J. Interv. Cardiol.* 16(5), 409–412 (2003).

64 Kapadia SR: Patent foramen ovale closure: historical perspective. *Cardiol. Clin.* 23(1), 73–83 (2005).

65 Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE: Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 86(6), 1902–1908 (1992).

66 Hijazi Z, Wang Z, Cao Q, Koenig P, Waight D, Lang R: Transcatheter closure of atrial septal defects and patent foramen ovale under intracardiac echocardiographic guidance: feasibility and comparison with transesophageal echocardiography. *Catheter. Cardiovasc. Interv.* 52(2), 194–199 (2001).

■ Initial description of intracardiac echocardiography guidance for defect closure of interatrial communications.

67 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL: Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. *Heart* 91(9), 1173–1175 (2005)

68 Spies C, Khandelwal A, Timmemanns I, Kavinsky CJ, Schrader R, Hijazi ZM: Recurrent events following patent foramen ovale closure in patients above 55 years of age with presumed paradoxical embolism. *Catheter. Cardiovasc. Interv.* 72(7), 966–970 (2008).

69 Taaffe M, Fischer E, Baranowski A *et al.*: Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-StarFLEX versus helex occluder). *Am. J. Cardiol.* 101(9), 1353–1358 (2008).

■■ Large, randomized comparison of three different devices for PFO closure.

70 Balbi M, Casalino L, Gnecco G *et al.*: Percutaneous closure of patent foramen ovale in patients with presumed paradoxical embolism: periprocedural results and midterm risk of recurrent neurologic events. *Am. Heart J.* 156(2), 356–360 (2008).

71 Silvestry FE, Naseer N, Wiegers SE, Hirshfeld JW Jr, Herrmann HC: Percutaneous transcatheter closure of patent foramen ovale with the Amplatzer Cribriform septal occluder. *Catheter. Cardiovasc. Interv.* 71(3), 383–387 (2008).

72 Spies C, Khandelwal A, Timmermanns I, Schrader R: Incidence of atrial fibrillation following transcatheter closure of atrial septal defects in adults. *Am. J. Cardiol.* 102(7), 902–906 (2008).

■ Study defining the prevalence of atrial fibrillation following PFO and atrial septal defect closure.

73 Staubach S, Steinberg DH, Zimmermann W *et al.*: New onset atrial fibrillation after patent foramen ovale closure. *Catheter. Cardiovasc. Interv.* 74(6), 889–895 (2009).

74 Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand W, Kleinman CS: PFO closure complications from the AGA registry. *Catheter. Cardiovasc. Interv.* 72(1), 74–79 (2008).

■■ Analysis of the Amplatzer registry to define the frequency of device erosions.

75 Krumsdorf U, Ostermayer S, Billinger K *et al.*: Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. *J. Am. Coll. Cardiol.* 43(2), 302–309 (2004).

■■ Large series summarizing incidence of device-related thrombus formation after PFO and atrial septal defect closure.

76 Magid DJ, Calonge BN, Rumsfeld JS *et al.*: Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* 284(24), 3131–3138 (2000)

77 Aslam F, Iliadis AE, Blankenship JC: Percutaneous closure of patent foramen ovale: success and outcomes of a low-volume procedure at a rural medical center. *J. Invasive Cardiol.* 19(1), 20–24 (2007).

78 Meier B, Lock JE: Contemporary management of patent foramen ovale. *Circulation* 107(1), 5–9 (2003).

79 Alameddine F, Block PC: Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: acute results from the forecast registry. *Catheter. Cardiovasc. Interv.* 62(4), 512–516 (2004).

80 Mullen MJ, Hildick-Smith D, de Giovanni JV *et al.*: Biostar Evaluation Study (BEST): a prospective, multicenter, Phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 114(18), 1962–1967 (2006).

81 Sievert H, Horvath K, Zadan E *et al.*: Patent foramen ovale closure in patients with transient ischemia attack/stroke. *J. Interv. Cardiol.* 14(2), 261–266 (2001).

82 Khositseth A, Cabalka AK, Sweeney JP *et al.*: Transcatheter Amplatzer device closure of atrial septal defect and patent foramen ovale in patients with presumed paradoxical embolism. *Mayo Clin. Proc.* 79(1), 35–41 (2004).

83 Masura J, Gavora P, Formanek A, Hijazi ZM: Transcatheter closure of secundum atrial septal defects using the new self-centering

Amplatzer septal occluder: initial human experience. *Cathet. Cardiovasc. Diagn.* 42(4), 388–393 (1997).

84 Zahn EM, Wilson N, Cutright W, Latson LA: Development and testing of the helex septal occluder, a new expanded polytetrafluoroethylene atrial septal defect occlusion system. *Circulation* 104(6), 711–716 (2001).

85 Buscheck F, Sievert H, Kleber F *et al.*: Patent foramen ovale using the premere device: the results of the closeup trial. *J. Interv. Cardiol.* 19(4), 328–333 (2006).

86 Ewert P, Soderberg B, Dahnert I *et al.*: ASD and PFO closure with the solysafe septal occluder – results of a prospective multicenter pilot study. *Catheter. Cardiovasc. Interv.* 71(3), 398–402 (2008).

87 Reiffenstein I, Majunke N, Wunderlich N, Carter P, Jones R, Sievert H: Percutaneous closure of patent foramen ovale with a novel flatstent. *Expert Rev. Med. Devices* 5(4), 419–425 (2008).

88 Schwerzmann M, Windecker S, Wahl A *et al.*: Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. *Heart* 90(2), 186–190 (2004).

89 Meier JM, Berger A, Delabays A *et al.*: Percutaneous closure of patent foramen ovale: head-to-head comparison of two different devices. *EuroIntervention* 1(1), 48–52 (2005).

90 Herrmann HC, Silvestry FE, Glaser R *et al.*: Percutaneous patent foramen ovale and atrial septal defect closure in adults: results and device comparison in 100 consecutive implants at a single center. *Catheter. Cardiovasc. Interv.* 64(2), 197–203 (2005).

91 Mckenzie JA, Edwards WD, Hagler DJ: Anatomy of the patent foramen ovale for the interventionalist. *Catheter. Cardiovasc. Interv.* 73(6), 821–826 (2009).

92 Ruiz CE, Alboliras ET, Pophal SG: The puncture technique: a new method for transcatheter closure of patent foramen ovale. *Catheter. Cardiovasc. Interv.* 53(3), 369–372 (2001).

93 Giardini A, Donti A, Formigari R *et al.*: Comparison of results of percutaneous closure of patent foramen ovale for paradoxical embolism in patients with versus without thrombophilia. *Am. J. Cardiol.* 94(8), 1012–1016 (2004).

94 Saver JL: Emerging risk factors for stroke: patent foramen ovale, proximal aortic atherosclerosis, antiphospholipid antibodies, and activated protein C resistance. *J. Stroke Cerebrovasc. Dis.* 6(4), 167–172 (1997).