Managing young and middle-aged patients with cryptogenic ischemic stroke and a patent foramen ovale (PFO) is a common clinical dilemma for neurologists, cardiologists, and primary care physicians. Each year, ≈18 000 patients in the United States and 345 000 worldwide, aged 18 to 60, present with a PFO and an embolic stroke of otherwise undetermined source (Figure 1). Leading treatment options to prevent stroke recurrence include antiplatelet medications, anticoagulant medications, and percutaneously placed PFO closure devices. Lacking randomized trial data, choosing among these options was long a quandary for physicians. But major new trial results in 2017 to 2018,6–9 added to earlier trials reported in 2012 to 2013,10–12 have transformed the evidential foundation for PFO management. This topical review appraises and synthesizes the accumulated trial findings and considers how they may best inform physician and patient treatment decision-making.

Pathophysiology

Right-to-left shunts enable thrombi that form in, and dislodge from, the venous system to bypass filtration in the pulmonary vasculature, paradoxically cross to the arterial tree, and travel to and occlude recipient cerebral arteries. PFOs are the most common causes of right-to-left shunts, present in about one quarter of all adults. During fetal life, the interatrial septum separating the right and left atria initially forms with a tunnel, the foramen ovale, that enables maternally oxygenated blood to bypass the fetal pulmonary circulation and nourish arterial beds directly. This interatrial passage closes in most individuals during the first 3 months after birth. However, in about one quarter of the population, the passage remains patent lifelong. The mean diameter of persisting PFOs is 4.9 mm (range, 1–19 mm), more than sufficient to allow passage of emboli large enough to occlude the middle cerebral artery stem (3 mm) and major cerebral cortical branches (1 mm).

Because venous thrombosis is common in adults, and venous thrombi generate numerous migrating emboli, right-to-left shunting can expose patients to substantial ischemic stroke risk though only a fraction of blood flow actually passes through the PFO. Silent thrombus formation in the deep and superficial venous system is a staple of human adult life, occurring at a rate of perhaps 4% per year overall, and 10% during each long-haul plane flight.13 When a deep venous thrombus (DVT) develops, it can serve as the nidus for a barrage of thromboemboli directed at the right atria, 300 to 50 000 emboli per hour.14 Atrial septal aneurysms (ASAs) are an additional atrial septal abnormality that may interact with, and potentiate risk of, a PFO. The term ‘aneurysm’ is a misnomer, as the defect does not consist of a weakened blood vessel wall, but rather a hypermobile interatrial septum that protrudes alternately into the right and left atria each cardiac cycle.

Clinical Epidemiology

In the general population, PFOs are detected on transesophageal echocardiography (TEE) in ≈20% to 25% of individuals, ASAs are present in 2.2%, and 83% with ASAs also have a PFO. In contrast, among young and middle-aged patients with cryptogenic ischemic stroke, PFOs are present more frequently, in ≈50% to 60%. On the basis of a meta-analysis of case–control studies,4 with additional estimate correction for potential publication bias (Supplemental Figure I in the online-only Data Supplement), young and middle-aged patients with a cryptogenic ischemic stroke have a 2.3-fold increased relative risk of having a PFO present, compared with age-matched individuals with a phanerogenic (known cause) ischemic stroke. From these observations, probability theory dictates that, when young or middle-aged cryptogenic stroke patients are found to have a PFO, the PFO is the mechanism of the stroke in 73% of individuals and incidental in 27% (Supplemental Figure I in the online-only Data Supplement).

Received December 22, 2017; final revision received March 18, 2018; accepted March 20, 2018.

From the Comprehensive Stroke Center and Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA (J.L.S.); Department of Neurology, University Hospital Bern, University of Bern, Switzerland (H.P.M.); and Department of Neurology and Comprehensive Stroke Center, Tufts University School of Medicine, Boston, MA (D.T.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.018153/-/DC1.

Correspondence to Jeffrey L. Saver, MD, Geffen School of Medicine at UCLA, 710 Westwood Plaza, Los Angeles, CA 90095. E-mail jsaver@mednet.ucla.edu.

(Stroke. 2018;49:1541-1548. DOI: 10.1161/STROKEAHA.117.018153.)

© 2018 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.117.018153
Diagnosis

PFOs can be detected by transthoracic echocardiography, TEE, or transcranial Doppler ultrasound (TCD). Of these tests, transthoracic echocardiography is the least sensitive, detecting only 50% to 60% of PFOs found on TEE or TCD. Compared with gold standard autopsy diagnosis, TEE has a sensitivity of ≥90% and specificity >95%. TCD detects 90% to 100% of PFOs found on TEE and up to 10% missed with TEE; TCD may detect small PFOs missed by TEE in part as stronger Valsalva maneuvers can be elicited, and confirmed by waveform monitoring, during TCD than TEE. TEE and TCD are complementary. Both provide PFO detection and quantification of shunt size. TEE, if tolerated by patients, uniquely characterizes PFO anatomy and presence of an ASA and assesses the presence of competing proximal sources of embolism, including aortic arch atherosclerosis, atrial appendage thrombi, and signs of atrial cardiopathy. TCD uniquely quantifies the cerebral burden of paradoxical embolism, on both bubble study and during 30 minutes of monitoring for spontaneous microembolism, and assesses the presence of competing distal arterial sources of embolism.

All young and middle-aged patients presenting with ischemic stroke should undergo investigations to identify large artery atherosclerosis, cerebral small artery microatherosclerosis, nonatherosclerotic arteriopathies, structural and dysrhythmic cardiac sources of embolism, and arterial (and, if right-to-left shunt present, venous) hypercoagulable states. The presence of a high-grade alternative source of stroke greatly lessens the likelihood that a medium-grade source like PFO is causative; and the presence of another medium-grade source reduces the likelihood to a lesser degree. Even when aortic, cervical, and cerebral vessel imaging has not identified substantial large artery atherosclerosis, the mere presence of risk factors for vascular disease, such as hypertension, hyperlipidemia, diabetes mellitus, and tobacco use, mildly diminishes the likelihood a detected PFO is causally related to the stroke.

In young and middle-aged patients with cryptogenic ischemic stroke, in contrast to older patients, low burden paroxysmal atrial fibrillation (AF) is infrequently found. In the CRYSTAL-AF trial (Cryptogenic Stroke and Underlying AF), 3 years of continuous monitoring with an inserted loop recorder revealed low burden paroxysmal AF among only 3% of cryptogenic ischemic stroke patients age <54 years and 4% aged 54 to 61 years. In patients in this age range, it is reasonable to screen for paroxysmal AF with continuous inpatient cardiac telemetry during the index stroke admission, or, in patients not hospitalized, with 24 hours to 7 days of ambulatory monitoring. More prolonged ambulatory cardiac monitoring is reasonable in the small subset of patients with structural, electrophysiological, or blood biomarker evidence of atrial cardiopathy.

Absolute certainty that a detected PFO is the mechanism of a particular ischemic stroke is rare—achieved when echocardiography or other imaging catches thrombi in the act, wriggling through the atrial septum. But the probability that a discovered PFO is causally related to an otherwise cryptogenic ischemic stroke is increased by 5 types of additional clinical features:

- Presence of, or disposition to, venous thrombosis: Likelihood of PFO complicity in the ischemic stroke is strongly increased when concurrent deep or superficial venous thromboembolism is present on noninvasive lower extremity ultrasound, pelvic computed tomography or magnetic resonance venography, or pulmonary computed tomography arteriography performed within the first 48 to 72 hours after stroke onset (before time for venous thrombosis to develop secondarily). Negative noninvasive testing by no means rules out a venous source—the great preponderance of venous clots are superficial (eg, calf) or small, deep thrombi discoverable only on invasive contrast venography; but invasive venography causes patient discomfort so is not usually obtained. Circumstances promoting venous thrombosis are also suggestive that a PFO is pathogenic, including recent immobility (such as extended plane or car travel, surgery, or illness); laboratory findings of a venous hypercoagulable state; imaging showing anatomic causes of venous congestion, such as May-Thurner syndrome; or history of prior venous thromboembolism.

Pure venous hypercoagulable states, such as protein C and S deficiencies, factor V Leiden mutation, and prothrombin gene mutation, likely increase the likelihood the PFO is causally related, as they foster venous thromboemboli that may pass through the PFO. In contrast, mixed arterial–venous hypercoagulable states, such as
antiphospholipid antibodies or hyperhomocysteinemia, have bidirectional effects. They promote both venous thromboemboli that may pass through the PFO but also arterial thrombi that may form in situ in the cerebral arterial tree, unrelated to the PFO.

- Increased right-to-left shunt flow, permanently or transiently: The greater the volume of right-to-left flow across the PFO on imaging, the greater the chance that a venous thromboembolus will swerve across the interatrial shunt rather than flow directly from right atrium to right ventricle. Resting greater right-to-left flow may arise from anatomically large PFO size and from chronic pulmonary hypertension hemodynamically fostering paradoxical flow. Transient increased right-to-left flow may arise from Valsalva maneuver, when forceful expiration against a closed glottis momentarily increases thoracic pressure. Stroke onset coincident with a Valsalva maneuver supports PFO culpability. Careful history-taking should determine whether the ictus occurred during or immediately after heavy lifting, straining at stool, sexual intercourse, coughing, sneezing, or vomiting. Moreover, Muller maneuver, forceful inspiration against a closed glottis, momentarily decreasing thoracic pressure, may also be followed by an increase in right-to-left flow, due to increased intrathoracic pressure swings. In a patient with sleep apnea, stroke onset during sleep is suggestive, as a common setting for Muller maneuver is vigorous inspiration attempts during apneic periods. Sleep apnea is also associated with pulmonary hypertension, which may increase right-to-left shunt flow across a PFO.

- ASA: ASAs potentiate stroke risk in patients with PFO, possibly by (1) hemodynamically fostering access to the PFO of venous thromboemboli arriving in the right atrium or the right or left atria by fostering turbulent flow, with platelet activation, or flow stasis, in perianeurysm pockets or via incomplete left atrial emptying, with clotting protein cascade activation.

- Recipient brain artery or territory typical of embolism: Typical recipient sites in the cerebral circulation for proximal emboli are large main arterial trunks (causing large combined superficial-deep infarcts or isolated, large deep infarcts) and small distal arterial branches (causing isolated superficial infarcts). Emboli much less commonly enter small deep penetrator arteries (causing isolated, small deep infarcts). Large or superficial infarcts in multiple cerebrovascular territories are particularly suggestive of a proximal source of embolism, though this pattern is present in only one sixth of PFO patients.

- Absence of risk factors for atherosclerosis: As mild atherosclerotic disease is a common competing potential cause of ischemic stroke, PFO causality is supported by the absence of demographic and medical risk factors for plaque development, including younger patient age and absence of hypertension, hyperlipidemia, diabetes mellitus, and tobacco use. The Risk of Paradoxical Embolism Score uses absence of atherosclerotic risk factors and infarct topography, though not other features, to quantify the likelihood that a PFO is causally related to stroke in individual patients.

### Treatment Options

Treatment options for secondary prevention of recurrent stroke in cryptogenic ischemic stroke patients with PFO include, alone or in combination, antiplatelet therapy, anticoagulant therapy, surgical PFO closure, and percutaneous PFO closure.

Until recently, in the absence of any randomized trials showing that any of these regimens were better than no treatment at all, the conventional treatment approach was medical therapy, most often with antiplatelet agents alone, and less often with vitamin K–dependent oral anticoagulants alone. Among the medical therapy options, US national practice guidelines weakly endorsed antiplatelet therapy as preferred. Although physiological reasoning suggests that anticoagulation might be superior to antiplatelet therapy, as anticoagulants better avert stasis thrombi arising in veins, anticoagulation is also associated with increased bleeding, and comparative studies are only weakly suggestive of an efficacy advantage. The 2 randomized trials directly comparing anticoagulant against antiplatelet therapy in subgroups of patients with PFOs and cryptogenic ischemic stroke found nonsignificant efficacy differences: PICSS trial (PFO in Cryptogenic Stroke Study; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.16–1.67; P=0.28) and CLOSE trial (PFO foramen ovale closure or anticoagulants versus antiplatelet therapy to prevent stroke recurrence; HR, 0.44; 95% CI, 0.11–1.48; P=0.18). In addition, minor bleeding complications were significantly and major bleeding complications nominally, more frequent among anticoagulated patients. These randomized controlled trial findings align with a larger, individual participant data meta-analysis of 12 prospective observational studies and randomized trials: anticoagulation compared with antiplatelet therapy (HR, 0.75; 95% CI, 0.44–1.27).

Compared with older anticoagulants, newer, non–vitamin K–dependent oral anticoagulants are promising options, given their more predictable blood levels, reduced bleeding rates, and comparable efficacy in prevention of DVT, but have not yet been studied in any large cohort of PFO patients.

Surgical PFO closure, requiring thoracotomy and cardiopulmonary bypass with their attendant risks, is rarely pursued as a standalone therapy. It may be a useful option when a patient is undergoing cardiac surgery for another indication. In observational series, open surgical closure had minimal perioperative mortality, but morbidity included AF, pericardial effusion, postoperative bleeding, infection, and postpericardiotomy syndrome. The annual event rate for recurrent stroke or transient ischemic attack has ranged from 0% to 9%. Recurrence of cerebral ischemia may be related to incomplete PFO closure by open surgical treatment, occurring in up to 73% of patients.

Percutaneously placed PFO closure devices are a less invasive approach to anatomic management and have advanced substantially in the quarter century since their first use in humans. Device designs differ in important ways that affect ease of delivery, efficacy in achieving complete closure, and adverse effects. Devices tested in randomized trials may be grouped into 2 broad classes, based on frame shape: the first generation of devices had umbrella-clamshell contours, with some frame projection away from the septal surface, whereas later developed devices had double-disk contours, a more compact profile potentially less prone to complications.
In a randomized trial directly comparing 3 closure devices against one another, including 1 umbrella-clamshell device (CardioSEAL STARflex occluder [C]) and 2 double-disk devices (Amplatzer PFO occluder [A] and HELEX occluder [H]), better outcomes were observed with the double-disk devices, including fewer recurrent ischemic events (A, 1.4%; H, 4.1%; C, 5.9%), less thrombosis on device (A, 0%; H, 4.1%; C, 5.9%), less AF (A, 3.6%; H, 2.3%; C, 12.3%).36

Six randomized trials have now compared PFO closure devices with medical management alone and provide the first firm evidence to guide treatment selection. Collectively the trials enrolled 3560 fully-reported patients followed for 13850 patient-years (Table). They differed in several important aspects, including devices tested in the device arm, medications tested in the medication arm, permitted qualifying events, and extent of workup mandated to exclude competing causes of stroke (Table; Figure 2). These differences explain variations among trial results and provide insights into optimal treatment deployment.

Overall, with regard to clinical efficacy, the trials demonstrate a beneficial reduction in recurrent ischemic stroke with PFO device closure plus long-term medical antithrombotic (primarily antiplatelet) therapy compared with long-term medical antithrombotic therapy (antiplatelet or anticoagulant) alone. In study-level meta-analysis, device closure, compared with medical therapy alone, reduced the rate of recurrent ischemic stroke (HR, 0.30; 95% CI, 0.13–0.68; P=0.004; Figure 3; Supplemental Table I in the online-only Data Supplement). There was evidence of heterogeneity of treatment benefit across different device classes (P [subgroup difference]=0.02), with a substantial, and highly statistically significant, reduction in recurrent stroke with double-disk devices (HR, 0.20; 95% CI, 0.08–0.54; P=0.001) contrasting with a less pronounced, and formally non-significant, effect with an umbrella-clamshell device (HR, 0.90; 95% CI, 0.41–1.98; P=0.79). In the 5 double-disk trials, the event rate for recurrent ischemic stroke over 5 years after randomization was 6.0% on medical therapy versus 1.8% with device closure plus long-term antiplatelet therapy. Tissue-defined transient ischemic attacks were not reduced, likely in part because of their less reliable diagnostic recognition.

The fully-reported medical therapy groups in these trials consisted of a mix of patients treated with antiplatelet agents and anticoagulant agents in 4 of the 6 trials and patients treated with antiplatelets alone in 2 trials. In contrast, the protocol-permitted early concomitant medical antithrombotic therapy among device group patients was confined to antiplatelet agents alone in 5 of the 6 trials, and early anticoagulation was used in <1% of device-treated patients. Among the 3 trials with separately reported medical therapy treatment subgroups, there was evidence of heterogeneity of treatment effect depending on the type of medical antithrombotic therapy (P [subgroup difference]=0.02). Compared with medical antiplatelet therapy alone, device closure plus long-term medical antiplatelet therapy was superior in averting recurrent stroke (HR, 0.19; 95% CI, 0.06–0.56; P=0.003;
In contrast, in the underpowered comparison of medical therapy with anticoagulants alone versus device closure plus long-term antiplatelet therapy, no benefit of device closure was noted (HR, 1.32; 95% CI, 0.43–4.03).

The trials also provided important information on technical efficacy in achieving PFO closure and on periprocedural and long-term safety of the closure devices. After device placement, there was effective PFO closure (no or only trace, residual shunting) in 93% to 96% of patients in double-disk trials and in 87% in the umbrella-clamshell trial. Immediate, serious, procedure-related complications were infrequent among the 1780 of 1889 patients allocated to the device groups who actually underwent a placement procedures and included access site or retroperitoneal hemorrhage in 1.01%, pericardial tamponade in 0.17%, and cardiac perforation in 0.06%. The most common complication of device placement was AF, but the great preponderance of AF events were transient episodes occurring in the first 4 to 6 weeks after device placement, during the first settling of device elements into atrial tissue. Occurring in 3.2% of patients undergoing a device procedure, these generally self-limited, periprocedural AF events have less likelihood of serving as a new stroke source, compared with AF events that occur later. Among the 4 double-disk device trials with available data, device placement showed a nonsignificant increase in annual risk of AF in the postperiprocedural period, 0.39%

**Figure 2.** Trial populations and event rates. A, Heat map display of stringency of entry criteria in selecting patients likely to have pathogenic rather than incidental patent foramen ovales (PFOs). Cell coloring: green—most stringent; gray—intermediate; and red—least stringent. B, Heat map display of characteristics of enrolled patients and treatments. Cell coloring conveys likely effect on power of study to detect PFO-specific treatment effect: green—heightens; gray—intermediate; and red—lessens. ASA indicates atrial septal aneurysm.

**Figure 3.** Forest plot of trials comparing PFO closure devices plus long-term medical antithrombotic (primarily antiplatelet) therapy against medical antithrombotic (antiplatelets or anticoagulants) therapy alone, for deterrence of recurrent ischemic stroke. Wherever available, data reflect ischemic stroke defined using the modern tissue-based definition. Forest plot analyzes hazard ratio, rather than odds or risk ratio, because of the imbalance in duration of study follow-up between treatment groups in all trials. CI indicates confidence interval; IV, inverse variance; and MT, medical therapy.
versus 0.26% per year (HR, 1.50; 95% CI, 0.77–2.93; P=0.24; Supplementary Figure III in the online-only Data Supplement). DVT and pulmonary embolism tended to occur more frequently in follow-up in the device than medical group in 1 trial, but not the other 4. The risk was particularly increased among the small proportion of patients, 3.6%, who had a history of previous, clinically manifest, unprovoked DVT before trial entry. For these uncommon patients, lifelong anticoagulation to avert recurrent DVT and pulmonary embolism may be beneficial,37 with or without concomitant PFO closure to further prevent paradoxical embolization.

The trials provide evidence that certain patient subgroups may have greater or lesser reduction in recurrent ischemic stroke from device placement. In trials of double-disk devices, 3 patient features were associated or likely associated with magnified reduction in recurrent ischemic stroke with device therapy: (1) ASA (HR, 0.13 versus 0.43; P [subgroup difference]=0.005; Supplemental Figure IV in the online-only Data Supplement); (2) larger shunt sizes, across 4 size levels (P [subgroup difference]=0.07; Supplemental Figure V in the online-only Data Supplement); and (3) index ischemic stroke topography not confined to a single, deep, penetrating artery (HR, 0.34 versus 2.25; P [subgroup difference]=0.04; Supplemental Figure VI in the online-only Data Supplement).

The magnitude of the benefit conferred by PFO closure device placement is moderate overall, higher in select patients, and in a range likely to be deemed clinically worthwhile by an important proportion of patients and families. Among all patients enrolled in the randomized trials and randomized among device closure plus antiplatelet therapy compared with antiplatelet therapy alone, the number needed to treat to prevent 1 recurrent ischemic stroke over 5 years was 24. Among patients with ASA, comparing device therapy plus antiplatelets to medical therapy, the number needed to treat to avert 1 stroke over 5 years was 13, and among patients with moderate-substantial shunts, the number needed to treat was 18. The 5-year time frame for this analysis is likely conservative with regard to benefit estimate. Young and middle-aged ischemic stroke patients with PFO and first cryptogenic ischemic stroke have decades of future at-risk years; modest annual reductions in stroke rates, if sustained, have many years to additionally accrue value. These estimates may also be conservative as some patients with perceived high recurrence risk on medical therapy were treated with device closure outside randomized trials, rather than enrolled and randomized.

An important reason that the annual recurrent ischemic stroke reduction is modest is that event rates in patients treated with medical therapy alone are low to start with, 1.2% per year across the 6 RCTs, placing a ceiling on how much further benefit device placement can confer. This low recurrence rate on medical therapy is less than with other causes of stroke and accords with the status of PFOs as medium-, not high-, grade risk sources for embolism.38 Consequently, patients have a welcome choice between 2 good options—medical therapy alone, with a modest recurrence rate, or closure device combined with antiplatelet therapy, with a dramatic relative, and moderate absolute, further reduction in risk.

Device placement dramatically reduces recurrent ischemic strokes of otherwise undetermined origin, but not recurrent ischemic strokes of determined, non-PFO origin, which continue to accumulate at low frequencies in both treatment groups.6 Likely, some of the patients with a recurrent stroke of determined cause harbored other sources of stroke that were discounted or inapparent at the time of the initial investigation. In addition, as patients age, new risk factors for recurrent stroke emerge, including atherosclerosis and AF. Closing the PFO will prevent future PFO-related strokes, but not strokes due to other causes. The mechanisms of recurrent ischemic strokes of determined cause in patients treated with double-disk devices were diverse; intrinsic small vessel disease was most common, but also large artery atherosclerosis, dilated cardiomyopathy, and other mechanisms.6 Antithrombotic therapy can reduce recurrent events from many of these. Accordingly, it is reasonable to treat patients who undergo device closure with lifelong gentle antiplatelet (or possibly anticoagulant) therapy as well, rather than discontinuing all antithrombotic agents after device endothelialization, to provide ongoing protection against recognized and unrecognized possible competing causes of the initial stroke.

Management Recommendations

Selection of a treatment strategy should be patient-centric, informed by the clinical trial evidence, and tailored to the presentation, findings, and preferences of each individual. Young and middle-aged cryptogenic stroke patients with PFO should know that both of the well-studied treatment options are good choices: recurrence rates are low with both antiplatelet therapy alone and device therapy added to antiplatelet therapy; and that recurrence rates are lower with device placement plus antiplatelet therapy. In addition, long-term anticoagulation alone and device placement plus long-term anticoagulation (after initial antiplatelet therapy until device endothelialization is completed) are promising, not yet sufficiently studied, options. In patients with features which may potentiate the benefit of device placement, including ASA, substantial shunt size, and embolic topography of the index stroke, device placement plus antiplatelet therapy may be especially attractive. In patients with a history of overt deep venous thrombosis, and possibly patients with venous hypercoagulable states, long-term anticoagulation with or without device placement may be preferred, to avert DVT and PE, as well as recurrent ischemic stroke. In patients in whom anticoagulation is contraindicated due to past bleeding complications or bleeding-prone conditions, device placement is preferred. Similarly, for patients in whom frequent or prolonged interruption of oral anticoagulation may be anticipated, because of multiple surgical or invasive procedures, pregnancy, or medication nonadherence, device placement is an attractive option.39

At the systems level, the management of patients with PFO and cryptogenic stroke requires close coordination between neurologists and cardiologists expert in the evaluation and treatment of neurocardiovascular disease.40 An emerging model is a jointly run specialized outpatient clinic at which cryptogenic stroke patients, with or without PFO, can be efficiently evaluated by both specialties. Neurologists’ insights on distinctive features of the stroke presentation and topography, and cardiologists’ insights on distinctive features of the PFO anatomy and other cardiac structural and rhythm findings, can be synthesized into an integrated perspective on likely stroke mechanism and likely...
benefits and risks of the different therapeutic options for consideration by patients and families. Such joint specialty collaboration is facilitated by the US Food and Drug Administration labeling for PFO closure devices, which specifically states that the population for whom closure devices are indicated are patients who have been “…deemed by a neurologist and a cardiologist to have had a cryptogenic stroke following an evaluation to exclude known causes of ischemic stroke.”

**Future Directions**

Among the important areas that would benefit from further study are:

- Predictive models to identify patients who benefit a lot, a little, or not at all: A pooled, individual participant-level data meta-analysis of the completed trials is desirable to develop predictive models identifying combinations of patient characteristics associated with magnified, reduced, and absent benefit of device closure over medical therapy alone.
- Role of anticoagulation, including newer oral anticoagulants: Additional randomized trials are needed to determine the role of (1) anticoagulation alone, and (2) anticoagulation combined with PFO closure; both are promising, but currently not fully proven, treatment options.
- Role of new PFO closure devices: Three newer classes of PFO closure devices have entered development: (1) tunnel insertion devices; (2) bioabsorbable devices; and (3) suture devices. All reduce device surface exposure in the left atrium that may provoke thrombosis. Tunnel insertion devices are especially well suited for closure of long PFO tunnels. The new device classes may improve closure rates above those attained by double-disk devices which yield excellent, >95%, rates of effective closure (no or only trace shunting), but only moderate, ≈75%, rates of complete closure (no shunting at all).
- Patients over age 60: Older patients are more likely to have competing low-medium risk potential causes of the index stroke, reducing the likelihood that a discovered PFO is causally related to the cryptogenic stroke. But older individuals are also more prone to venous thromboembolism, and those with a PFO are prone to more right-to-left shunting, in part because of a higher prevalence of sleep apnea, increasing the likelihood that a discovered PFO is causally related to the cryptogenic stroke. Also, older individuals may be more prone to the complication of closure device–induced AF. Given these age-related differences, RCTs in individuals over age 60 are needed. Pending those studies, PFO device closure might be deployed highly selectively, especially in younger old patients, age 61 to 65, and after more extensive workup for paroxysmal AF, with at least 2 to 4 weeks of ambulatory monitoring.
- Refractory migraine with aura: The validation of PFO closure as a treatment to prevent recurrent ischemic stroke provides support for additional studies of PFO closure as a treatment for refractory migraine with aura preceding most attacks, which may be due to minor paradoxical emboli provoking episodes of cortical spreading depression.

**Conclusions**

The development of PFO closure device therapy has followed the 5-stage life cycle common to technological advances: technology trigger, peak of inflated expectations, trough of disillusionment, slope of enlightenment, and plateau of productivity. Initially (2000–2011), based on nonrandomized case series, enthusiasm for device closure was rampant, slowing enrollment in RCTs as some physicians were unwilling to refer patients to trials, so certain were they of dramatic benefit. Next (2011–2016), when initial randomized trials showed only suggestive, not definitive, evidence of modest treatment advantage, disappointment was sharp, and several authorities prematurely pronounced that PFO closure devices were not beneficial. Finally, in the past year (2017–2018), additional results from randomized trials have ushered in a degree of enlightenment, confirming that PFO closure devices are of genuine benefit, but that the magnitude of benefit is moderate and, to date, demonstrated only for carefully selected young and middle-aged patients with cryptogenic ischemic stroke. PFO closure devices combined with antiplatelet therapy are a useful addition to the therapeutic armamentarium. Additional reduction in recurrent stroke rates can be achieved when neurologists and cardiologists, working collaboratively, perform detailed etiologic evaluations, exclude other causes of stroke, identify high-risk patient features, and provide nuanced treatment recommendations to young and middle-aged ischemic stroke patients with PFO and otherwise cryptogenic ischemic stroke.

**Disclosures**

Dr Saver and Dr Thaler report contracted payments for service on clinical trial steering committee from St Jude Medical/Abbott. The other author reports no conflicts.

**References**


