Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on Patent Foramen Ovale Closure Devices

Tina L. Pinto Slottow, MD; Daniel H. Steinberg, MD; Ron Waksman, MD

Abstract—Patent foramen ovales (PFOs) are common congenital cardiac defects that are more prevalent among patients experiencing cryptogenic stroke than among those with strokes of known origin. Medical treatment for these processes is often considered inadequate, and mechanical closure of the PFO is an attractive, albeit controversial, alternative. Although it is plausible that percutaneous PFO closure will reduce the rate of recurrent stroke in these patients, randomized trials examining the efficacy of devices in this setting have not been completed. In 2007, the Food and Drug Administration convened a meeting of the Circulatory System Devices Panel to discuss the necessity of randomized trials, as well as obstacles to trial enrollment and completion. (Circulation. 2007;116:677-682.)

Key Words: heart septal defects, atrial stroke instrumentation

While clinical equipoise exists when there is a balance of countervailing forces or evidence, the situation for PFOs can more accurately be described as evidence-lacking.

—Dr William Maisel

No prospective trial of percutaneous closure of patent foramen ovales (PFOs) among patients who have experienced cryptogenic stroke has been completed, and no device has been approved by the Food and Drug Administration (FDA) for PFO closure after cryptogenic stroke. Thus, the safety and effectiveness of devices for this indication are unknown.

Current therapy for these patients consists of antiplatelet and antithrombotic medications. For a brief time, humanitarian device exemptions (HDEs) were approved in “high-risk” populations to allow a physician to place an occluding device in a patient with presumed paradoxical embolism; however, use became so common that the HDE was withdrawn. Devices that are approved for closure of atrial and ventricular septal defects are currently deployed “off-label” in this patient population.

Enrollment in trials to answer the important questions of efficacy and safety has been slow, so slow that in 2007, the FDA convened a meeting of the Circulatory System Devices Panel (CSDP) to address a number of issues: (1) What obstacles have prevented completion of a randomized trial? (2) Are randomized trials essential to answer the clinical question? (3) How can trial design be altered to improve recruitment and facilitate timely completion?

PFO and Cryptogenic Stroke

The sequential formation, fusion, and regression of the septum primum and secundum create an interatrial tunnel termed the foramen ovale. This tunnel serves a vital role in embryonic development because it allows oxygenated blood from the inferior vena cava to bypass the lungs and pass directly to the systemic circulation via the left ventricle. At birth, the decrease in pulmonary vascular resistance and the increase in left atrial pressure press the septa together and lead to functional closure. In the majority of people, the flaps fuse over the ensuing 2 years. For unknown reasons, the foramen remains patent in up to 35% of children. In an autopsy study of 965 normal hearts, the prevalence of PFO was 27% overall and decreased with age: 34% in patients aged 30 to 35 years to 20% in patients aged >80 years.

Cryptogenic stroke refers to an ischemic cerebrovascular accident that occurs in the absence of a significant risk factor or clear cause. A biologically plausible theory involves a paradoxical embolism across the PFO, but the exact mechanism of cryptogenic stroke is unknown. Thirty percent to 40% of ischemic strokes in patients >55 years of age have no identifiable cause.

Conventional therapy for prevention of recurrent events in patients with cryptogenic stroke includes both antiplatelet therapy (aspirin, dipyridamole, or clopidogrel as single agents or in combination) and anticoagulation with coumadin. It is of particular interest to provide safe and effective treatments for cryptogenic stroke because, by definition, it occurs in the absence of modifiable risk factors. The young age of the population affected and the potentially catastrophic physical and psychological consequences of recurrent stroke render prevention of further events a strongly desirable goal. Although considered to be effective in reducing the rates of recurrent events, medical therapy has significant limitations.
There is neither expert consensus nor sufficient quality evidence to determine which approach, antiplatelet or antithrombotic, is superior. Also, despite medical therapy, up to 25% of patients with cryptogenic stroke experience recurrent stroke or transient ischemic attack within 4 years of the initial event. This has led a number of expert clinicians to believe that mechanical closure should be the primary treatment modality for patients with PFO after cryptogenic stroke.

Retrospective studies have demonstrated that a PFO is present more frequently in patients with cryptogenic stroke than in those with stroke of known origin: A PFO is observed in 21% to 23% of patients with a determined cause of cerebrovascular accident and in 45% to 54% of patients with cryptogenic stroke. Patients with cryptogenic stroke and a PFO may have a higher risk of recurrent events than those without a PFO, although medically treated patients have been shown to not vary in recurrence rate based on the presence or absence of a PFO. Two recent prospective studies of unselected patients found that the presence of a PFO was not associated with stroke. The first found 140 (24.3%) of 577 patients to have a PFO, but at a median follow-up of 5 years, this was not associated with stroke. The second evaluation of 1100 patients, of whom 164 (14.9%) had a PFO, likewise found no significant association with stroke at a mean follow-up of 6.6 years.

No randomized trials of medical therapy compared with PFO closure have been reported. A systematic review of 10 nonrandomized, unblinded studies included 1355 patients who underwent device closure versus 895 medically treated patients and reported that the rate of recurrent neurological embolic events at 1 year ranged from 0% to 4.9% in the closure patients and from 3.8% to 12% in the medical therapy patients. The latter group was different from the former, however, with regard to a number of factors, including incidence of diabetes mellitus and smoking. Major complications such as death, hemorrhage requiring transfusion, cardiac tamponade, need for surgical intervention, and fatal pulmonary embolus occurred in 1.5% of patients whose PFO was closed, with minor complications occurring in 7.9%. A summary of available evidence is presented in Table 1.

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy and the American Heart Association (AHA)/American Stroke Association Council on Stroke Practice Guidelines recommend antiplatelet therapy after cryptogenic stroke in the majority of patients. Warfarin use is suggested in the setting of known deep venous thrombosis or documented hypercoagulable state (Table 2).

Professional societies have commented on the use of closure devices as a therapy for cryptogenic stroke in the presence of a PFO. The American Academy of Neurology (AAN) found “insufficient evidence regarding the effectiveness of either surgical or endovascular closure of PFO” and promotes encouraging patients with cryptogenic stroke and PFO to participate in research protocols. The AHA/American Stroke Association states, “Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO”; however, “PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy (Class IIb, Level of Evidence C).” These organizations, as well as leaders in the field, have echoed the FDA’s call for randomized trials.

FDA 2007 CSDP Meeting

FDA representatives began the session by outlining the history and clinical concerns that prompted the meeting. No closure devices are currently approved for use in patients with a PFO. Indications for available closure devices are for atrial septal defects and high-risk ventricular septal defects. The FDA has been calling for randomized trials to determine the risks and benefits of the use of devices for PFO closure for the treatment of cryptogenic stroke for many years, specifically making recommendations at CSDP meetings in 1997 and 2002. The current standard of care for patients with cryptogenic stroke and a PFO is medical therapy, but off-label use of atrial septal defect and ventricular septal defect closure devices does occur.

The 1997 CSDP meeting discussed atrial septal defect and PFO closure devices and concluded that randomized controlled trials are essential in determining the safety and effectiveness of PFO closure after cryptogenic stroke. The clinical end points of interest were freedom from recurrent stroke and reduced need for anticoagulation. The 2002 CSDP meeting considered limited approval of PFO closure where data were once again inadequate. The retrospective study of high-risk patients was not found to be acceptable proof of benefit. The importance of randomized trials was reiterated, as was the need for standardized medical regimens in the closure and standard therapy arms. Clinical end points of interest were defined as incidence of stroke and death at 2 years.

Given the lack of good data, the FDA approved HDEs in 2000 and 2002 for 2 percutaneous devices in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO who failed medical therapy. An HDE is a special type of approval intended to encourage device development for rare conditions for which the population affected is <4000 per year. To qualify, a device only needs to demonstrate safety and probable benefit. The HDEs for PFO closure in recurrent cryptogenic stroke were withdrawn in 2006 after FDA review concluded that the US population that could be treated under them was much greater than 4000 patients per year. Currently, investigational device exemption single-arm studies are available to allow patients who meet these criteria to have access to PFO closure devices.

In spite of these previous CSDP meetings and the determination that numerous patients in the United States could be eligible for trials, enrollment has been slow to the point where sponsors have said it is not feasible to complete a randomized study. Possible reasons for sluggish recruitment included patient and physician bias and a strong desire to avoid warfarin therapy in young patients. The FDA’s questions to the panel involved deciding whether lower sample sizes, broader patient populations, multiple control options, or novel statistical methods could be used to facilitate completion of a randomized trial.
TABLE 1. Summary of Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Type</th>
<th>Population</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Lechat et al1</td>
<td>160</td>
<td>Case-control</td>
<td>60 Patients &lt;55 y old with cryptogenic stroke vs 100 control patients</td>
<td>PFO present in 40% of stroke patients and 10% of control patients. P = 0.001</td>
</tr>
<tr>
<td>Northern Manhattan Stroke Study10</td>
<td>95</td>
<td>Retrospective</td>
<td>95 Patients &gt;39 y old with first ischemic stroke underwent TEE; 33% of total population (+) PFO</td>
<td>PFO present in 45% of cryptogenic stroke patients and 23% of patients with known stroke cause. P = 0.02</td>
</tr>
<tr>
<td>Overell et al11</td>
<td>4862</td>
<td>Meta-analysis of case-control studies</td>
<td>2842 Patients with ischemic stroke divided into 1679 patients with known cause of stroke or 1163 patients with cryptogenic stroke and 2020 control patients stratified by presence or absence of PFO</td>
<td>OR of PFO (95% CI): Stroke vs control: All ages: 1.83 (1.25 to 2.66)&lt;55 y old: 3.1 (2.29 to 4.21)&gt;55 y old: 1.27 (0.8 to 2.01) Cryptogenic vs known: All ages: 3.16 (2.3 to 4.35)&lt;55 y old: 6.00 (3.72 to 9.68)&gt;55 y old: 2.26 (0.96 to 5.31)</td>
</tr>
<tr>
<td>PICSS5</td>
<td>630</td>
<td>Prospective</td>
<td>265 Patients with cryptogenic stroke and 365 with known stroke origin, 34% of total population (+) PFO</td>
<td>At 2 y, no difference in time to recurrent stroke or death based on PFO status among all stroke patients (HR, 0.96; 95% CI, 0.62 to 1.48; P = 0.84) or cryptogenic stroke patients (HR, 1.17; 95% CI 0.6 to 2.37; P = 0.65)</td>
</tr>
<tr>
<td>Messe et al4</td>
<td>1211</td>
<td>Meta-analysis of PICSS and French PFO study</td>
<td>846 Cryptogenic and 365 known-cause stroke patients</td>
<td>Relative risk of recurrent stroke or death in patients with PFO 0.96 (95% CI, 0.59 to 1.55)</td>
</tr>
<tr>
<td>Meissner et al12</td>
<td>585</td>
<td>Prospective</td>
<td>585 Unselected patients &gt;45 y old underwent TEE, 24% of total population (+) PFO</td>
<td>At 5-y follow-up, PFO was not significantly associated with stroke: HR, 1.46; 95% CI, 0.74 to 2.88; P = 0.28</td>
</tr>
<tr>
<td>Northern Manhattan Stroke Study13</td>
<td>1100</td>
<td>Prospective</td>
<td>1100 Patients with no history of stroke &gt;39 y old underwent TTE, 15% of total population (+) PFO</td>
<td>At 6.6-y follow-up, PFO was not significantly associated with stroke (HR, 1.64; 95% CI, 0.87 to 3.09; P = 0.28)&lt;60 y old: 3.41 (0.76 to 15.25) ≥60 y old: 1.49 (0.76 to 2.95)</td>
</tr>
<tr>
<td>Khairy et al14</td>
<td>2250</td>
<td>Meta-analysis</td>
<td>1355 Patients who underwent PFO closure and 895 patients with PFO treated medically after cryptogenic stroke. Medical therapy varied on the basis of discretion of the treating physician. Data uncontrolled, with varying definitions and baseline imbalances in demographics, including age, sex, diabetes mellitus, and smoking status.</td>
<td>One-year recurrent stroke: PFO closure: 0% to 4.9%, medical therapy: 3.8% to 12% PFO closure complications: major 1.5%, minor 7.9%</td>
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</table>

TEE indicates transesophageal echocardiography; (+) PFO, positive for PFO (ie, PFO present); PICSS, Patent foramen ovale In Cryptogenic Stroke Study; OR, odds ratio; HR, hazard ratio; and TTE, transthoracic echocardiography.

The proof of principle, ie, that PFO closure will reduce the incidence of cryptogenic stroke, has not been made. The FDA’s representative, Dr Billy Dunn, stated that the relationship between stroke and PFO was “definitely uncertain” and that echocardiographers were less likely to find a PFO if an alternate cause of stroke was known.19

The FDA presented several arguments supporting its requirement for a randomized trial. PFO as a cause of cryptogenic stroke is a diagnosis of exclusion and is completely dependent on appropriately ruling out all potential causes. Because of the lack of certainty of causation, randomized trials are critical. Also, choice of medical therapy varies by prescribing physician and individual patient characteristics. This is reasonable given that no trial has shown 1 medical regimen to be superior to another, but it does introduce variance that would be best addressed in a randomized trial. Third, there are many known and unknown confounders in this population, including age, comorbid conditions, and hypercoagulable states. Adjustment alone is unlikely to be as robust as randomization for the creation of comparable groups. Finally, selection bias is a particular problem in the evaluation of PFO closure, because physicians and patients bring their respective feelings on the subject to the table when coming to a decision. Follow-up neurological exams may be tainted by a physician’s awareness of treatment choice and personal feelings about the effectiveness of that therapy.19

Enrollment continues to be slow despite trial modifications such as the inclusion of transient ischemic attack patients, longer enrollment windows after the initial event, multiple medical therapy arms, the increased role of neurologists as
investigators, and trial design changes, such as unequal randomization. The 2007 CSDP meeting was convened because device companies urged the FDA to revisit the need for randomized trials, and the panel’s input on this question was requested.

A closed session in which industry representatives presented their concerns occurred, followed by public statements by the AAN, the AHA, and the American College of Cardiology. The professional societies were frequently represented by members who are active clinical investigators in ongoing PFO closure trials.

Dr Steven Kittner from the AAN believes it highly plausible that patients who are guided to or choose closure are a lower-risk group than patients who receive medical therapy; this bias cannot be controlled for with statistics. The panel had addressed the idea of pooling control patients across trials for improved numbers, and Dr Kittner was concerned about this bias cannot be controlled for with statistics. The panel agreed that the FDA and professional societies should work to restrict reimbursement for PFO closure outside the setting of a trial, which would limit off-label use and boost enrollment in trials. The AAN endorsed the idea of establishing proof of principle with a randomized controlled trial and then assessing the safety and efficacy of individual devices separately.

Dr John Ring, representing the AHA, stated that the risks and benefits of device closure are unknown and that it is difficult to provide guidelines given the large knowledge gap in this population. A randomized trial is essential to truly answer the crucial questions: Does PFO predispose one to cryptogenic stroke? If so, how? Does cryptogenic stroke recurrence risk vary with age, comorbid conditions, or PFO type? Does drug or device therapy affect outcome?

The lack of balanced groups in the current literature, despite the awareness and study of this problem for more than a decade, is surprising, especially given the large population at risk. Dr Larry Latson, a clinical investigator in a number of PFO closure trials, spoke about the fears of patients who have suffered stroke, are concerned about recurrence, and want the “easy” fix of closure rather than a lifetime of medical therapy. He also stated that medical therapy does not prevent all recurrences and that despite the lack of a trial demonstrating superiority of warfarin over antiplatelet therapy, many patients are treated with the former. He promoted the use of hard end points (ie, permanent disability) as being more useful clinically than transient ischemic attacks and recommended MRI at the beginning and end of a trial to evaluate patients for asymptomatic neuroembolic events. Dr Murat Tuzcu, representing the American College of Cardiology, concurred that for therapy to be evidence-based, a randomized trial is required, and he noted that failure of enrollment does not change the fundamental need for good evidence.

Panel Recommendations
At the conclusion of these presentations, the CSDP was in general agreement that randomized trials are absolutely necessary to determine the efficacy of percutaneous septal occluders in preventing recurrent cryptogenic stroke. There was much discussion on the possibility of pooling control patients. One thought was to pool all the medical therapy patients from previously collected data to make appropriate power calculations for future trial design. The other thought was to have companies share the data in their control arms to increase the numbers of patients and events. Some panel members were concerned about pooling patients across studies given differences in protocols, end-point definitions, data collectors, and timing of data collection. The panel was also

<table>
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<th>Association</th>
<th>Recommendations</th>
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<tr>
<td>American College of Chest Physicians</td>
<td>Antiplatelet therapy after cryptogenic stroke should include 1 of the following: (1) aspirin 50 to 325 mg daily; (2) aspirin 25 mg and extended-release dipyridamole 200 mg twice daily; or (3) clopidogrel 75 mg daily. Antiplatelet agents are recommended instead of oral anticoagulation unless a patient has a well-documented prothrombotic disorder. After cryptogenic ischemic stroke, the presence of a PFO, antiplatelet therapy is recommended instead of warfarin unless a patient has evidence of deep venous thrombosis.</td>
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<tr>
<td>American Academy of Neurology</td>
<td>After cryptogenic stroke, evidence indicates the risk of recurrent stroke or death does not vary between patients with and without PFOs who are treated medically. There is insufficient evidence to determine the superiority of antiplatelet agents vs warfarin. There is insufficient evidence regarding the effectiveness of PFO closure.</td>
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<tr>
<td>AHA/American Stroke Association</td>
<td>After noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (class I, level of evidence B). Aspirin (50 to 325 mg/d), aspirin and extended-release dipyridamole in combination, and clopidogrel are all acceptable options for initial therapy (class IIa, level of evidence A). After ischemic stroke or TIA in patients with a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (class IIa, level of evidence B). Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation, such as underlying hypercoagulable state or evidence of venous thrombosis (class IIa, level of evidence C). Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIb, level of evidence C).</td>
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</table>

TIA indicates transient ischemic attack.
uncomfortable with the high penalty to device companies if all of the data on controls were shared, although the pooling of limited data (ie, incidence of recurrent stroke in the population) could be beneficial.

FDA regulations do not prohibit the pooling of data from patients receiving various devices; thus, multiple companies could work in a joint effort to permit a trial of appropriate size that would provide the proof of principle, ie, that closure of PFO after cryptogenic stroke lowers recurrence of stroke compared with medical therapy alone. The complications associated with and effectiveness of individual devices in achieving PFO closure could then be evaluated separately in trials, using the joint trial as justification for use in this clinical setting. Separating “proof of principle” from “proof of device” would be acceptable to the FDA and could make it easier to complete a randomized trial. The reluctance of sponsoring companies to share data is a major impediment to this type of collaboration and could punish manufacturers of older devices that have accumulated more data than those who have developed devices more recently.

The panel found it odd that despite plentiful off-label use of septal occluders, there are no registry data that follow up patients who have been treated, and the panel felt handicapped by this lack of data. Off-label use was described as the biggest impediment to enrollment in the current randomized trials. Reining in off-label use is challenging, however, because the FDA cannot regulate it. Despite the fact that closure is clearly not the standard of care after a first cryptogenic stroke on the basis of the guidelines of various professional societies, it is believed to be commonly done, although no presenter at the meeting could quantify the magnitude of off-label use.

Solutions to this dilemma proposed by the panel include expansion of the number of centers participating in clinical trials and improvements in education of patients and physicians—perhaps with Web sites designed by professional societies—to raise awareness that PFO closure has never been shown to provide benefit in this situation. Although the propriety of demanding that a commercial company with commercial interests answer an important clinical question is questionable, the panel believed that the question would not be answered in a timely fashion if one were to rely on the major professional societies or the National Institutes of Health. Finally, caution about the pathogenesis of a disease process is questionable, the panel believed that the question would not be answered in a timely fashion if one were to rely on the major professional societies or the National Institutes of Health. Finally, caution was advocated when addressing the idea of relaxing entry criteria to facilitate enrollment, because this might yield uninterpretable data.

The panel agreed with the current AAN and AHA/American Stroke Association guidelines concluding that insufficient evidence exists to evaluate the efficacy of percutaneous PFO closure for prevention of recurrent cryptogenic stroke. Despite slow enrollment and the request of sponsors to discard the requirement for randomized trials, the panel firmly asserted that randomized trials are of critical importance in determining safety and efficacy in this clinical setting.

Conclusions

In summary, patient and physician education is critical in the pursuit of an answer to this clinical problem (Table 3).

### Table 3. FDA CSDP Recommendations

<table>
<thead>
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<th>Recommendation</th>
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<tr>
<td>1. Randomized controlled trials of PFO closure to prevent recurrent stroke are required.</td>
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<td>2. A “proof of principle” trial with pooled data demonstrating that PFO closure does prevent recurrent stroke could allow this question to be answered in a timely fashion, if sponsors are amenable to cooperating and sharing data. “Proof of device” trials demonstrating that an individual device effectively closes a PFO could be done separately.</td>
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<tr>
<td>3. “Off-label” closure should be discouraged. Enrollment in ongoing trials should be encouraged.</td>
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<tr>
<td>4. Patients and physicians should be educated about the lack of evidence of benefit of closure and the need for completion of trials.</td>
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Off-label use should be discouraged, and patients should be educated about the fact that the benefits of PFO closure are controversial and not well-studied. Randomized trials are crucial, and physicians and patients should be educated on the importance of enrolling in trials to allow this question to be answered. Although pooling controls across studies and other statistical tricks may be of benefit, there are ultimately enough patients and enough need for appropriate-sized trials, and the key may be in taking the quest to the individual patient and physician level.

Disclosures

None.

References


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