PFO Closure Strategies to Prevent Cryptogenic Stroke Recurrence

Considerations when choosing an oral anticoagulant, antiplatelet therapy, or closure device for recurrent cryptogenic stroke prevention when a PFO is present.

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Patent foramen ovale (PFO) is fairly common in the general population and is even more common in patients who have cryptogenic stroke (25% vs 40%, respectively).[1] For this reason, paradoxical embolism through a PFO is believed to be causally related to cryptogenic stroke and transient ischemic attack (TIA). Therefore, it stands to reason that PFO closure should prevent further occurrences of stroke or TIA. However, not all PFOs are pathogenic, and not all cryptogenic strokes are related to PFOs.

TO CLOSE OR NOT TO CLOSE?

Three randomized controlled trials have examined PFO closure with two different percutaneous devices in patients who have had previous cryptogenic strokes (CLOSURE I, RESPECT, and PC trials).[2-4] All three trials failed to demonstrate a statistically significant reduction in stroke with PFO closure versus medical therapy, largely because of very low event rates in both arms. However, in the RESPECT trial, a post hoc as-treated analysis revealed a significant reduction in stroke, lending support to PFO closure (hazard ratio [HR], 0.273; $P = .0067$).[3] A meta-analysis of all three trials finally demonstrated a statistically significant reduction in recurrent stroke with PFO closure (HR, 0.58; $P = .0433$).[5]

In light of these cumulative data, the US Food and Drug Administration (FDA) convened a meeting of the Circulatory System Devices Panel in May 2016 to consider a premarket approval application for the Amplatzer PFO occluder device (Abbott Vascular). The panel, composed of cardiologists and neurologists, was largely supportive of PFO closure, and the FDA subsequently approved the device in October 2016.[6] The FDA also requested that the RESPECT trial investigators repeat an analysis of the data after extended follow-up, which was presented at the Transcatheter Cardiovascular Therapeutics meeting in Washington, DC, in November 2016. The primary endpoint of reduction in recurrent ischemic stroke for the intention-to-treat population was finally met (HR, 0.55; $P = .046$), with participating patients and investigators persevering through almost 10 years of follow-up.

Recently, the results of the REDUCE and CLOSE trials were presented. In carefully selected stroke patients, REDUCE showed a 77% relative reduction in recurrent stroke with PFO closure, and CLOSE showed similar results with a 5-year absolute risk reduction for recurrent stroke of 4.9%. For more detailed coverage of the REDUCE and CLOSE data, please see page 26.

MEDICAL THERAPY

The preferred medical therapy for secondary stroke prevention (ie, antiplatelet vs anticoagulation) remains unclear for patients with cryptogenic stroke. The largest meta-analysis of 2,385 cryptogenic stroke patients failed to show any difference between therapies for a composite endpoint of stroke, TIA, or death (adjusted HR, 0.76; 95% confidence interval [CI], 0.52–1.12) or stroke alone (adjusted HR, 0.75; 95% CI, 0.44–1.27). For now, the American Academy of Neurology has endorsed antiplatelet therapy in patients with no other indications for anticoagulation.[7] The CLOSE trial randomized patients to one of three treatment arms (antiplatelet, oral anticoagulation, or PFO closure) and completed enrollment in France in December 2016 (NCT00562289). The results will hopefully shed more light on optimal medical therapy for secondary stroke prevention. In the meantime, physicians and patients should focus on aggressive risk factor modification, and choice of antithrombotic therapy should be based on each patient's comorbidities.

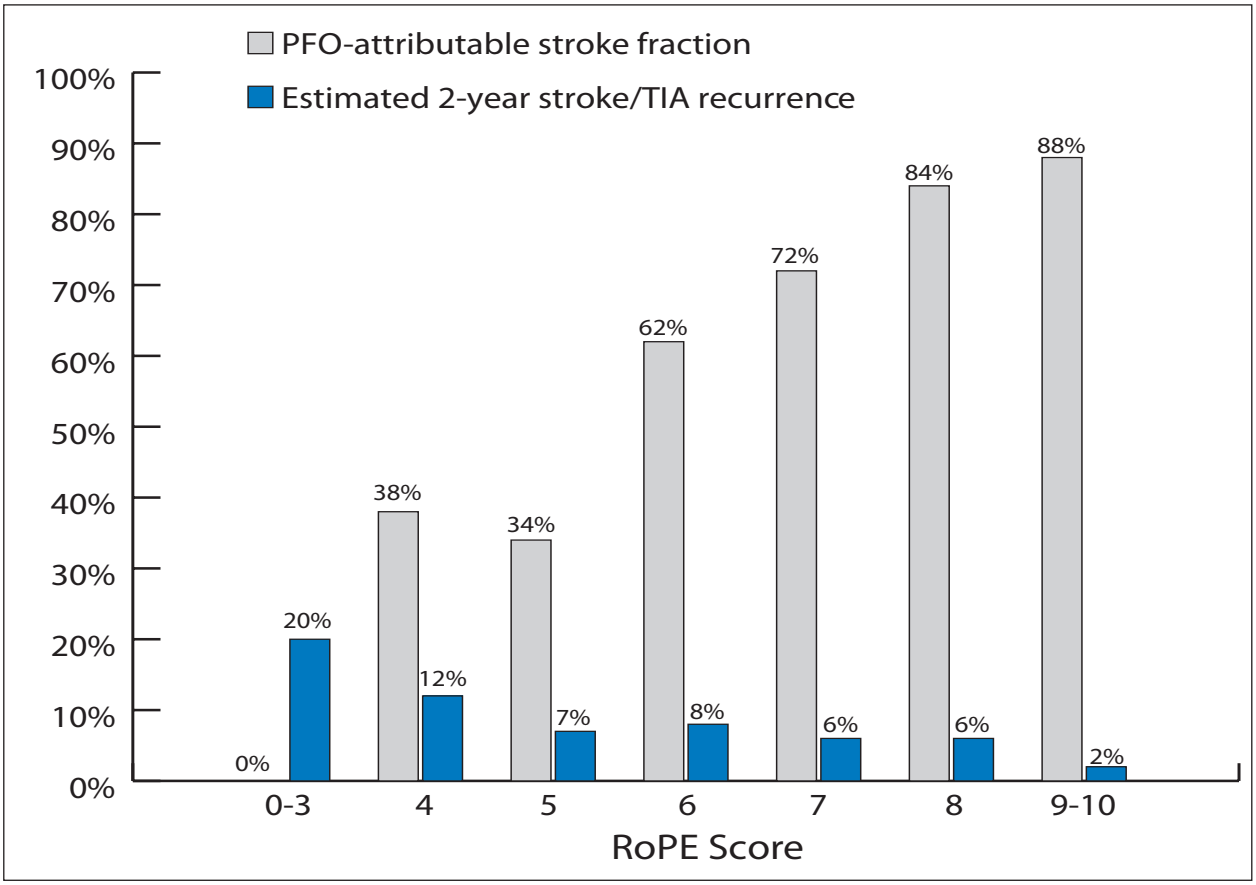

Figure 1. RoPE score interpretation. A higher RoPE score indicates a higher likelihood that stroke or TIA was related to a PFO and a low likelihood of recurrence. A lower RoPE score indicates a higher likelihood that stroke or TIA was caused by factors unrelated to PFO and higher likelihood of recurrence.

WHO SHOULD UNDERGO PFO CLOSURE?

The American Academy of Neurology released a practice advisory update after the FDA panel meeting that adopted a very conservative approach to PFO closure.[7] The update recommended clinicians to counsel patients who are considering PFO closure that (1) having a PFO is common; (2) it is impossible to determine with certainty whether the PFO caused the stroke or TIA; (3) the effectiveness of PFO closure for reducing stroke risk is uncertain; and (4) the procedure is associated with relatively uncommon, yet potentially serious, complications. Overall, the American Academy of Neurology recommended that PFO closure should not be offered to patients with cryptogenic stroke outside of a research setting, except in the context of recurrent strokes despite adequate medical therapy with no other mechanism identified.

Many cardiologists would disagree with points three and four and the overall recommendation above, particularly given the results from the extended follow-up of the RESPECT trial, which showed a significant reduction in stroke with PFO closure and low rates of bleeding (0.57%), atrial fibrillation (0.25%), and deep venous thrombosis or pulmonary embolism (0.57%). Importantly, in the RESPECT trial, there were no device embolizations, erosions, or thrombosis, and there were no intraprocedural strokes.

Of course, not every PFO should be closed in a patient with cryptogenic stroke. The Risk of Paradoxical Embolism (RoPE) score is a useful tool to evaluate the likelihood that a stroke or TIA was PFO related (Table 1).[8] The higher the score, the higher the likelihood that stroke or TIA was related to PFO (Figure 1). However, the RoPE score does not predict the likelihood of a recurrent stroke or TIA—this is an important distinction. An older patient with a low RoPE score in whom stroke or TIA was more likely caused by vascular disease is more likely to have recurrent stroke or TIA than a younger patient with a PFO and no vascular risk factors (Figure 1).

Furthermore, patient selection for PFO closure should not be based on PFO morphology. Some operators consider that a large shunt or hypermobile interatrial septum is

TABLE 1. RoPE SCORE CALCULATOR	
Patient Characteristic	**Points**
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Nonsmoker	+1
Cortical infarct on imaging	+1
Age (y)	
18–29	+5
30–39	+4
40–49	+3
50–59	+2
69–69	+1
≥ 70	+0
Total RoPE score	0–10

higher priority for closure and, conversely, would not close a small PFO with a normal septum. However, transesophageal echocardiographic analysis from the RoPE database failed to show any difference in shunt size, presence or absence of shunt at rest, or hypermobile interatrial septum between patients with high versus low RoPE scores.[9] Subgroup analysis of the pooled PFO closure trial data also failed to show an incremental benefit of closure in patients with large versus small shunts or patients with or without atrial septal aneurysms.[5]

Therefore, it is reasonable to consider PFO closure in patients aged 18 to 60 years with neurologist-confirmed cryptogenic stroke and a high RoPE score. In patients older than 60 years, the treatment effect of PFO closure is likely outweighed by other causes of stroke. Decision making becomes more complex in patients with cryptogenic stroke, PFO, and conventional vascular risk factors. For example, should a cryptogenic stroke patient with poorly controlled hypertension and a PFO undergo closure? Should a young stroke patient with atrial fibrillation and a PFO undergo closure? Can the physician know with certainty that the hypertension or atrial fibrillation caused the stroke and not the PFO? An alternative approach would be to consider PFO, hypertension, and atrial fibrillation as equal risk factors for stroke and treat all of them.

THE HEART-BRAIN TEAM

Multidisciplinary shared decision making is common in many areas of medicine, including advanced heart failure and structural heart disease. The FDA panel strongly advised that any decision regarding PFO closure be considered by a neurologist and cardiologist, and this recommendation was included in the approved indications for use for the Amplatzer PFO occluder:

> The Amplatzer PFO Occluder is indicated for percutaneous transcatheter closure of a PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.[6]

Thus, best practice in 2017 comprises careful exclusion of known causes of ischemic stroke (including monitoring for atrial arrhythmias), evaluation of the likelihood of PFO relatedness using the RoPE score, risk factor and lifestyle modification, and involvement of the patient and the multidisciplinary team in the decision-making process. Unanswered questions include whether patients with cryptogenic stroke who are older than 60 years should undergo PFO closure, whether novel oral anticoagulants are superior to antiplatelet therapy for secondary stroke prevention, and whether PFO closure for primary stroke prevention is warranted in high-risk groups such as scuba divers or pregnant women with prior deep vein thrombosis/pulmonary embolism. ■

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