EDITORIAL

Odyssey of Patent Foramen Ovale: Closure in Cryptogenic Stroke: The Canary in the Coal Mine of Clinical Trials?

Sreekanth Vemulapalli, MD; Manesh R. Patel, MD

Cryptogenic stroke is defined as a symptomatic cerebral infarct for which no probable cause is identified after a standard diagnostic workup. They may be more common in younger patients,[1] in whom traditional stroke and atherosclerotic risk factors are less common, although there is no particular age cutoff above or below which cryptogenic stroke cannot be diagnosed. As a result, estimated stroke recurrence rates of 1.6% at 7 days, 4.2% at 30 days, 5.6% at 90 days, 14% to 20% at 2 years, and 33% at 5 years may be particularly devastating given the large number of patient-years at risk for the young.[1]

Possible etiologic mechanisms for cryptogenic stroke include cardiac embolism secondary to occult atrial myopathies (atrial fibrillation, cardiac amyloidosis) or aortic atheromatous disease, paradoxical embolism, hypercoagulable states, substenotic cerebrovascular disease, or as yet undiscovered mechanisms. Interestingly, many of the proposed mechanisms of cryptogenic stroke would suggest an underlying pathology responsive to anticoagulation (atrial fibrillation, paradoxical embolus, hypercoagulable states) or antiplatelet therapy (substenotic cerebrovascular disease). Nevertheless, optimal medical therapy for cryptogenic stroke remains unclear. WARSS (Warfarin–Aspirin Recurrent Stroke Study) compared aspirin versus warfarin among noncardioembolic stroke patients and found no significant difference in recurrent stroke or death at 2 years.[2]

In the setting of unclear benefit of anticoagulation over antiplatelet therapy, the association between patent foramen ovale (PFO) and atrial septal aneurysm (ASA) and high recurrent stroke represented a potential alternative therapeutic target. A Bayesian attributable risk analysis of data from 12 studies suggested that among patients with cryptogenic stroke and PFO, the PFO may be causally related to the stroke in 50%.[3] However, despite strong observational data linking PFO with or without ASA to recurrent cryptogenic stroke, a series of randomized trials of antithrombotic therapy versus PFO device closure failed to show a benefit with PFO device closure.[4–6] In retrospect, each trial suffered from design flaws—particularly the CLOSURE I (Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale) trial, which included patients with lacunar infarcts who presumably would not have benefited from PFO closure to prevent strokes related to paradoxical emboli. In addition, as a group, these trials suffered from a number of problems that affected their ability to distinguish the impact of medical versus device therapy. First, expected rates of recurrence after cryptogenic stroke used to design these studies were based largely on population/epidemiologic studies from the 1990s and early 2000s.[1] In the interim, technological improvements in neuroimaging (diffusion weighted magnetic resonance imaging, computed tomography angiography) and adoption of prolonged ECG monitoring and echocardiography into the workup for stroke[7] likely increased the sensitivity of stroke diagnosis and the likelihood of identifying stroke etiology. These changes over time have resulted in a decrease in the both the percentage of strokes that are cryptogenic and the likelihood of stroke recurrence. Consequently, rates of recurrent stroke in these initial clinical trials of PFO closure were lower than expected and made type II error more likely. Second, because of ambiguity regarding optimal medical therapy, this was often left to the discretion of the site investigator and thus may have introduced heterogeneity into the trial comparison.

Subsequent trials published in 2017 with more stringent entry criteria aimed at identifying anatomic factors consistent with higher risk of paradoxical embolism as the mechanism of cryptogenic stroke (CLOSE [Patent Foramen Ovale Closure or Anticoagulation versus Antiplatelets after Stroke] trial,[8] ASA or "large" shunt; GORE-REDUCE [Patent Foramen Ovale or Antiplatelet Therapy for Cryptogenic Stroke] trial,[9] "moderate" or "large" shunt with or without ASA) or extended follow-up (RESPECT [Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke] trial)[10] have shown that PFO closure, at least in the trial populations, is superior to medical therapy for the prevention of recurrent stroke. Given the

From the Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Durham, NC.

Correspondence to: Sreekanth Vemulapalli, MD, Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Box 3026, Durham, NC 27710. E-mail: sreekanth.vemulapalli@duke.edu

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strength of these data, the US Food and Drug Administration approved the Amplatzer PFO occluder (Abbott Vascular) (October 2016) and the GORE Helex/Cardioform device (Gore Medical) (April 2018) for PFO closure in cryptogenic stroke.

How to explain the discrepancy in the findings between the initial 3 trials and the subsequent 3 trials published in 2017? Given that we now have multiple negative and positive trials of similar size, how do we know whether the negative trials suffered from type II error or the positive trials suffered from type I error? First, we will consider the RESPECT trial, which enrolled patients with a PFO (no high-risk features required) and initially reported in 2013, with a total of 980 patients and 2.1 years of median follow-up, and then again subsequently in 2017 as an exploratory analysis, with 5.9 years of median follow-up. Despite having differential loss to follow-up between the medical therapy and PFO closure groups, at 5.9 years of median follow-up there was a statistically significant reduction in recurrent stroke in the PFO closure group that appeared to be of greatest impact among those with ASA or large shunt and compared with those treated with antiplatelets rather than anticoagulants. These analyses suggest that perhaps the initial, prespecified analysis of the trial was negative because of low event rates that resulted from insufficient length of follow-up, insufficient numbers of high recurrence risk (ASA and large shunt) patients, and heterogeneous medical therapy (antiplatelets and anticoagulants). The GORE-REDUCE and CLOSE trials do not help to further distinguish the relative contributions of these factors to the failure of the initial 3 trials in PFO closure, as both the GORE-REDUCE and CLOSE trials enrolled patients with high-risk anatomic factors and confined medical therapy to antiplatelets. The clinical trial purist might suggest that PFO closure for cryptogenic stroke should be reserved for patients meeting the entry criteria of the GORE-REDUCE and CLOSE trials (patients aged <60 years with cryptogenic stroke and high-risk anatomic findings, eg, ASA or moderate to large right to left shunt). However, important real-world clinical questions relating to the potential causes of failure in the initial 3 trials remain: How does PFO closure compare with anticoagulation with warfarin? How does PFO closure compare with anticoagulation with direct oral anticoagulants? How does PFO closure compare with medical therapy in patients with and without high risk anatomical findings? What is the impact of age on the potential benefit of PFO closure over medical therapy? What is the long-term clinical impact of the increased risk of atrial fibrillation seen after PFO closure?

Enter the systematic review and meta-analysis by Turc et al in this issue of the *Journal of the American Heart Association*,[11] in which the authors attempt to answer these questions. The authors hypothesized that initial trials in PFO closure were negative partly because of a lack of patient-years of follow-up. As a result, in addition to following best practices in meta-analyses, they also used a trial sequential analysis framework, whereby they conceptually treated each individual trial as an interim analysis in a larger theoretical study encompassing all patients within the individual trials. By adopting this framework, they adjusted their α threshold (risk of saying there is no difference when there is one) to become more stringent with the addition of each trial to the meta-analysis. Even with this appropriately more stringent approach, the authors showed that PFO closure was associated with a lower risk of recurrent stroke compared with antithrombotic therapy (anticoagulation or antiplatelet; relative risk: 0.36; 95% confidence interval [CI], 0.17–0.79). In addition, they have confirmed the hypothesis-generating results of the RESPECT trial, in which the effect of PFO closure on stroke recurrence was larger in patients with ASA or large shunt (relative risk: 0.27; 95% CI, 0.11–0.70) compared with patients without those features (relative risk: 0.80; 95% CI, 0.43–1.47). Although the authors also find that PFO closure is statistically similar to anticoagulation for the prevention of recurrent stroke (hazard ratio: 0.14; 95% CI, 0.00–1.45), the wide CI around the point estimate reflects that this analysis was limited to a single randomized controlled trial and included only 353 patients. Although the pooled complication rates were found to be 2.4% (95% CI, 1.03–4.25) and new-onset atrial fibrillation was more frequent in PFO closure (relative risk: 4.33; 95% CI, 2.37–7.89), detailed analysis of the impact of postprocedural atrial fibrillation was not possible because of low numbers and heterogeneity in the approach to treatment among the various trials.

These results give us confidence that PFO closure is superior to antithrombotic therapy (antiplatelet or anticoagulant at the discretion of the clinician) and that this is driven primarily in those with ASA or large shunt. In addition, although the authors are to be praised for their comprehensive and careful approach to this meta-analysis, a number of clinically important considerations remain, including the role of anticoagulation. The authors rightly point out in their discussion that committing an individual aged <60 years to indefinite anticoagulation is a significant burden and acknowledge that further work is needed in this area. Because this aspect was not the primary focus of their analysis, the authors did not apply the trial sequential analysis framework to this question to assess the adequacy of the available sample size, and 353 patients available in the present study to answer this question is likely insufficient. The NAVIGATE ESUS (Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source) trial comparing rivaroxaban versus aspirin for the prevention of stroke and systemic embolism after cryptogenic stroke was stopped early for futility with an excess of bleeding and no difference in efficacy versus aspirin—questions remain regarding the appropriateness of the trialed dose (15 mg daily).[12] The ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial (NCT03192215) will test the impact of apixaban on stroke recurrence among patients with cryptogenic stroke and atrial cardiopathy. A

related question requiring more data is the natural history of the postprocedural atrial fibrillation associated with PFO closure. Is this truly transient, as has been asserted, or might it be more durable and potentially require anticoagulation? In young patients seeking to avoid antithrombotic therapy, the answer to this question may have significant clinical impact.

Why has it taken us 6 major trials and nearly 15 years to get to this point where we have begun to understand the role of PFO closure in cryptogenic stroke but still have clinically significant questions to be answered? Was it simply that early trials were underpowered or suffered from heterogeneity of medical therapy or did not, in retrospect, properly define the target population? Or was it the fact that one of the earlier devices tested (STARFlex device) (NMT Medical Inc) appeared to be less effective in PFO closure, or perhaps the medical community's seeming preference to close PFOs off-label rather than randomize patients into clinical trials? The story of the unfolding of the evidence supporting PFO closure in cryptogenic stroke highlights the impact of the rapid evolution in diagnostic technologies on the definition of this population, the rapid iteration of on- and off-label device technologies, and the time and resource costs currently associated with phase 3 clinical trials. To answer the remaining questions, such as the role of anticoagulation in cryptogenic stroke, the role of PFO closure in patients aged >60 years, and the length of dual antiplatelet therapy after closure, we need the ability to conduct more rapid trials at lower cost using existing infrastructure. A number of initiatives are currently under way that will bring us a few steps closer to the rapid, low-cost trials needed to answer these remaining questions. First, the ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness) trial[13] has taken advantage of a common data model to derive standardized data elements from electronic health records at multiple institutions. Based on these defined common data elements, a computable phenotype can be designed to identify patient populations of interest. In this regard, future work would need to be done to incorporate the relevant data elements to define cryptogenic stroke and PFO into the common data model. Second, in ADAPTABLE, a combination of electronic health records, private insurance claims, and Medicare claims data are being used for event ascertainment with a plan to validate this method with selected physician adjudication. Indeed, previous work has validated the use of administrative claims to identify myocardial infarction,[14] and future work will be necessary to validate ischemic stroke. As the pace of evolution in diagnostic testing, medical knowledge, and medical devices accelerates, our infrastructure for evidence generation will need to transform accordingly to more efficiently answer evolving clinical questions.

Disclosures

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