JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 7, NO. 8, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.03.006

EDITORIAL COMMENT

The Paradox of Paradoxical Embolism and Recurrent Stroke*

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Ischemic stroke is a complex condition with multiple possible causes, but up to 30% to 40% of patients have no identifiable source despite a "thorough" evaluation; that is, the strokes are cryptogenic. Paradoxical embolism via a patent foramen ovale (PFO) is the cause of some of those cryptogenic strokes, which has led to a great interest in percutaneous closure of PFOs. However, 3 randomized trials have not shown superiority of PFO closure over medical therapy, casting a great deal of doubt over the utility of percutaneous PFO closure (1-3). The concept of PFO closure is sound, so the question is: why were the trials unable to show benefit? The answers to that question are simple and complex at the same time, and are not entirely known. The complexity of stroke is poorly understood by many, including physicians. This often leads to a desire to simplify the evaluation and treatment, creating generalizations such as "a PFO is present, therefore

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it is the cause of the stroke." These cookbook approaches cause detrimental clinical and scientific effects. In other words, patient selection is the most essential aspect of any stroke trial, and this is where the PFO closure trials may have failed.

To address this concern, in this issue of *JACC: Cardiovascular Interventions*, Elmariah et al. (4) conducted a post-hoc analysis of the CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale) trial to identify risk factors for recurrent stroke. They performed an analysis of the intention-to-treat population by evaluating traditional stroke and vascular disease risk factors (hypertension, diabetes mellitus, and so on), as well as atrial fibrillation/flutter that had developed after randomization. Most importantly, they also categorized patients with the Risk of Paradoxical Embolism (RoPE) score, which was not devised until after the CLOSURE trial had ended (5). This score was shown in a retrospective study of 3,674 patients to be able to: 1) predict the likelihood of PFO in cryptogenic stroke patients; and 2) define the PFO-attributable risk (6). The RoPE score (range 0 to 10) gives patients points for factors that favor paradoxical embolism and removes points for factors that favor other etiologies; hence, a low score (e.g., 0) is associated with a low (approaching 0%) risk of stroke attributable to the PFO, whereas a high score (e.g., 10) has a >80% PFO-attributable risk of stroke.

In this analysis, the investigators found that patients with recurrent neurological events (in the CLOSURE I study, these were defined as stroke or "hard" transient ischemic attack [TIA]) had a higher prevalence of traditional vascular (i.e., atherosclerosis) risk factors, especially hypertension, diabetes mellitus, ischemic heart disease, and higher body mass index. On multivariable analyses, they found that diabetes, index event as TIA, and post-closure development of atrial fibrillation predicted recurrent ischemic events. When they compared the RoPE scores and the risk of recurrent events, they found that "paradoxically," the risk of recurrent events (14.5% risk) was highest in those with the lowest RoPE score (≤5). The investigators correctly concluded that a "substantial proportion of recurrent events within the CLOSURE I trial were not due to paradoxical embolization." Atherosclerosis was a likely cause of many of the recurrent events. Reassuringly, they also found that a RoPE score >5 was found in 85.6% of patients in the CLOSURE I trial, indicating that the trial had enrolled mostly appropriate patients, but their risk of recurrent events was only 4.2%. Therefore, the 14% of patients with atherosclerosis risk factors included in the trial muddied the waters sufficiently to decrease

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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the power of the trial of finding superiority of PFO closure. This was exacerbated by the fact that there was not a standardized medical treatment regimen for the medical arm. Those patients could be treated with warfarin or aspirin at the discretion of the treating physician, and there was no stipulation on risk factor control. The endovascular arm, however, was treated with dual antiplatelet therapy for 6 months, which has recently been shown in a Chinese population to be superior to a single agent for stroke prevention (7).

The other important finding by Elmariah et al. (4) was that an index event of TIA was a predictor of recurrent neurological events, mostly recurrent TIA, with a hazard ratio of 4.66 ($p < 0.0001$). This highlights a major limitation of the CLOSURE I trial and an important point for other stroke prevention trials: the index TIA events may not have been ischemic at all. Mimics of cerebral ischemia such as migraine (which has a high prevalence in those with PFO and stroke), epilepsy, or psychiatric conditions, to name a few, may have been the real causes. Not only are these patients important to exclude from future trials, but they likely represent a large proportion of patients who are referred for PFO closure in the real world. The authors correctly concluded that future trials, if any, should only include patients with stroke or TIA, with imaging confirmation performed as in the other 2 PFO trials (2,3).

The limitations of this analysis are clearly enumerated by the authors, but are primarily due to issues with the dataset such as a low number of neurological events as well as enrollment bias in the CLOSURE I trial because of the ready availability of PFO closure devices on the market during enrollment and the 10 years it took to enroll the 909 patients. Also, as the authors note, causation is implied, but cannot be proven, by these data.

Still, taken together, the findings of this post-hoc analysis of the CLOSURE I trial represent a very important addition to the knowledge base. They reinforce the importance of proper patient selection for clinical trials. This aspect of clinical trial design is often compromised, not maliciously, but by external pressures to complete trials as quickly as possible. Randomized trials are incredibly expensive to conduct, and overly strict inclusion/exclusion criteria slow recruitment and prolong enrollment. In fact, the sponsor and manufacturer of the device used in the CLOSURE I trial, NMT Medical Inc., was essentially bankrupted by the 10-year trial. Relatively lax entry criteria, on the other hand, create heterogeneity and often lead to negative trials; this is a very real phenomenon in stroke trials, with recent trials of intracranial stenting and endovascular acute stroke therapy failing to prove efficacy, at least in part because of less than perfect patient selection (8). These data also reinforce the importance of thorough evaluation of all TIA and stroke patients, especially the young. A carotid duplex ultrasound and an echocardiogram, commonly the only evaluations a patient receives, are not sufficient. The entirety of the relevant vasculature from the heart to the small branches of the brain should be evaluated; prolonged monitoring for atrial fibrillation and tests for hypercoagulability should also be considered before a diagnosis of paradoxical embolism is contemplated (9). Last, these data should be used by clinicians in helping to decide which (rare) patient may be a candidate for PFO closure.

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KEY WORDS embolic stroke, patent foramen ovale, PFO closure