Critique of Closure or Medical Therapy for Cryptogenic Stroke With Patent Foramen Ovale
The Hole Truth?

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It is widely accepted that venous thromboemboli can gain access to the left atrium through a patent foramen ovale (PFO). In stroke patients, this mechanism is generally presumed when no other source of stroke is found and a PFO is discovered. Rarely is a thrombus caught straddling the interatrial septum across a PFO. It is intuitively obvious that if the PFO is closed, then a patient cannot experience another similar event. Why even test the theory? After all, there has not yet been a randomized trial of another equally obvious and widely applied therapeutic intervention (parachute vs sham parachute to prevent abrupt deceleration on landing).1

The 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 (CLOSURE I) trial is the first randomized controlled trial to report the results of endovascular PFO closure in comparison with medical therapy.2 The authors, investigators, and late sponsor deserve congratulations for guiding the trial to conclusion. The target population and assumptions of recurrence were defined consistent with the understanding of cryptogenic ischemic events at the time that the trial was being designed. The device, a derivative of the pioneer Rashkind device for closing septal defects and one of the first in widespread use for closing septal defects, had a decent track record. However, according to CLOSURE I, the “parachute” did not work as anticipated. The composite end point of stroke, transient ischemic attack or death, was seen in 6.8% in the medical therapy group and in 5.5% of the closure group (P=not significant) after 2 years of follow-up. The respective figures for cardiovascular death were 0 vs 0, for stroke were 3.1% vs 2.9%, and for transient ischemic attack were 4.1% vs 3.1%. None of these differences was statistically significant.

What happened in CLOSURE I? How could the study fail to demonstrate the benefit that, to many, is so obvious? Perhaps this is another example of “the great tragedy of science,” as defined by T. H. Huxley in the 19th century, “the slaying of a beautiful hypothesis by an ugly fact.”3

When someone comes to read the CLOSURE I article, they do so with 1 of 2 prejudices: (1) PFO closure does not prevent recurrent stroke or (2) it does. We suggest that the study will not change many minds. For those attributing little importance to paradoxical embolism or those who are concerned about the safety of the procedure, CLOSURE I is confirmatory; the answer is finally at hand and it is time to investigate other treatment strategies. For those persuaded by the logic and benefit of closing the PFO, CLOSURE I offers an opportunity to illustrate how trials can go wrong despite the best intentions of the investigators.

Wrong Patients, Wrong Device, Wrong Outcome Assumptions

Wrong Patients

More than one-quarter of index events in CLOSURE I were transient ischemic attacks, as were more than half of the outcome events (captured initially by unblinded local investigators before moving on to the blinded Clinical Events Committee at the Harvard Clinical Research Institute). Less than two-thirds of the baseline magnetic resonance imaging scans showed acute stroke (Anthony Furlan, unpublished data, presented at the 28th Princeton Stroke Conference, May 2012). But this was meant to be a test of secondary stroke prevention. Without imaging confirmation, the trial becomes heavily dependent on the clinical judgment of individual investigators. The intention was to include subjects who had already had an episode of cerebral ischemia. Including patients with neurological symptoms that were not caused by ischemia, cryptogenic, or otherwise would be a mistake. It would lower the outcome rate of recurrent stroke. But confusingly, it may increase the rate of recurrent neurological events that are interpreted as transient ischemic attack but that are actually attributable to migraine, seizure, or other mechanisms. The cardiologists and neurologists who participated in the trial disagreed significantly about how to treat these patients.4 These differences may have affected the advice given to potential subjects and their subsequent recruitment. An

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evaluation of site differences in the characteristics of enrolled subjects may be illuminating.

The prevalence of PFO in the general population is high (≈25%) and so discovering one, even in a patient with cryptogenic stroke, is not the same as making a diagnosis of paradoxical embolism. The Risk of Paradoxical Embolism (RoPE) Study has shown that there are baseline patient characteristics that can predict whether a discovered PFO is likely to be pathogenic or incidental.2-7 Closing an incidental PFO is not going to prevent non-PFO–related stroke recurrence but will expose the patient to procedural and device risks. PFO closure is designed to prevent paradoxical embolism, and so the outcome of interest should be recurrent cryptogenic stroke (paradoxical embolism is generally “presumed” from within this diagnostic category). A lacune was detected in 104 of the 562 diffusion-weighted imaging–positive baseline scans (18%), which is a concerning high prevalence of possible small vessel disease as the index event. There are also indications from the mechanisms of the recurrent events that subjects with incidental PFO were included. Aortic arch disease and the risk factors for lacunar stroke surely did not appear de novo within the 2 years of follow-up, yet they were adjudicated mechanisms for some of the recurrences. Other reported outcome mechanisms are more difficult to understand, why was an adjudicated “conversion disorder” considered an ischemic outcome event, transient or otherwise?

Wrong Device

Concerns about the performance of the STARflex occluder were prominent enough in Bern that its use was abandoned a decade ago. Inferior device performance might explain why the incidence of the primary end point was no different in the 2 treatment groups. Procedural success, defined by the protocol as “implantation of 1 or more devices during the index procedure with no procedural complications,” was achieved in 89.4%, and so failed in >10% of procedures. Effective closure was assessed at 6 months with a surveillance transesophageal echocardiogram. This required procedural success and a residual shunt across the PFO of grade 0 or 1. This benchmark was met in only 86%, a rate of closure that is less than what has been reported with contemporary devices such as the Amplatz PFO occluder.8 It should be noted that according to the CLOSURE I protocol, a shunt of grade 1 could be part of a successful procedural outcome and also was an inclusion criterion sufficient to be enrolled into the study. According to Furlan et al.,2 of the 909 subjects in the study, 428 (47%) had a “trace” shunt of 1 to 10 bubbles at baseline.

Arrital fibrillation was seen during follow-up in 9 of the 362 subjects (2.4%) with a device implanted as compared with 3 of the 462 medically treated patients (0.6%). Of course, atrial fibrillation represents a proven stroke etiology. It would be unfortunate if PFO closure, even if it successfully obliterated the conduit for paradoxical embolism, introduced as a complication another high-risk stroke mechanism. Some of these patients probably already experienced undetected paroxysmal atrial fibrillation at baseline (although lower in the medical group than has been reported in earlier cryptogenic stroke cohorts8), but the difference between the groups strongly suggests a high arrhythmogenic potential from the device. Future studies with other devices will reveal if this risk is specific to the STARflex.

Finally, but of considerable concern, is the incidence of thrombus formation on the device. A previous study10 reported a thrombus rate of 6% using the STARflex device, which is higher than the 1.1% reported during CLOSURE I. But this is still high when compared with other available devices (0.3% for the Amplatzer PFO occluder and 0.8% with the Gore Helex device).10 Because endotherialization is not complete for several months, left-side thrombus formation may explain recurrent events, especially in the early period after device implantation. Again, replacing a relatively benign natural history (recurrent paradoxical embolism)11 with the introduction of another stroke mechanism that may have a worse natural history (device-related thromboembolism) is not likely to be a successful treatment strategy.

Wrong Outcome Assumptions

PFO-related events tend to occur over decades rather than over years, let alone months. Follow-up was stopped at 2 years in CLOSURE I, which is especially frustrating because longer follow-up could have been obtained in all patients—the first subject was enrolled June 23, 2003, and the last one was enrolled October 24, 2008. The authors concede that the assumptions on which efficacy would be determined were “ambitious.” They were based on observations from published case series, which we have argued are unreliable for reasons of publication bias, confounding by indication, outcome ascertainment problems, and other reasons.11 Early procedural complications from PFO closure may be acceptable if there is a long-term reduction in recurrent stroke when compared with medical therapy alone. But even a clinically relevant reduction, for example of 50%, would require >4 years of follow-up in a population the size of the CLOSURE I cohort to become significantly beneficial if the outcome rate is only 2.5% per year—even assuming no procedural complications. A recent study with nonrandomized, but propensity-matched, cohorts (closure vs medical therapy) with 10 years of follow-up showed an event rate in the medical treatment group that was similar to CLOSURE I. The Kaplan-Meier curves continued to diverge even out to 5 years of follow-up.12

It is becoming clearer that extended follow-up (>2 years) and/or a large population undergoing observation will be needed to demonstrate a reduction in recurrent stroke with PFO closure. A frequent criticism of all PFO closure trials is that they are underpowered because of the size of the population being studied and too brief follow-up duration. Those that are ongoing or are yet to report (the PC-Trial, RESPECT, REDUCE,15 and CLOSE16) will have periods of follow-up that are longer than that of CLOSURE I. Whether these periods are long enough remains to be seen. Is it possible that even with the concerns mentioned that CLOSURE I could have been a positive study if the follow-up period simply had been extended? The authors defend the design of the trial, including the short follow-up with another assumption about the timing of recurrent events, namely that recurrences would be early and then level-off. However, the outcome rate appears to have been fairly constant over the 2-year follow-up period. A tantalizing subgroup analysis of young patients in CLOSURE I who were treated per protocol (rather than intention to treat) just missed

Closing Thoughts and Dangerous Knowledge
It is clear that patient selection and device characteristics will determine the effectiveness of this treatment. However, if this technology is approved and devices are freely available, are physicians going to be equally stringent with selection criteria? Evidence from other examples of patient selection for treatment outside of clinical trials suggests that practicing physicians may not always adhere to the inclusion and exclusion criteria that led to approval of the therapy.17 Of course, this allows for the application of clinical judgment by doctors who understand the limitations of summary results of clinical trials18 and who nevertheless must apply them to their individual patients. In the cryptogenic stroke and PFO arena, we owe it to our patients to inform them as honestly as possible about the state of knowledge and how it applies to their particular circumstances. The risk/benefit ratio will be a close one.

What, then, of the patient’s perspective? Every case series and all of the randomized trials have emphasized recurrent neurological events and mortality as the end points of interest. For young patients with cryptogenic stroke and PFO, the need to comply with medical therapy for decades into the future and the anxiety of living “with the hole still open” or, conversely, the anxiety of living with a cardiac implant may be outcomes of even greater interest, although clearly more difficult to measure. Patient advocacy groups19 and government agencies20 have been actively pursuing ways to allow input from those who really matter—those with the PFO—to enter into the discussion. It would be unfortunate to “close the book”21 on PFO closure based on this 1 trial. Thanks to CLOSURE I, significant progress has been made in understanding this population and this procedure. Huxley, again, offers some wisdom:

The saying that a little knowledge is a dangerous thing is, to my mind, a very dangerous adage. If knowledge is real and genuine, I do not believe that it is other than a very valuable possession, however infinitesimal its quantity may be. Indeed, if a little knowledge is dangerous, where is the man who has so much as to be out of danger?22

Let us wait for the results of RoPE, the PC-Trial, RESPECT, REDUCE, and CLOSE, and then we can combine those results with input from our patients, and then, perhaps, we will begin to see our way clear of danger.

Disclosures
Dr Thaler is on the steering committee for the RESPECT trial (AGA Medical/St Jude).

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