Transcatheter PFO Closure Update

A look at the current status of randomized trials and how the results may affect future treatment choices.

BY MICHAEL S. KIM, MD, AND JOHN D. CARROLL, MD

Patent foramen ovale (PFO) has been associated with an array of clinical syndromes, including cryptogenic stroke (CS), migraine headache, systemic hypoxemia from platypnea-orthodeoxia syndrome and sleep apnea, and arterial gas embolism from decompression illness.[1] The management strategy for patients with possible clinically significant PFO, however, remains at the heart of both intense investigation and equally passionate controversy. Although the feasibility, safety, and clinical efficacy of transcatheter PFO closure using an array of implantable devices has been demonstrated in both observational studies and case series, the availability of analogous randomized controlled trial data remains scarce. Furthermore, the currently available clinical data (both randomized and nonrandomized) on the potential benefits of transcatheter PFO closure remain both largely debatable and altogether inconsistent.[2-8] Due in large part to the widely variable clinical data, and the pending results of ongoing randomized clinical trials, the United States Food and Drug Administration (FDA) has yet to approve the use of any transcatheter closure device in the treatment of PFO-related conditions.

This article addresses the current status of randomized controlled trials of transcatheter PFO closure in the United States, paying special attention to transcatheter PFO closure used in the treatment of CS and migraine headache, and the impact of such trials on the future treatment of patients with PFO-related clinical syndromes.

PFO CLOSURE AND CRYPTOGENIC STROKE

The fiery debate surrounding the safety and efficacy of transcatheter PFO closure as a therapy for the prevention of recurrent CS is fueled by two competing forces: (1) a large quantity of observational evidence touting its benefits and (2) available randomized controlled data refuting its efficacy. The number of patients reported in observational studies of transcatheter PFO closure outnumbers patients enrolled in the only randomized clinical trial with publicly available data by a factor of ten.[7] In Europe, where a litany of implantable devices have been granted CE Mark approval for transcatheter PFO closure, the appropriateness of therapy is left to the discretion of the treating physician. The patient and physician's paths to transcatheter PFO closure in the United States, where FDA approval for transcatheter PFO closure procedures and FDA-approved PFO closure devices do not yet exist, is much more circuitous and fundamentally uncertain. Although there are three randomized controlled trials investigating the safety and efficacy of transcatheter PFO closure in the treatment of recurrent CS in the United States (one that is published, one that has completed enrollment, and one that is still enrolling), all remain both challenged by a plethora of positive observational data and stymied by the abundant "off-label" use of implantable devices (Table 1). As such, enrollment into these trials was, or remains, both slow and plagued with logistical challenges, which ultimately begs the question: How applicable are, or will, the data be on a widespread scale?

CLOSURE I

As of March 2012, CLOSURE I[9] represents the first and only randomized controlled trial investigating transcatheter PFO closure for secondary prevention of recurrent CS/transient ischemic attack (TIA) with published data. CLOSURE I enrolled 909 patients randomized 1:1 to transcatheter PFO closure using the StarFlex Septal Closure System (NMT Medical Inc., Boston, MA) with 6 months of dual-antiplatelet therapy composed of aspi-

TABLE 1. CURRENT US RANDOMIZED TRIALS INVESTIGATING PFO CLOSURE FOR CRYPTOGENIC STROKE

	 **StarFlex Septal Closure System**	 **Amplatzer PFO Occluder**	 **Helex Septal Occluder**
Sponsor	NMT Medical Inc.	St. Jude Medical, Inc.	Gore & Associates
Randomized Trial	CLOSURE	RESPECT	REDUCE
Key Trial Design Feature(s)	• Prospective, 2-arm superiority trial	• Prospective • Event-driven adaptive design	• Prospective
Number of Patients	• 909 patients (fixed sample size)	• 980 patients (via adaptive design and mandated follow-up = 2,300 patient-years)	• 664 patients
Medical Therapy Regimen	• ASA • Warfarin • Combination ASA/warfarin	• ASA • Warfarin • Clopidogrel • ASA with dipyridamole	• ASA
Primary Endpoint	• 2-year incidence of stroke or TIA • All-cause mortality for first 30 days • Neurologic mortality from ≥ 31 days	• Recurrence of nonfatal stroke • Postrandomization death and fatal ischemic stroke	• Freedom from recurrent ischemic stroke or imaging-confirmed (by MRI) TIA
Major Inclusion Criteria	• Documented, definite TIA or CS • PFO present	• CT or MRI evidence of CS within 270 days of randomization • PFO present • Lacunar strokes and TIAs excluded	• Presence of CS or TIA of presumed embolic infarction verified by MRI and a neurologist within 180 days of randomization • PFO present
Trial Status	• Closed • Published 03/2012 (*N Engl J Med* 2012;366:991–999)	• Closed • Data expected late 2012	• Ongoing

ASA, aspirin; CS, cryptogenic stroke; TIA, transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging; PFO, patent foramen ovale.

rin and clopidogrel, or to best medical therapy (aspirin, warfarin, or a combination of the two). The results of the study were first presented at the American Heart Association 2010 Scientific Sessions and were eventually published in the *New England Journal of Medicine* in March 2012. Disappointingly, the results of CLOSURE I demonstrated no significant differences in the primary endpoint of recurrent stroke (3.2% for transcatheter closure vs 3.5% for medical therapy; $P = .80$) or TIA (3.2% vs 4.6%; $P = .31$) at 2-year follow-up (composite endpoint of 5.8% vs 7.7%; $P = .28$). The incidence of both major vascular complications (3.2% vs 0%; $P < .001$) and atrial fibrillation (5.7% vs 0.7%; $P < .001$) were significantly higher in the transcatheter PFO closure group.

When comparing results from CLOSURE I to the plethora of observational evidence demonstrating the efficacy of transcatheter PFO closure for the secondary prevention of recurrent CS, the obvious question emerges: What went wrong? Although case series and nonrandomized data repeatedly suggested efficacy of transcatheter closure in the CS patient population (subsequently leading to the rapid adoption of off-label

transcatheter PFO closure), the randomized trial failed to support the notion. On the surface, the results of CLOSURE I imply that transcatheter PFO closure offers no significant benefit (while carrying the potential to induce harm) over best medical therapy, but many experts maintain that the study actually raised more questions than it answered. First, the device cohort demonstrated an arguably suboptimal 86.1% closure rate (meaning that 13.9% of patients were left with a residual shunt), calling into question the overall efficacy and performance of the StarFlex device. In addition, the inclusion of patients with TIAs may have unexpectedly undermined the study from the onset, because the clinical description, diagnosis, and etiology of TIA is much more variable than even that of a stroke. Finally, and perhaps most interestingly, outcome rates in the closure arm of CLOSURE I were nearly four times higher than event rate estimates based on previous nonrandomized studies.[7] This finding is both enlightening and disturbing, as it engenders criticism of patient screening techniques and points to an inherent study design failure to enroll only those patients with highly suggestive PFO-related events. The CLOSURE I investigators discovered that a clinical explanation other than paradoxical embolism could be found to explain a recurrent stroke or TIA in close to 80% of patients studied, suggesting that many of the presumed initial CS observed in the study population were not cryptogenic at all.

The real world impact of the published results of CLOSURE I remains to be seen. The data from CLOSURE I raise obvious concerns as to the true widespread applicability of the study's results and prompts additional questions that will hopefully be addressed by future randomized studies. Will alternative devices with potentially lower incidences of both residual shunt and procedure complications result in clinical findings different than CLOSURE I? Will physicians surrender and admit that PFO closure has no place in treating patients with CS, or will they continue to stand firm in the belief that PFO closure may benefit some patients? Will insurance companies choose to refuse reimbursing an unproven therapy, despite the continued controversy on the subject? In light of the study's faults, the authors of this review argue that while CLOSURE I failed to show a benefit of PFO closure in patients with recurrent CS, it does not completely rule out the possibility that PFO closure may still be beneficial in some patients. The study's inherent challenges and limitations may also suggest that perhaps randomized controlled trials do not represent the best mechanism by which to achieve "closure" of the subject of PFO closure in preventing recurrent CS, and rather that registries focused on more purified patient populations (young patients without vascular risk factors who have a documented cerebrovascular infarct) may ultimately be of greater benefit. Nonetheless, until additional randomized clinical trial data investigating the utility of transcatheter PFO closure in the secondary prevention of recurrent CS become available, the scientific community is left to continue scrutinizing the CLOSURE I trial and struggling with how to apply it to everyday practice and patient care.

RESPECT

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial is a randomized clinical trial investigating the safety and efficacy of transcatheter PFO closure using the Amplatzer PFO Occluder (St. Jude Medical, Inc., St. Paul, MN) in the secondary prevention of recurrent CS versus medical management. At the time that this article was written, RESPECT had achieved study completion; however, data were not yet publically available.

Beyond studying an implantable closure device that has been reported to have fewer device/procedure-related complications with higher closure rates[10,11] than the StarFlex device studied in CLOSURE I, RESPECT capitalized on several of the criticized trial design decisions that plagued CLOSURE I (Table 1). First, unlike CLOSURE I, which set out to enroll a predetermined number of patients based on statistical power calculations, RESPECT was designed to be both event-driven and adaptive, where patient enrollment would continue until a predetermined stopping rule was achieved. In addition, all enrolled subjects were required to continue follow-up until a regulatory decision was made by the FDA, thereby providing the investigators with the potential for a significantly greater number of patient-years of follow-up than competing trials. Perhaps most importantly, RESPECT aimed to enroll only patients with both a PFO and a stroke documented by computed tomography (CT) and/or magnetic resonance imaging (MRI) and selectively excluded patients with either lacunar strokes or TIAs. In doing so, the trial positioned itself to study patients who were inherently more likely to have a stroke that was causally linked to a PFO and not a stroke associated with another, nonshunt-related etiology (ie, hypertension, carotid artery disease, microcerebrovascular disease, etc.).

Outside of the United States, the sister trial to RESPECT (Randomized Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale [PFO] Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism [PC-Trial]) completed enrollment of 414 patients in 2009.[12] Final results of the PC-Trial are expected in early 2012.

In early January 2012, St. Jude Medical, Inc. (who acquired AGA Medical in November 2010), announced the closure of the RESPECT trial. Over a span of 8 years, the trial successfully enrolled 980 patients, yielding greater than 2,300 patient-years of clinical data. Although details of the trial's completion are not yet publicly available, it is known that the trial achieved one of the predesignated stopping rules governed by clinical events. Preliminary results from RESPECT are anticipated in late 2012.

REDUCE

REDUCE is a third randomized clinical trial investigating the safety and efficacy of transcatheter PFO closure using the Gore Helex Septal Occluder, (Gore & Associates, Flagstaff, AZ) in the secondary prevention of recurrent CS and imaging-confirmed shunt-related TIA when compared to medical therapy alone. Investigators for REDUCE have touted its stricter enrollment criteria (patients with ischemic stroke or TIA confirmed by MRI, excluding patients with deep vein thrombosis or documented thrombi), unique device design, and lack of warfarin use in the medical therapy arm (thus comparing device closure to aspirin therapy alone) (Table 1). Some experts, however, have argued that these strict entry criteria will only serve to further reduce the observed stroke rate in the study population and that the proposed 664-patient sample size will not be large enough to observe a statistically significant difference between patient cohorts.

Unlike CLOSURE I and RESPECT, REDUCE is ongoing and continues to enroll patients. In the first several years of enrollment, the trial has achieved only 15% to 20% of its total enrollment.

PFO CLOSURE AND MIGRAINE HEADACHE

Despite recent epidemiological data suggesting that up to 18% of women and 6% of men worldwide suffer from migraine headaches, our understanding of migraine physiology and the optimal treatment for migraine headaches remain limited.[13,14] Information on the potential link between migraines and PFO began to surface in the early 2000s when many single-center reports demonstrated precipitous improvements in migraine frequency in patients undergoing PFO closure for nonmigraine indications.[15-17] These reports subsequently laid the groundwork for several randomized trials investigating the safety and efficacy of transcatheter PFO closure for the treatment of migraine headache. To date, only one randomized trial (MIST) has completed enrollment and reported data, while a second (PREMIUM) continues to enroll. Two other randomized trials (ESCAPE and MIST II) were recently discontinued in the United States due to prohibitively slow enrollment.

MIST

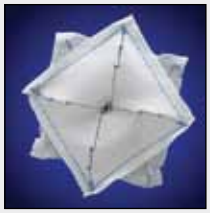
The Migraine Intervention With StarFlex Technology (MIST) trial was the first, and currently only, randomized trial investigating the safety and efficacy of transcatheter PFO closure with the StarFlex Septal Closure System (NMT Medical Inc.) in the treatment of migraine headaches. The randomized, double-blind, and sham-controlled trial design was viewed as an exciting and incredibly bold investigation and carried the hope of elucidating the presumed causative link between migraine headache and PFO. At the study's onset, thousands of migraine patients called to participate in the trial, reaffirming their frustration with both conventional and unconventional migraine therapies. Before the study's conclusion, reports circulated confirming a high percentage of enrolled patients with large right-to-left shunts through a PFO, laying the groundwork for a potentially landmark validation of previous suspicions. The scientific community waited with baited breath.

In the spring of 2006, preliminary results of MIST were publicly presented. In total, 432 patients were assessed for a right-to-left shunt by transthoracic echocardiography, of which shunts were detected in 260 (60%) patients, with 163 (38%) patients interpreted as having shunts due to a moderate or large PFO. In the end, only 147 patients (due to failure to progress to randomization, patient's declining randomization due to personal reasons, patients lost to follow-up, etc.) were ultimately divided into two study cohorts—device arm and sham procedure arm (ie, control). To everyone's surprise, however, the study failed to achieve its primary endpoint of complete cessation of migraines (ie, migraine cure) during the 6-month analysis period.

The preliminary data suggested that the preplanned secondary endpoint of a 50% reduction in migraine days was achieved in 42% of patients in the device arm versus 23% of patients in the sham-procedure arm, reaching statistical significance ($P = .038$). Although humbling in the failure to achieve its primary endpoint, MIST's report that migraine frequency may be significantly reduced by transcatheter PFO closure was encouraging. Based largely on the preliminary results of MIST, a reduction in migraine frequency (rather than complete cure) became the primary endpoint in subsequent randomized PFO trials organized in the United States. While somewhat dimmed by the results of MIST, the hope that transcatheter PFO closure may remain a viable therapeutic alternative in the treatment of migraine sufferers remained bright.

Dishearteningly, when the final MIST trial results were published in 2008, MIST was reported as a completely negative study with failure to achieve statistical significance for both the primary and secondary endpoints.[4] In addi-

TABLE 2. CURRENT US RANDOMIZED TRIALS INVESTIGATING PFO CLOSURE FOR MIGRAINE HEADACHE

	 **StarFlex Septal Closure System**	 **Amplatzer PFO Occluder**
Sponsor	NMT Medical Inc.	St. Jude Medical, Inc.
Randomized Trial	MIST	PREMIUM
Key Trial Design Feature(s)	• Prospective • Randomized • Double-blind • Sham-controlled	• Prospective • Randomized • Double-blind • Sham-controlled
Number of Patients	• 147 patients randomized	• 230 patients
Primary Endpoint	• Migraine headache cessation (ie, cure) during analysis phase	• Reduction in number of reported headache attacks during analysis phase
Major Inclusion Criteria	• ≥ 5 migraine headache days/month, but at least 7 headache-free days/month • Reported history of having failed at least 2 classes of preventive medication • Moderate to large RLS secondary to PFO	• Failure/refractory/unresponsive to 3 classes of preventive medication • Presence of a PFO with a significant shunt (≥ grade 4 with Valsalva by TCD)
Trial Status	• Complete with published data • Negative trial	• Ongoing

RLS, right-to-left shunt; TCD, transcranial Doppler.

tion, patients in the device arm experienced more serious adverse complications (including cardiac tamponade, pericardial effusion, and retroperitoneal bleed) than originally anticipated or clinically acceptable based on contemporary standards of care. Although the results of the MIST trial were sobering, experts in the field highlighted flaws in the trial design (lack of an established independent core lab for echocardiographic analysis, higher-than-anticipated rate of procedural complications with device closure, unreported incidence of residual shunting post-device closure, etc.), which they believed ultimately handcuffed the ability of the trial to achieve its predetermined clinical endpoints. In addition, experts argued that the expectation of transcatheter PFO closure to "cure" migraine headaches was fundamentally unrealistic, and that instead, a reduction in migraine frequency may have been a more realistic primary endpoint. Nonetheless, until additional randomized data emerge on the safety and efficacy of PFO closure in the treatment of migraines, the water surrounding the causative link between PFO and migraines will remain muddied, at best.

PREMIUM

The PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management) trial is the second and only remaining randomized trial investigating the safety and efficacy of PFO closure (using the Amplatzer PFO Occluder, St. Jude Medical, Inc.) in the treatment of migraines being conducted in the United States. Analogous to MIST, PREMIUM is a prospective, randomized, sham-controlled, double-blind, multicenter study and compares transcatheter device closure of a PFO with best medical therapy (aspirin ± clopidogrel). Learning from the potential downfalls of MIST, however, PREMIUM was designed with the primary endpoint of a reduction in the number of migraine attacks with a range of secondary outcomes, including change in the Migraine Disability Assessment Score (MIDAS), reduction in use of acute and/or rescue migraine medications, complete defect closure, and improvement in quality of life (Table 2). Enrollment into PREMIUM is ongoing, and

it remains to be seen whether the results will ultimately help to clear versus agitate the unsettled situation surrounding PFO and migraines.

CONCLUSION

Based on available clinical evidence, it is impossible to proclaim with any degree of certainty that transcatheter PFO closure is beneficial to patients, whether in secondary prevention of recurrent CS or in treatment of migraine headaches (or both). Although data from prospective, randomized clinical trials suggest that PFO closure offers no statistically significant benefit over best medical therapy for either clinical indication, the litany of observational and anecdotal evidence pointing to the contrary cannot be ignored. While the scientific community eagerly awaits data from the "more refined" clinical trials, such as RESPECT, REDUCE, and PREMIUM, the argument can be made for allocating equivalent resources to gain a fundamental understanding of the pathophysiology of the disease states in question, rather than first "assuming" a causative link exists and subsequently designing clinical trials to prove it.

The additional case can be made that perhaps randomized trials, which have been crippled in this particular field by slow enrollment and unrealistic expectations, are not the ideal method for clarifying the potential association between PFO and various disease states. The organization of large, multicenter registries, such as the International PFO Consortium (www.pfoconsortium.org), may be better suited to achieving clarity on the issues at hand. Finally, despite the inherent limitations of observational evidence (confounded by indication, variable follow-up, dropout rates, information bias, etc.), such data are commonly quoted to rationalize physiologically plausible associations between PFO and various clinical conditions, thereby justifying the use of approved closure devices in an off-label fashion.[18] While the authors of this article neither condone nor condemn such a practice, we agree with a recent joint ACC/AHA/ASA Science Advisory in acknowledging that off-label use may serve to inherently undermine the ability to obtain reliable and valid scientific data through recruitment into randomized clinical trials, and that every effort should be made to maximize patient enrollment into meaningful clinical trials.[19]

The practice of PFO closure in the United States remains profoundly controversial, with continued hope that resolution on the matter is not far off. Until the day of clarity comes (if ever), physicians will continue to fight the good fight in the war between sound clinical judgment justifying transcatheter PFO closure in many cases and scientific evidence/regulations arguing against it. ■

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THE CLOSURE I DATA MAY NOT HAVE BEEN WHAT MANY HAD HOPED FOR, BUT THE RESULTS STILL HOLD GREAT VALUE

BY ANTHONY J. FURLAN, MD, PRINCIPAL INVESTIGATOR OF CLOSURE I

CLOSURE I has been criticized as underpowered. The estimated 2-year event rates of TIA plus stroke (2% for device; 6% for medical) were based on a conservative review of the available (observational) literature. We included strictly defined and independently adjudicated TIA because, based on the available literature, we estimated the required sample size would be prohibitive for stroke alone; our results confirm the wisdom of that decision. Following patients for > 2 years would also not likely make a difference, especially for stroke. A recent propensity observational study from Bern found no difference in the stroke rates between device and medical therapy out to 15 years (Wahl A, Juni P, Mono ML, et al. *Circulation*. 2012. http://circ.ahajournals.org/content/125/6/803.abstract. Accessed March 29, 2012.).

The inclusion and exclusion criteria of CLOSURE I, determined by the Executive Committee, balanced recruitment feasibility with "purity." The patients in the trial were considered representative of patients being closed off-label. An overly "pure" population (eg, age < 40 years, no risk factors, large shunt, atrial septal aneurysm, cortical infarct on MR) would have severely restricted recruitment. While such subgroups may represent a more true paradoxical embolism risk, their recurrent neurological event rate is probably even lower, making it more difficult to prove that device is superior to medical therapy.

Much is made of our procedural success and complication rates, but these are the only PFO device performance data acquired prospectively in a randomized trial with independent core laboratory adjudication. These rates reflect a more realistic and unbiased result than observational single-case series. More importantly, residual shunting was unrelated to recurrent neurological events. Atrial fibrillation was more common in the device arm and was related to recurrent neurological events in a few patients in both study arms. Occult atrial fibrillation is likely more common in patients with cryptogenic stroke than previously thought; all patients should probably have a 30-day event monitor. The diagnostic approach to cryptogenic stroke requires more standardization.

We did not find device use inferior to medical therapy, but one must take cost and risk into account. Some patients may still prefer device closure, but proving that device is superior to medical therapy for reducing stroke will be difficult. The results suggest that any benefit of device is likely to be small. It would require > 4,000 patients to confirm the slight trend favoring device use seen in CLOSURE I, which was driven entirely by more TIA in the medical arm.

Where do we go from here? Unfortunately registries, although certainly easier than randomized trials, cannot be used to establish clinical efficacy. The FDA rejected a proposed follow-up objective performance criteria single-arm study when several "purified" subgroup analyses we performed (eg, age < 40 years, cortical infarcts only, no risk factors) from the CLOSURE I dataset failed to show a convincing trend in favor of device use.

Interventionists often describe the results of CLOSURE I as "disappointing" and ask, "What went wrong?" Was it really "disappointing" for patients or for health care costs that aspirin seems to work as well as a $10,000 patch in the heart? Our goal in CLOSURE I was to determine the best treatment for our patients with PFO and stroke. The only thing "wrong" was our bias that device use would prove superior. We do not claim that CLOSURE I is the final answer but rather puts a "brake" on the overuse of off-label device closure for PFO. We await the results of RESPECT and REDUCE, which use slightly more "pure" selection criteria and an event-driven (stroke) endpoint. Regardless of those results, simple observations will no longer suffice.

Readers are also referred to a recent review in *Stroke* of observational and randomized evidence related to PFO closure and medical treatments. (Kitsios GD, et al. Patent foramen ovale closure and medical treatments for secondary stroke prevention. *Stroke*. 2012;43:422–431.)

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