JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 11, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.10.001

EDITORIAL COMMENT

Closure of the Patent Foramen Ovale

Because We Can, Should We? and in Whom?*

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In this issue of *JACC: Cardiovascular Interventions*, Inglessis et al. (1) report clinical outcomes for 800 consecutive patients undergoing closure of a patent foramen ovale (PFO) at 1 major referral center, using a variety of closure devices. The overwhelming majority of patients (94%) were treated for a cryptogenic stroke (CS) or transient ischemic attack (TIA), with few patients treated for hypoxemia (2%), peripheral embolus (2%), or migraine headaches (2%). Device placement was successful in 99%, and effective PFO closure was achieved in 93%, with 1 intraprocedural death from aortic dissection. At a mean follow-up of 43 months, the incidence of recurrent cerebrovascular accident (1.6%) or TIA (1.2%) was low, and only 4 patients (0.5%) died of neurologic causes (stroke or subarachnoid hemorrhage).

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How does this study enhance our current perspectives regarding PFO closure? Along with recent data from multicenter randomized trials, such large observational studies tell us that "we can" perform this procedure effectively. Device placement has proved successful in 89% to 99% in 3 randomized trials, with effective closure of the shunt in 86% to 96% (2–4). Enrollment in these trials was quite protracted, fueling speculation that many patients perceived to be at higher risk of recurrent neurological events on clinical grounds or based on structural characteristics of the septum may have been directed away from randomized studies and toward certain PFO closure on an off-label basis. Thus, the results of this observational study reassure us that the procedure can be performed at low risk in a broader population than those considered stable enough on clinical grounds to submit to randomization with a significant chance of assignment to medical therapy alone. It is also encouraging that no device thrombosis was observed in this study despite the presence of an underlying hypercoagulable state in 28% of patients, generally an exclusion for enrollment in the randomized clinical trials.

The current report also highlights the critical need to apply invasive technologies in patients most likely to derive benefit and to ensure technical expertise of the operators. Even in this highly skilled catheterization laboratory, several cases of tamponade and device embolization occurred, with 1 procedural mortality. It should be noted that multiple different closure devices were used at this center during the course of the study, and some of these events may reflect a learning curve. The large, randomized trials each utilized a single device consistently, with no procedural mortality reported (2–4).

Another looming question has been the potential for proarrhythmic effects of PFO closure. Although the incidence of atrial fibrillation following device closure is not reported by Inglessis et al. (1), in 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, the STARFlex device (NMT Medical, Boston, Massachusetts) was associated with significantly higher rates of atrial fibrillation than was medical therapy (5.7% vs. 0.7%; $p < 0.001$) (3). By contrast, atrial fibrillation occurred at similar rates after PFO closure with Amplatzer devices (St. Jude Medical, Plymouth, Minnesota) compared with medical therapy in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial (2.9% vs. 1.0%; $p = 0.16$) and in the PC-Trial (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) (3% vs. 1.5%; $p = 0.13$) (2,4).

Reassured that "we can" perform PFO closure with a low rate of procedural complications in both highly selected studies and in broader populations, the more critical question is "should we" offer this therapy to patients with cryptogenic stroke or other adverse sequelae of right-to-left shunting through a PFO? The report from Inglessis et al. highlights a very low incidence of recurrent stroke (1.6%) and TIA (1.2%) after PFO closure for CS, even in a population not subjected to the selection biases of randomized trials. However, this observational study cannot address the relative efficacy of device closure plus medical therapy versus medical therapy alone. In all 3 recent randomized clinical trials, PFO closure plus medical therapy in patients with CS has been associated with a numerically lower incidence of recurrent adverse neurological events, but the differences have not reached statistical significance on an intention-to-treat basis (2–4). Importantly, in the RESPECT trial, device closure plus medical therapy did prove statistically superior

*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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to medical therapy alone in the prespecified *per-protocol* and *as-treated* analyses (2). For clinicians treating young patients who have sustained sometimes devastating strokes with no plausible explanation other than paradoxical embolus through a PFO, these data provide some hope that clinical outcomes may be improved with device closure. PFO closure may also have a role in selected cases of symptomatic hypoxia due to interatrial right-to-left shunting (5) or unexplained peripheral paradoxical embolism, although randomized trial data are lacking. PFO closure has clearly not shown benefit in the treatment of migraine headaches (6).

The data, therefore, suggest that "we should" maintain PFO closure in our interventional armamentarium, but "in whom" should we utilize this therapy? In the case of CS, this determination remains elusive. Early observational data suggested a hypermobile interatrial septum or a large shunt in the setting of PFO might increase the risk of cryptogenic stroke or TIA. However, such anatomic features have not emerged as independent predictors in the context of randomized trials (2–4). More recently, the RoPE (Risk of Paradoxical Embolism) study, which combined multiple observational registries, could not substantiate an association of these echocardiographic findings with embolic stroke (7). Rather than using echocardiographic findings to predict risk of CS, the alternative approach is to identify characteristics of the stroke that strongly favor paradoxical embolus through a PFO as a realistic etiology. In the RoPE analysis, PFO was significantly more prevalent with strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts as compared with strokes that were not apparent, smaller, deep, or accompanied by other chronic infarcts (7). A 10-point RoPE score has also been developed to stratify the risk of underlying PFO in stroke patients. In this model, a lack of vascular risk factors, absence of prior stroke, younger age, and presence of radiologically apparent cortical stroke are associated with a higher prevalence of PFO and a lower risk of recurrent stroke or TIA (8). Efforts are also underway to elucidate potential genetic predispositions to ischemic stroke. Such genome-wide association studies may help identify CS patients at increased risk of recurrent adverse neurologic events who may benefit most from PFO closure (9). The potential strategy of targeting PFO closure to CS patients with high RoPE scores or an adverse genetic profile is appealing. Nevertheless such models require validation, and at this point, this targeted approach remains speculative.

How then should we approach patients with cryptogenic stroke? The devastating consequences of stroke compel us to optimize all diagnostic evaluations, secondary prevention measures, and therapeutic interventions for this condition. In addition to standard evaluations, the study by Inglessis et al. (1) emphasizes the need for a careful screening for hypercoaguable states in CS. The measurable incidence of new-onset atrial fibrillation in this population with or without device closure highlights the importance of a thorough evaluation for arrhythmias as well. Further study of optimal medical therapy is also essential. In the randomized CS trials, 80% of the medically treated patients received aspirin alone. With multiple novel antiplatelet agents and anticoagulants now available, the potential role of these pharmacological therapies needs to be investigated. In addition to optimal medical therapy, PFO closure may have a therapeutic role in selected patients. Clearly, we need more data, and appropriate patients should be directed to available clinical trials and registries whenever possible. Innovation to develop less obtrusive closure devices or novel methods to seal interatrial septal connections may advance the field as well.

"We can" close PFOs effectively. On the basis of the clinical experience to date in and out of clinical trials, "we should" be able to offer PFO closure, but only in very high-quality, highly experienced centers. The question of "in whom" remains elusive. At present, it seems most prudent to apply this technology in the context of a multidisciplinary program to ensure judicious use in those patients most likely to benefit, and with the commitment to generate data through clinical trials or registries to help improve our future management of these high-risk patients.

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REFERENCES

1. Inglessis, et al. Long-Term Experience and Outcomes With Transcatheter Closure of Patent Foramen Ovale. J Am Coll Cardiol Intv 2013; 6:1176–83.
2. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368: 1092–100.
3. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366: 991–9.
4. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083–91.
5. Fenster BE, Nguyen BH, Buckner JK, Freeman AM, Carroll JD. Effectiveness of percutaneous closure of patent foramen ovale for hypoxemia. Am J Cardiol 2013;112:1258–62.
6. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention with STARflex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARflex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397–404.
7. Thaler DE, Ruthazer R, Di Angelantonio E, et al. Neuroimaging findings in cryptogenic stroke patients with and without patent foramen ovale. Stroke 2013;44:675–80.
8. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013;81:619–25.
9. Meschia JF, Arnett DK, Ay H, et al. Stroke Genetics Network (SIGN) study: design and rationale for a genome-wide association study of ischemic stroke subtypes. Stroke 2013;44:2694–702.

Key Words: patent foramen ovale ■ stroke.