Patent Foramen Ovale

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Structural-heart-disease specialists perform procedures that will correct anatomic abnormalities of the heart, such as patent foramen ovale (PFO): a congenital opening in the interatrial septum. In utero, the foramen ovale is an extremely important structure, because it enables oxygenated blood from the placenta to travel from the fetus's right atrium into the left atrium; the blood then flows into the left ventricle and is directed outward to the rest of the body. After birth, as the lungs expand, the left atrial pressure increases until it exceeds the right atrial pressure. This pressure differential theoretically causes the PFO to close and to fuse. In approximately 25% of the adult population, however, the foramen ovale remains open. This condition has been implicated as a cause of cryptogenic strokes. The assumption is that an embolus originating in the venous circulation travels through the PFO and reaches the brain (paradoxical embolus). Cryptogenic strokes are common. Of the approximately 800,000 strokes that occur each year in the United States, 600,000 are ischemic, and about 200,000 are cryptogenic. Of those cryptogenic strokes, about 70,000 per year could be associated with a PFO.

In the U.S., percutaneous PFO closure is a controversial issue. In patients who have a PFO and a history of cryptogenic stroke, either aspirin or warfarin therapy is the first therapeutic choice, according to guidelines from the American College of Chest Physicians,[1] the American Heart Association/American Stroke Association,[2] and the American Academy of Neurology.[2] Percutaneous PFO closure is an acceptable alternative to medical therapy (warfarin or aspirin only) in patients who have a 2nd (that is, recurrent) cryptogenic stroke, despite optimal medical therapy. Medical therapy with warfarin is associated with an approximately 22% two-year risk of bleeding. In young patients who have had a cryptogenic stroke, decades-long warfarin therapy might impose an unacceptably high lifetime risk of bleeding, and percutaneous PFO closure should perhaps be considered earlier.

Percutaneous PFO closure with either the STARFlex device* (the former NMT Medical, Inc.; Boston, Mass) or the AMPLATZER™ Multi-Fenestrated Septal Occluder ("Cribriform") (St. Jude Medical, Inc.; St. Paul, Minn) has been superior to medical therapy in nonrandomized clinical trials. This approach involves an off-label use of devices that were designed for atrial septal closure.

The results of several randomized trials have recently been published. They add to the PFO closure controversy but might shed some scientific light on the matter.

The CLOSURE I trial (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)[3,4] enrolled a total of 909 patients. The cumulative incidence (Kaplan-Meier estimate) of the primary endpoint (composite of stroke or transient ischemic attack [TIA] during 2 yr of follow-up, death from any cause during the first 30 d, or death from neurologic causes between 31 d and 2 yr) was 5.5% in the closure group (447 patients) compared with 6.8% in the medical-therapy group (462 patients) (adjusted hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.45–1.35; P=0.37). The respective rates for the 2 groups were 2.9% and 3.1% for stroke (P=0.79) and 3.1% and 4.1% for TIA (P=0.44). The CLOSURE I trial had many shortcomings, so the conclusions that can be drawn from it are limited. First, 5 years passed before enough patients could be enrolled in the study. Second, although the initial sample size was 1,600 patients, both the sample size and the endpoints had to be recalculated for 900 patients, due to slow enrollment. In fact, during the 9 years consumed by the trial before its completion, about 80,000 patients worldwide

*This device is no longer available.

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had their PFOs closed percutaneously. Third, the trial was underpowered: the rate of events in the medical-therapy group was much lower than expected, and the crossover rate in that group was significant. Fourth, the STARFlex device used in the CLOSURE I trial was associated with increased rates of atrial fibrillation and of thrombus formation on the device itself.

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)[5] added to the controversy regarding percutaneous PFO closure. In this trial, event rates were also lower than expected. The primary endpoint (composite of death, nonfatal stroke, TIA, or peripheral embolism) occurred in 7 (3.4%) of the 204 patients in the closure group and in 11 (5.2%) of the 210 patients in the medical-therapy group (HR for closure vs medical therapy, 0.63; 95% CI, 0.24–1.62; $P=0.34$). Nonfatal strokes occurred in 1 patient (0.005%) in the closure group and in 5 patients (2.4%) in the medical-therapy group (HR, 0.20; 95% CI, 0.02–1.72; $P=0.14$). Transient ischemic attacks occurred in 5 closure-group patients (2.5%) and in 7 medical-therapy patients (3.3%), respectively (HR, 0.71; 95% CI, 0.23–2.24; $P=0.56$). This was another underpowered trial that, again, showed no benefit of percutaneous PFO closure.

The 3rd recently published randomized trial is the RESPECT trial (Randomized Evaluation of recurrent Stroke comparing PFO closure to Established Current standard of care Treatment).[6] This prospective, multicenter, randomized, open-label, 2-arm superiority trial tested whether PFO closure with an AMPLATZER device was, together with medical therapy, superior to medical therapy alone for preventing recurrent stroke in patients with cryptogenic stroke *and* a PFO. Patients had an acute focal neurologic deficit and symptoms that either 1) persisted for at least 24 hours or 2) persisted for less than 24 hours and were associated with a documented cerebral infarct on magnetic resonance imaging or computed tomography; patients also had a PFO, as documented by a transesophageal echocardiographic (TEE) microbubble study. They were excluded if a mechanism for the index stroke other than paradoxical emboli could be identified. Medical therapy was left to the discretion of the physician: aspirin, warfarin, aspirin plus clopidogrel (early), and clopidogrel or aspirin plus dipyridamole.

The primary endpoint was a composite of nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The sample-size calculation was performed with the expectation of a primary endpoint of 4.3% for medical therapy and 1.05% for AMPLATZER-device therapy; the authors estimated that the study would have 80% power to show a 75% reduction in events with closure. It is important to note that, if inter-group dropout rates differed significantly, an exposure-stratified comparison would be performed. Prespecified analyses included intention-to-treat, per-protocol, and as-treated cohorts. Planned follow-up evaluation at 1 month and at 6, 12, and 24 months was to be performed by a board-certified neurologist. In addition, the study required TEE at 6 months and brain imaging for all clinically suspected neurologic events, to confirm ischemic stroke. Figures 1 and 2 show the results. The trial's conclusions can be summarized as follows:

1) The superiority of PFO closure with AMPLATZER-plus-medical therapy over medical therapy alone was not shown by an intention-to-treat analysis. This can be explained by the fact that patients assigned to the closure group had strokes before receiving the device.

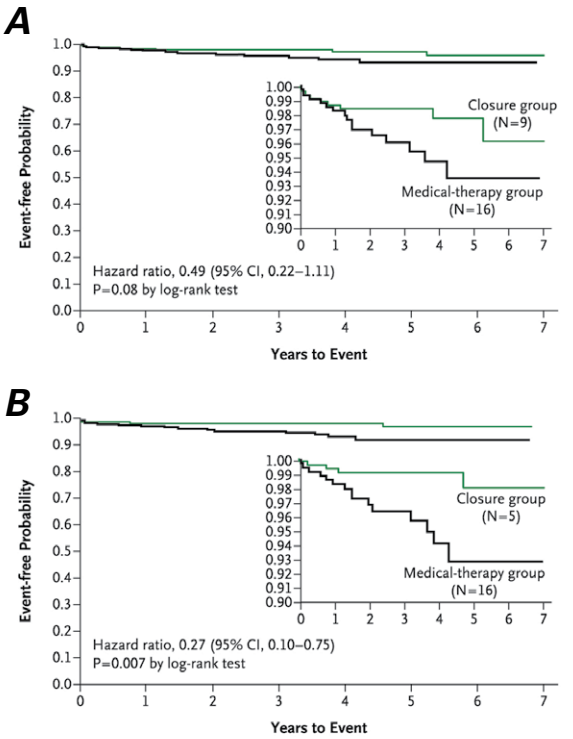

Fig. 1 *Primary endpoint events in the intention-to-treat and as-treated cohorts.* ***A****) In the intention-to-treat cohort, there were 25 primary endpoint events, all of which were recurrent nonfatal ischemic strokes; 9 occurred in patients who were assigned to the closure group and 16 in patients assigned to the medical-therapy group. Three patients with recurrent ischemic stroke who had been randomly assigned to the closure group did not have a device in place at the time of the recurrent stroke.* ***B****) The as-treated cohort included all patients who received a protocol-approved treatment and adhered to the protocol-mandated medical treatment; in this cohort, patients were classified according to the treatment they actually received, regardless of the randomization assignment. The insets show the same data on an enlarged y axis.*

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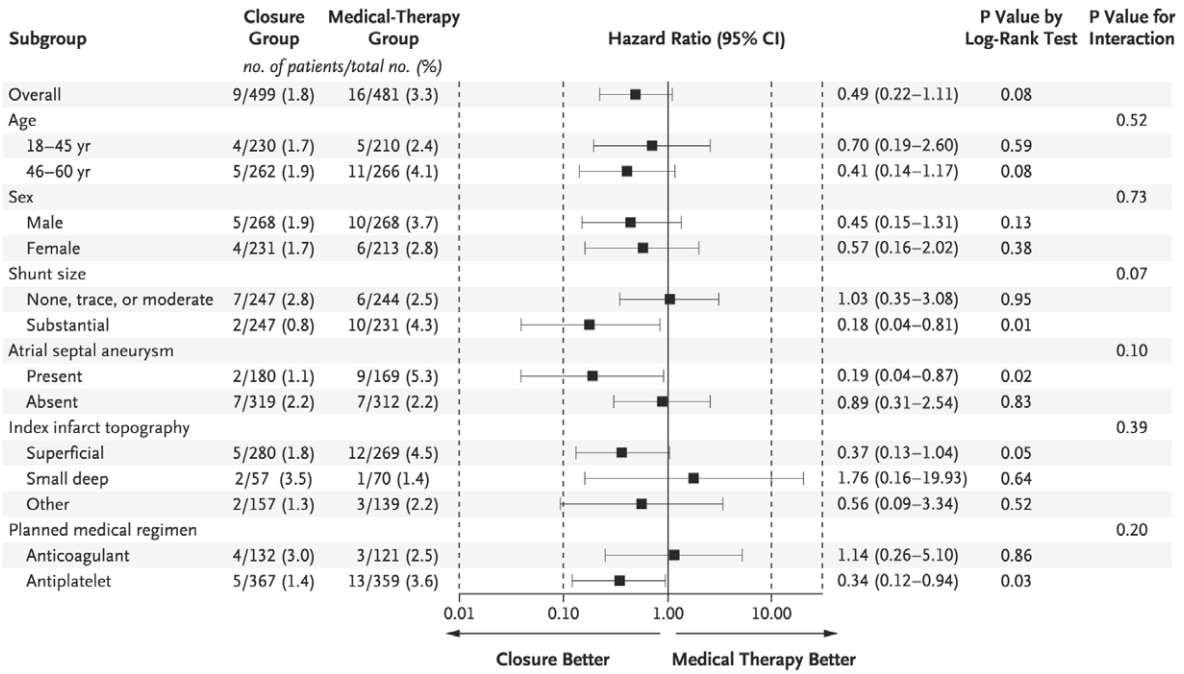

Fig. 2 *Analysis of the primary endpoint according to subgroup, in the intention-to-treat cohort. Potential heterogeneity of the treatment effect was noted with respect to 2 baseline characteristics, with a suggestion of greater risk reductions with closure than with medical therapy alone in patients with an atrial septal aneurysm or a substantial shunt size. The percentages are Kaplan-Meier estimates of the event rates.*

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2) Prespecified analysis of the per-protocol and as-treated cohorts showed significant superiority of PFO closure with the AMPLATZER device.

3) No major harm was associated with closure, because complication rates for the procedure were low, and atrial fibrillation rates were similar in comparing the control with the treated arms.

4) Although the trial's conclusions were not definitive, they strongly suggested a benefit for closure when patients were carefully selected on the basis of brain imaging, especially when patients had larger shunts and atrial septal aneurysms.

In summary, percutaneous PFO closure to prevent recurrent cryptogenic stroke remains a controversial issue. Clinicians and patients should decide together—on a case-by-case basis—whether PFO closure is advisable or not. Preliminary evidence shows a therapeutic effect in patients with image-proven cryptogenic stroke and a high-risk PFO anatomy (atrial septal aneurysm and a large right-to-left shunt).

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