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# Patent foramen ovale and the risk of cryptogenic stroke

**T**HE ARTICLE BY ROTH AND ALLI in this issue describes in depth more than 10 years of research that addresses the question, Should we close a patent foramen ovale (PFO) to prevent recurrent cryptogenic stroke?

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There is no longer any doubt that PFO can be the pathway for thrombus from the venous circulation to go from the right atrium to the left atrium, bypassing the pulmonary capillary filtration bed, and entering the arterial side to produce a stroke, myocardial infarction, or peripheral embolus. Two questions remain: What should we do to prevent another episode? And is percutaneous closure of a PFO with the current devices preferable to medical therapy?

How much do we know about the risks and benefits of closure of PFO? I maintain that we know a great deal about interatrial shunt and paradoxical embolism as a cause of cryptogenic stroke. Prospective randomized clinical trials now give us data with which we can provide appropriate direction to our patients. Percutaneous closure is no longer an “experimental procedure,” as insurance companies claim. The experiment has been done, and the only issue is how one interprets the data from the randomized clinical trials.

The review by Roth and Alli comprehensively describes the observational studies, as well as the three randomized clinical trials done to determine whether PFO closure is preferable to medical therapy to prevent recurrent stroke in patients who have already had one cryptogenic stroke. If we understand some of the subtleties and differences between the trials, we can reach an appropriate conclusion as to what to recommend to our patients.

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A review of 10 reports of transcatheter closure of PFO vs six reports of medical therapy for cryptogenic stroke showed a range of rates of recurrent stroke at 1 year—between 0% and 4.9% for transcatheter closure, and between 3.8% and 12% for medical therapy.<sup>1</sup>

These numbers are important because they were used to estimate the number of patients that would be necessary to study in a randomized clinical trial to demonstrate a benefit of PFO closure vs medical therapy. Unlike most studies of new devices, the PFO closure trials were done in an environment in which patients could get their PFO closed with other devices that were already approved by the US Food and Drug Administration (FDA) for closure of an atrial septal defect. This ability of patients to obtain PFO closure outside of the trial with an off-label device meant that the patients who agreed to be randomized tended to have lower risk for recurrence than patients studied in the observational populations. From a practical standpoint, this meant that the event rate in the patients who participated in the randomized clinical trials (1.7% per year) was lower than predicted from the observational studies.<sup>2,3</sup>

Another way of saying this is that the randomized clinical trials were underpowered to answer the question. A common way of dealing with this problem is to combine the results of different studies in a meta-analysis. This makes sense if the studies are assessing the same thing. This is not the case with the PFO closure trials. Although the topic of percutaneous PFO closure vs medical therapy was the same, the devices used were different.

In the CLOSURE 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),<sup>3</sup> the device used was the STARFlex, which is no longer produced—and for good reasons. It is not as effective as the Amplatzer or Helex devices in

completely closing the right-to-left shunt produced by a PFO. In addition, the CardioSEAL or STARFlex device increases the risk of atrial fibrillation, which was seen in 6% of the treated patients.<sup>3</sup> This was the major cause of recurrent stroke in the CLOSURE trial. The CardioSEAL STARFlex device was also more thrombogenic.

In the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment),<sup>2</sup> which used the Amplatzer PFO closure device, there was no increased incidence of atrial fibrillation in the device group compared with the control group. Therefore, it is not appropriate to combine the results of the CLOSURE trial with the results of the RESPECT trial and PC trial,<sup>4</sup> both of which used the Amplatzer device.

Our patients want to know what the potential risks and benefits will be if they get their PFO closed with a specific device. They don't want to know the average risk between two different devices.

However, if you do a meta-analysis of the RESPECT and PC trials, which used the same Amplatzer PFO occluder device, and combine the number of patients studied to increase the statistical power, then the benefit of PFO closure is significant even with an intention-to-treat analysis. By combining the two studies that assessed the same device, you reach a completely different interpretation than if you do a meta-analysis including the CLOSURE trial, which showed no benefit.

The medical community should not uncritically accept meta-analysis methodology. It is a marvelous case example of how scientific methods can be inappropriately used and two diametrically opposed conclusions reached if the meta-analysis combines two different types of devices vs a meta-analysis of just the Amplatzer device.

If we combine the numbers from the RESPECT and PC trials, there were 23 strokes in 691 patients (3.3%) in the medical groups and 10 strokes in 703

patients (1.4%) who underwent PFO closure. By chi square analysis of this intention-to-treat protocol, PFO closure provides a statistically significant reduction in preventing recurrent stroke (95% confidence interval 0.20–0.89,  $P = .02$ ).

From the patient's perspective, what is important is this: If I get my PFO closed with an Amplatzer PFO occluder device, what are the risks of the procedure, and what are the potential benefits compared with medical therapy? We can now answer that question definitively. I tell my patients, "The risks of the procedure are remarkably low (about 1%) in experienced hands, and the benefit is that your risk of recurrent stroke will be reduced 73%<sup>2</sup> compared with medical therapy." In the RESPECT Trial, the as-treated cohort consisted of 958 patients with 21 primary end-point events (5 in the closure group and 16 in the medical-therapy group). The rate of the primary end point was 0.39 events per 100 patient-years in the closure group vs 1.45 events per 100 patient-years in the medical-therapy group (hazard ratio 0.27; 95% confidence interval 0.10–0.75;  $P = .007$ ).

Not all cryptogenic strokes in people who have a PFO are caused by paradoxical embolism. PFO may be an innocent bystander. In addition, not all people who have a paradoxical embolism will have a recurrent stroke. For example, if a young woman presents with a PFO and stroke, is it possible that she can prevent another stroke just by stopping her birth-control pills and not have her PFO closed? What is the risk of recurrent stroke if she were to become pregnant? We do not know the answers to these questions.

Your patients do not want to wait to find out if they are going to have another stroke. The meta-analysis of the randomized clinical trials for paradoxical embolism demonstrates that the closure devices are safe and effective. The FDA should approve the Amplatzer PFO occluder with an indication to prevent recurrent stroke in patients with PFO and an initial cryptogenic event. ■

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