

## LESS IS MORE

# Patent Foramen Ovale and Stroke Prevention— To Close or Not to Close A Teachable Moment

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## Story From the Front Lines

A 65-year-old man with a history of chronic obstructive pulmonary disease, hyperlipidemia, and hypertension was seen in clinic for hospital follow-up. He had previously been admitted to the hospital with slurred speech and aphasia and diagnosed as having a left middle cerebral artery ischemic infarct. Tissue plasminogen activator was administered with a positive neurologic outcome. His only residual deficit was numbness in 3 digits in his right hand impacting his dexterity, which was improving with therapy.

Initial workup to determine the cause of his stroke was unrevealing: no deep venous thrombosis (DVT) was seen on lower extremity ultrasonography; normal arteries were seen on carotid ultrasonography; and there was no thrombus in his left atrium. However, transesophageal echocardiography revealed a patent foramen ovale (PFO). He reported that the cardiologist wanted to close his PFO percutaneously to prevent future strokes. He was enthusiastic about pursuing this course of treatment and unaware of the data surrounding the efficacy, as well as the risks, of the procedure.

## Teachable Moment

Cerebral vascular accidents (CVAs) are a major cause of morbidity and mortality in the United States. In approximately one-third of CVAs, a cause is not determined, leaving patients and physicians with the frustrating diagnosis of cryptogenic stroke.<sup>1</sup> It is hypothesized that some cryptogenic strokes may be caused by a venous embolism passing through a PFO and into the systemic circulation.<sup>2</sup> While mechanically plausible, the role of PFO in CVA remains unclear. However, a wide range of therapies to address secondary prevention in patients with PFOs have been proposed and adopted, including percutaneous closure, antiplatelet therapy, and anticoagulation. These therapies have varying degrees of potential harm.

Initial observational studies and meta-analyses have indicated decreased recurrent CVAs with PFO closure. However, 3 randomized clinical trials have not borne out this same conclusion. In CLOSURE-I,<sup>2</sup> researchers compared medical therapy and PFO closure using the STARFlex Septal Closure System in patients with cryptogenic stroke or transient ischemic attack (TIA) and a PFO. They found no significant difference in the secondary end point of recurrent stroke: 2.9% vs 3.1% (95% CI, 0.41-1.98). Two other

randomized trials in 2013, PC<sup>3</sup> and RESPECT,<sup>4</sup> also failed to show clear benefit with PFO closure using the Amplatzer PFO Occluder. In PC, the recurrent stroke rate was 0.5% vs 2.4% (95% CI, 0.02-1.72).<sup>3</sup> In RESPECT, there was no difference in the primary composite outcome of nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization (0.66 events per 100 patient-years vs 1.38 events per 100 patient-years [95% CI, 0.22-1.11]).<sup>4</sup> Despite the study population being limited to those with CVA only, and not those with CVA or TIA, the results did not reach statistical significance.

Closure of a PFO is also not without risks. In CLOSURE-I,<sup>2</sup> PFO closure was associated with increased rates of atrial fibrillation (5.7% vs 0.7%). The higher risk of atrial fibrillation was not duplicated in either RESPECT<sup>3</sup> or PC.<sup>4</sup> Though the findings did not reach statistical significance, all 3 randomized clinical trials demonstrated a trend toward increased risk of serious adverse events in the procedural arm compared with medical therapy. It is not known how the risks of closure will compare with medical therapy in actual practice, since randomized clinical trials are generally not powered to detect important harms.

Though without clear benefit in every case, PFO closure may be beneficial for certain patients. Subgroup analysis of the RESPECT trial indicated improved outcomes with PFO closure when atrial septal aneurysm was present and shunt size was substantial.<sup>4</sup> Additionally, current guidelines recommend consideration of PFO closure in 2 circumstances (recommendations classified by the American College of Chest Physicians as grade 2C): recurrent cryptogenic stroke through aspirin therapy and cryptogenic stroke in the setting of both PFO and DVT.<sup>5</sup>

The role of PFO in cryptogenic stroke remains unclear. Existing evidence does not show a clear benefit in recurrent CVA prevention with PFO closure compared with medical therapy alone. Additional randomized trials currently ongoing may be able to more definitively answer this question through pooled meta-analysis, and they might better identify high-risk patients most likely to derive benefit from closure.

The perils associated with PFO closure, while uncommon, can be serious and may well outweigh the benefits of closure in many patients. Our patient decided to pursue closure despite knowing that there is no research showing definitive decreased recurrent

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stroke risk. He desired to do “everything possible to stay alive” and concluded that the risks of the procedure were minimal. It is imperative that physicians present to their patients the growing

body of evidence, including the uncertainty of clinical effectiveness of PFO closure, to engage them in shared decision making and prevent preference misdiagnosis.

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