Tipping Point for Patent Foramen Ovale Closure

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On the basis of what I had read previously in the Journal, I recently explained to my 44-year-old patient that closing his patent foramen ovale (PFO) after his stroke was not advisable. How can we now have three trials showing that closure prevents recurrent stroke, given that in the past 5 years, the Journal published articles from three other trials that showed the opposite? It would be simple if the conversion from a negative to a positive outlook with respect to PFO closure could be explained by studying the various antiplatelet and anticoagulant treatments, or the various durations of follow-up among the trials, or the tyranny of a P value of 0.05, as discussed previously by other editorialists, but I found it futile to discover the answer in these details.

I will review the history; a tabular summary is also provided as a scorecard to assist in following the trail of trials and their names (Table 1). It begins with the CLOSURE I trial in 2012; the findings were flatly negative but, as pointed out by an editorialist, the trial had entry criteria that allowed inclusion of patients who had had strokes such as lacunes that would not benefit from PFO closure. The extended follow-up of the RESPECT trial, reported in this issue of the Journal, is the most provocative of the trials with positive results because it serves as its own control, in that the entry criteria and treatments were the same as those of the original trial; the main difference was that the median duration of follow-up was 2.1 years in the original trial and 5.9 years in the extended follow-up. During that interval of follow-up, the number of patients who had a stroke increased from 9 to 18 in the PFO closure group and from 16 to 28 in the medical-therapy group (P = 0.046 for the difference between the treatment groups at the extended follow-up time point); note that there was a higher percentage of patients in the medical-therapy group than in the PFO closure group who withdrew from the trial before completion of the extended follow-up period. However, the longer duration of follow-up alone is probably not the reason for a change from negative to positive results, as evidenced by the PC trial, in which findings were again emphatically negative despite a mean duration of follow-up of 4 years.

A hint to explaining the discrepancies in results among the trials may be the stringent entry criteria in the CLOSE trial, the results of which are also reported in this issue of the Journal, which required that patients have a large interatrial shunt at rest (more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium) or an atrial septal aneurysm (a septum primum excursion greater than 10 mm). Although the rates of stroke in the PFO closure groups of all six PFO trials were low (generally less than 5%), in the CLOSE trial, no patient in the PFO closure group had a stroke, whereas stroke occurred in 6% of the patients in the antiplatelet-only group. The Gore REDUCE trial, a trial with positive results that are also reported in this issue of the Journal, represented a middle ground by including patients with a moderate-to-large interatrial shunt but not requiring that patients have an atrial septal aneurysm (approximately 20% of the patients in the PFO closure group were found to have one at the time of the procedure). Therefore, in patients who have had a stroke, are...
younger than 60 years of age, and have a PFO with characteristics that are highly likely to allow paradoxical embolism to occur, the effect of closure becomes persuasive.

An adjoining problem is the ill-defined and ill-used term “cryptogenic stroke.” In most trials, this term has been defined by the absence of an overt source of stroke. Hart and colleagues refined the definition by adding a category of strokes that they termed “embolic stroke of undetermined source” and described as “...a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources ...” — a category that is also defined by what is not found in the workup of stroke. A useful scale has been developed to estimate the likelihood that PFO is the cause of cryptogenic stroke on the basis of age and the presence of a cortical stroke on brain imaging, and again, on the basis of the absence of risk factors for atherosclerosis and the absence of a history of stroke or transient ischemic attack.

### Table 1. Six Trials of Patent Foramen Ovale Closure for Stroke with Results Published in the Journal:*,

<table>
<thead>
<tr>
<th>Trial Name (Year of Publication)</th>
<th>No. of Patients</th>
<th>Mean or Median No. of Years of Follow-up</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Hazard Ratio†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials with negative findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOSURE I (2012)*</td>
<td>909</td>
<td>2</td>
<td>Antiplatelet therapy, warfarin, or both</td>
<td>Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization</td>
<td>0.78</td>
<td>0.37</td>
</tr>
<tr>
<td>PC (2013)**</td>
<td>414</td>
<td>4.1 (PFO closure group), 4.0 (medical-therapy group)</td>
<td>Antiplatelet therapy or anticoagulation‡</td>
<td>Composite of death, stroke, transient ischemic attack, or peripheral embolism</td>
<td>0.63</td>
<td>0.34</td>
</tr>
<tr>
<td>RESPECT (2013)**</td>
<td>980</td>
<td>2.1</td>
<td>Antiplatelet therapy or warfarin</td>
<td>Composite of recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization</td>
<td>0.49</td>
<td>0.08</td>
</tr>
<tr>
<td>Trials with positive findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gore REDUCE (2017)†</td>
<td>664</td>
<td>3.2</td>
<td>Antiplatelet therapy</td>
<td>Ischemic stroke and new brain infarction on imaging</td>
<td>0.23</td>
<td>0.002</td>
</tr>
<tr>
<td>CLOSE (2017)⁴</td>
<td>663</td>
<td>5.3</td>
<td>Antiplatelet therapy or anticoagulation‡</td>
<td>Stroke</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RESPECT extended follow-up (2017)⁷</td>
<td>980</td>
<td>5.9</td>
<td>Antiplatelet therapy or warfarin</td>
<td>Composite of recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization</td>
<td>0.55</td>
<td>0.046</td>
</tr>
</tbody>
</table>

* CLOSURE denotes Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence, 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, Gore REDUCE Gore HELEX Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO), PC Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism, and RESPECT Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

† The hazard ratio and P value are for the expected probability of stroke or other primary outcome after closure of the PFO versus medical treatment in the intention-to-treat analysis.

‡ Anticoagulation refers to any form of anticoagulation.
The evidence for causation of embolic stroke in any given person is, of course, circumstantial (e.g., atrial fibrillation or carotid stenosis), and it seems reasonable that the presence of a PFO and a sizable interatrial shunt should similarly no longer result in the categorization of a stroke as cryptogenic. One conclusion from the six trials described above is that the potential benefit from closure is determined on the basis of the positive characteristics of the PFO rather than on the basis of exclusionary factors that make a stroke cryptogenic. Restricting PFO closure entirely to patients with high-risk characteristics of the PFO may perhaps be too conservative, but the boundaries of the features that support the procedure are becoming clearer.

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