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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Device Closure of Patent Foramen Ovale for Cryptogenic Stroke: Patient Selection and Outcomes According to New Randomized Trials

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Abstract

Purpose of Review This review summarizes the most recent randomized clinical trials that studied the role of device-mediated patent foramen ovale (PFO) closure in patients after an ischemic stroke presumed to have been caused by a paradoxical embolism.

Recent Findings Three major randomized trials published in 2017 studied the strategy of using PFO closure for secondary prevention in patients between the ages of 18 and 60 who presented with an index stroke having characteristics of an embolic mechanism. All patients had a PFO that potentially could have enabled paradoxical embolism and other causes of stroke were excluded by a thorough neurologic and cardiac evaluation. Patients were randomized to PFO closure versus medical therapy alone using a variety of guideline-recommended medications. After multiple years of follow-up, all three trials showed superiority in the device arm versus the medical arm with a relative risk reduction of recurrent stroke from 46 to 100% and an absolute recurrent stroke reduction from 0.49 to 1.32% per year. Complications related to the procedure and the device were infrequent and mostly transient.

Summary These results have transformed the care of these patients, lead to FDA approval of two PFO closure devices, and started the process of updating guidelines. Patient selection is critically important since the presence of a PFO may be incidental. Therefore, both a neurologist and a cardiologist, who can also perform this procedure safely and effectively, should complete the initial evaluation and discuss their findings and recommendations with the patient as part of a shared decision-making process. There are remaining questions regarding how these trial results relate to older patients, patients with overt venothrombotic disease, and those with thrombophilia.

Keywords Patent foramen ovale · Stroke · Paradoxical embolism · Septal closure · Clinical trials · Atrial septal aneurysm

Introduction

The mechanism of stroke is unknown, i.e., cryptogenic, in many patients who are less than 60 years old at the time of their index stroke. After the observation that 40–50% of these patients have a patent foramen ovale, a hypothesis of pathophysiology was advanced that some patients with a cryptogenic stroke may, in fact, have had a stroke from a paradoxical embolic mechanism [1]. Unfortunately, there is no clear test or quantitative measurement that can be used to prove an enabling role of the PFO, the transient travels of an embolism, and an ischemic stroke that was due to an embolism lodged in a cerebral artery that passed through a PFO: it is the very rare patient who has echocardiographic visualization of an embolism passing through or attached to a PFO although findings during the initial stroke evaluation may suggest an embolism (Fig. 1). The second hypothesis that formed the basis of multiple randomized trials was that closure of the PFO with a medical device would eliminate this mechanism for recurrent stroke and could be more effective than taking life-long medications that have been previously shown to reduce the risk of recurrent stroke. PFO closure was therefore proposed as a targeted therapy and several PFO closure devices and delivery

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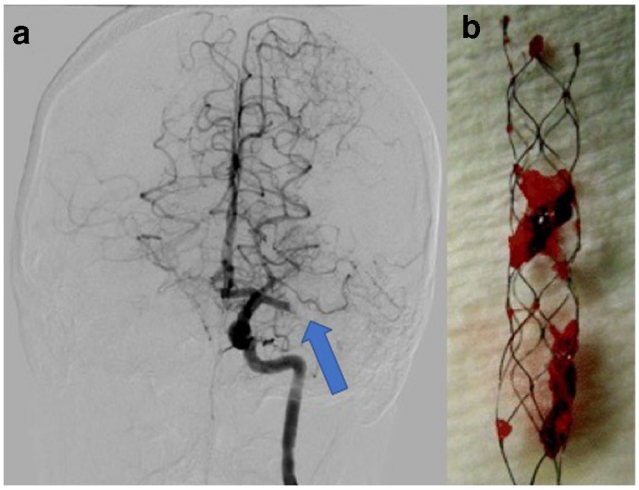

Fig. 1 **a** Cerebral angiogram from a young patient with an acute ischemic stroke reveals a cut-off (blue arrow) at the middle cerebral artery. **b** A retrieved thrombus caused dramatic improvement in stroke symptoms. Subsequently, the cause of the thrombotic occlusion was felt to be related to a paradoxical embolism thru a patent foramen ovale

systems were developed and then used in randomized clinical trials.

There were multiple challenges in designing and completing these clinical trials. There are multiple potential etiologies of ischemic stroke and neurologists often have a difficult time in ascertaining the cause of the stroke. Furthermore, a PFO is assumed to be an innocent remnant of the fetal circulation and population-based studies have not found it to be a stroke risk factor. Indeed, the presence of a PFO is frequently an incidental finding and is present in 25% of the general population [2].

For over a decade, the evidence had been observational. In 2012 and 2013, three initial trials of PFO closure were published in the New England Journal of Medicine, and they all missed their primary outcome. Based on those studies, it appeared that PFO closure did not have a role in secondary prevention [1, 3, 4].

There were important lessons learned from these three initial trials despite their negative findings. The trials had been underpowered and needed longer follow-up or more sensitive means of detecting recurrent strokes that may be clinically silent such as with brain NM imaging. Some PFO closure devices were safer and more effective in causing closure than others. Determining the ideal medical management comparison was also a vital lesson; PFO closure should be first compared to antiplatelet therapy, which had become the guideline-recommended therapy for preventing recurrent cryptogenic stroke.

There have been multiple observational trials and several initial randomized trials that were completed before the more recent trials. These and more recent trials are reviewed as well as other important topics in two recent comprehensive reviews [5, 6].

Recent Clinical Trials

Prior to 2017, other clinical trials of PFO closure had been reported and have been previously reviewed and incorporated into meta-analyses. Indeed, several of these clinical trials, particularly the RESPECT trials had results that strongly suggested that PFO closure was effective and safe in preventing recurrent stroke, and therefore the sponsor allowed continued follow-up of patients in this largest of all PFO closure trials.

RESPECT–long term was a medical device company sponsored trial performed at 69 sites in the USA and Canada. It was the largest trial enrolling 980 patients with a mean follow-up duration of 5.9 years. Patients randomized to the device arm received the Amplatzer PFO occluder and those randomized to the medical arm received any of five guideline-recommended medication regimens [7••].

The REDUCE trial was a medical device company sponsored trial performed at 63 sites in the Scandinavian countries, UK, USA, and Canada. It enrolled 664 patients with a mean follow-up duration of 3.5 years in the device arm and 3.2 years in the medical arm. Patients randomized to the device arm received the Gore Helex or Cardiform device and those randomized to the medical arm received antiplatelet therapy [8••].

The CLOSE trial was a French Ministry of Health-sponsored trial performed at 34 sites in France and Germany. It enrolled 664 patients in three arms with 238 patients in the device arm (using any available PFO device), 235 in an antiplatelet medication arm, and 187 in an anticoagulation arm that stopped before enrollment was complete. The mean follow-up duration was 5.4 years in the device arm and 5.2 years in the antiplatelet medical arm [9••].

In Table 1, the major patient characteristics are presented for the three trials. It is important to note the small but important difference in patients' characteristics among the three trials that was likely a major determinate for the variations among the three trials of treatment effect.

In Table 2, the procedural results and complications are presented for the three most recent trials (Fig. 2). PFO closure was successful in a very high percentage of patients in the device arm and major serious adverse events were low. There were no deaths in the trials that were felt to be related to the procedure, device, or enrollment in the study. Likewise, there were only two ischemic strokes adjudicated as being procedure or device related and these were in the 6-month window post-procedure that mandated classification as procedure related. Not shown in the table are the atrial fibrillation events occurring in the medical arm. In the RESPECT trial, there was no difference in atrial fibrillation rates post-procedure (i.e., not transient peri-procedure events) versus atrial fibrillation in the medical arm. Two of the recurrent strokes in the medical arm of RESPECT were in patients who developed atrial fibrillation. It should also be noted that the trials were conducted before the advent of long-term

Table 1 Patient characteristics from three recent randomized trials

Patient characteristics	RESPECT long term	REDUCE	CLOSE
Age (years, mean)	46.0	45.1	43.4
Sex (males, %)	54.7%	60.6%	59%
Systemic hypertension (%)	32%	25.7%	10.8%
Hypercholesterolemia (%)	39.9%	NA	40.7%
Diabetes mellitus (%)	7.55%	4.30%	2.55%
Smoking (%)	13.2%	12.8%	29.0%
PFO, large shunt (%)	48.8%	40%	92.3%
PFO, atrial septal aneurysm (%)	35.7%	20%	32.8%
Previous stroke (%)	10.6%	12.3%	3.6%

monitoring to exclude occult paroxysmal atrial fibrillation as a possible cause of their index stroke. This is now very important to perform, especially in patients who are at increased risk of atrial fibrillation due to older age, systemic hypertension, and obesity.

In Table 3, the efficacy endpoints of the three trials are presented. These results represent the intention to treat populations. All three trials demonstrated a statistically significant reduction of recurrent ischemic strokes in the device arm. This consistent demonstration of device closure superiority is vital to establish sufficient evidence for potential inclusion in professional society guidelines as a class 1 or 2a indication. The differences in the relative risk reduction in the three trials have several important components to understand. First, the trials enrolled similar patients but the CLOSE trial enrolled patients most likely to benefit from PFO closure in that they had less of a burden of traditional stroke risk factors and all patients had PFOs with a large degree of right to left shunting or the presence of an atrial septal aneurysm. Secondly, in CLOSE and REDUCE, the medication in the medical arm was antiplatelet therapy that provided a greater risk reduction in the device arm than present in RESPECT because approximately 20% of RESPECT patients in the medical arm were on anticoagulation.

Translating Clinical Trial Results to Clinical Practice

There are three important issues related to this topic. The first is the critical process of patient selection and shared decision-making with patients. The second issue is in procedure performance (Fig. 3). Finally, there are many unanswered questions from these clinical trials that need to be explicitly defined.

Table 2 Procedure results and adverse events

	RESPECT long term	REDUCE	CLOSE
Number of patients in device arm	499	441	238
Technical success, %	99.1%	98.8%	99.6%
Completeness of closure	72.2% (effective = 93.5%)	75.6%	(Effective = 93%)
Timing of evaluation of completeness of closure after procedure	6 months	12 months	10.6 months (mean)
Procedure SAE number (%)	2.4%	2.5%	5.9%
Device SAE number (%)	2.0%	1.4%	NA
Major bleeding number (%)	2.6%	1.8%	1%
Tamponade number (%)	0.4%	0%	0%
Device embolization number (%)	0%	3%	0%
Device thrombus number (%)	0%	2%	0%
All atrial fibrillation/flutter number (%)	4.8%	6.6%	4.6%
DVT and PE adjudicated as procedure related	3%	NA	NA

All adverse events were adjudicated by the Data and Safety Monitoring Board of each study

SAE, serious adverse event; DVT, deep venous thrombosis; PE, pulmonary embolism; RESPECT, recurrent stroke therapy comparing; PFO, closure to established current standard of care treatment trial)

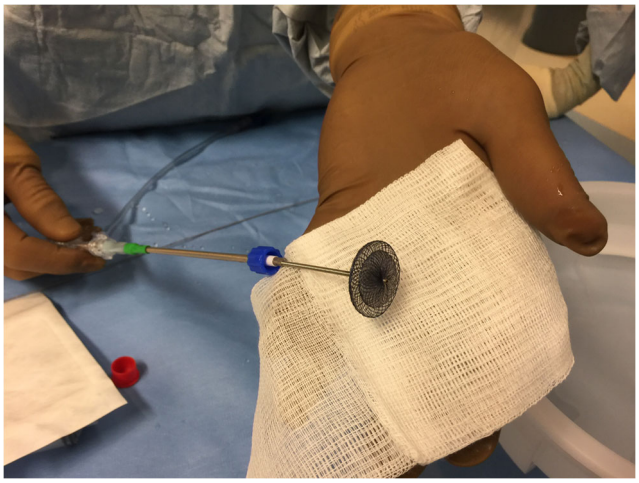

Fig. 2 The preparation of an Amplatzer PFO occluder is shown. Removal of any air in the device and delivery system is key to prevent air embolism during the procedure

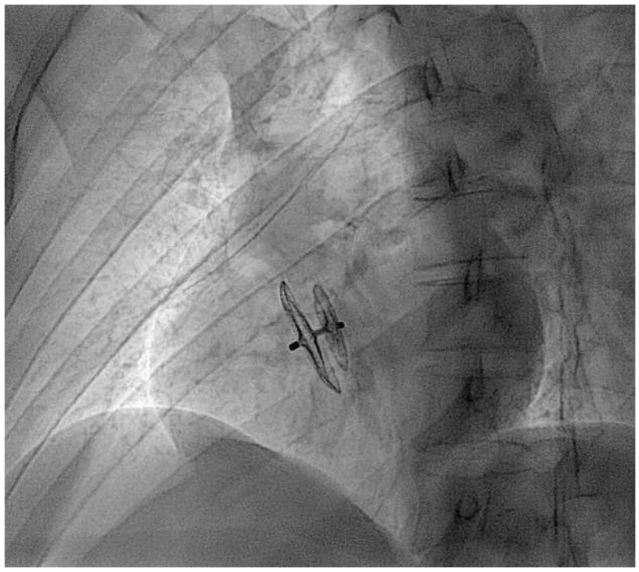

Fig. 3 A lateral X-ray view of an Amplatzer PFO occluder is shown with its larger disc in the right atrium and smaller disc in the left atrium

The trials studied a well-defined group of patients who all underwent an extensive evaluation that allowed them to be diagnosed as having had a cryptogenic stroke. This is key in practice settings and the evaluation by a neurologist provides the greatest likelihood of optimizing this aspect of patient selection. In a study of patients evaluated for PFO closure in a multidisciplinary clinic in Sweden, a significant proportion of the patients were not felt to be appropriate for PFO closure [10]. Our experience in our PFO clinic is similar with approximately 50% of patients found to have other explanations for their neurological symptoms. As a practical tip, it is useful to assess whether a patient being evaluated could have been enrolled in these trials. If they did not meet all inclusion criteria or had any exclusion, then there is a need to understand how applicable these clinical trial results are to the expected safety and efficacy of PFO closure. Finally, a PFO may be an incidental finding in a patient with stroke. A scoring system based on patient and stroke characteristics that can be used to assess the probability that a stroke is PFO related is the ROPE score [11]. It is, however, important to note that it has not been prospectively validated.

Patients need to be completely evaluated, and then the neurologist and cardiologist should provide their recommendations (Fig. 4). Patients and families need to be informed of the risks and potential benefits of the procedure, as well as whether the treatment effect for them is expected to be more or less than that seen in the clinical trials. Finally, they need to incorporate their treatment and management preferences.

The unanswered questions from these trials are important and relevant to many patients seen in practice. First, patients over the age of 60 were not studied in these trials because the majority of strokes in an older population are due to traditional risk factors. An individualized approach to evaluating patients over 60 is important, and it will be a small percentage of these patients who might be considered for PFO closure. In the RESPECT trial, those patients who had a recurrent ischemic stroke after they had become over 60 generally had an identifiable cause of the stroke that was not PFO related.

The trials have not provided a definitive answer to whether PFO closure is superior to anticoagulation with either vitamin

Table 3 Primary endpoint (all ischemic strokes) of three trials

	RESPECT long-term		REDUCE		CLOSE	
	Device arm	Medical arm	Device arm	Medical arm	Device arm	Medical arm*
Events/randomized patients	18/499	28/481	6/441	12/223	0/238	14/235
Event rates per 100 patient-years	0.32	0.86	NA	NA	NA	NA
Recurrent stroke risk reduction	62%		NA		NA	
Hazard ratio (95% confidence limits) and *P* value	0.38 (0.18–0.79)		NA		NA	
Number needed to treat in 5 years	42		25		20	
Recurrent stroke rate at 5 years	2.6%	5.0%	1.4%	5.4%	0%	5.0%

*Results for CLOSE trial are for the antiplatelet medical arm

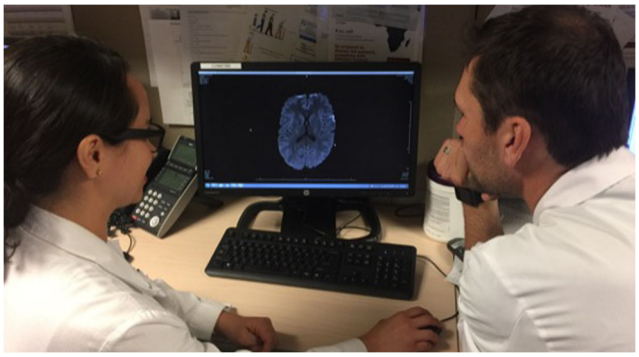

Fig. 4 The clinical trials required that patients were evaluated by both a stroke or vascular neurologist (left in picture) and interventional cardiologist (right in picture). Brain imaging was required and provided evidence of a likely embolic nature of the stroke

K antagonists or direct thrombin inhibitors. In addition, patients with active venothromboembolic disease (i.e., deep vein thrombosis and pulmonary embolism) have not been studied. The impact of thrombophilia was also not studied.

PFO closure has been shown to be an effective and relatively safe secondary prevention strategy, and there are no trials addressing its possible role in primary prevention. A clinical trial to study this question will be very challenging since 25% of the general population has a PFO and population-based studies have failed to show having a PFO is a stroke risk factor.

PFO Closure Prevents One Mechanism of Stroke

After PFO closure, it is problematic to say a person is "cured" of ever having another stroke. First, the assessment of their initial stroke as being from a paradoxical embolism is a clinical judgment and presumptive. Second, as patients age, strokes may occur from other mechanisms and this was seen in these trials. Therefore, patients need advice and treatment to reduce all other stroke risk factors such as treating systemic hypertension. Relevant to this point is that those treated with a device in these trials were generally all treated with antiplatelet therapy usually with low-dose aspirin long term.

Conclusions

The role of PFO closure as a targeted secondary prevention strategy following an ischemic stroke is now clearly established with its treatment benefit and the risks of the procedure well understood in a carefully defined patient population. PFO closure now needs to be well integrated into clinical practice where appropriate use is key to treating the right patient. Patient evaluation and clinical practice should be multidisciplinary and is highly nuanced requiring the integration of clinical data, brain imaging, and cardiac evaluation. Many important issues are not yet resolved but the lessons learned from the past decade provide clinicians and patients with a solid background and understanding of this novel therapy.

Compliance with Ethical Standards

Conflict of Interest John D. Carroll has served on the national steering committee of the RESPECT trial and has received payments for activities related to the work performed by the steering committee. These payments were from the study sponsors over the duration of the trial including AGA Medical, St. Jude Medical, and Abbott Vascular.

Adam M. Carroll declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent All procedures performed in the RESPECT trial involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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