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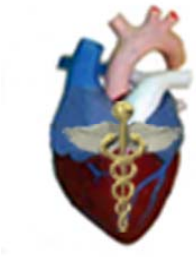

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EDITORIAL

Percutaneous Closure of Patent Foramen Ovale for Cryptogenic Stroke: The Issue is Finally Settled

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Abstract

Based on newer data from randomized controlled trials and meta-analyses, the previously controversial and highly debated issue of patent foramen ovale (PFO) closure in patients with cryptogenic stroke is finally settled in favor of closure over medical therapy for the secondary prevention of cryptogenic stroke attributable to paradoxical embolism. One PFO closure device has finally received FDA approval in October 2016.
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Key Words: cryptogenic stroke; paradoxical embolism; patent foramen ovale; percutaneous closure

Abbreviations: PFO = patent foramen ovale; RCT=randomized controlled trial; RoPe = risk of paradoxical embolism

PFO / Initial PFO Closure RCTs

It is estimated that every 1 in 4 individuals in the general population has a patent foramen ovale (PFO), [1, 2] which by itself does not increase the risk of ischemic stroke; [3] however, PFO is more prevalent among patients who have suffered a cryptogenic ischemic stroke, particularly among younger patients. [4] Although thrombi have been caught in the act with imaging techniques depicting them in transit through a PFO, [5, 6] the clinical benefit of percutaneous closure of a PFO after a cryptogenic stroke has been debated for the last two decades.[7, 8] The first three randomized controlled trials (RCTs) were finally and belatedly published (CLOSURE I, PC-Trial, RESPECT), but were not definitively conclusive. [9-12] The extended follow-up of the RESPECT trial, however, provided the data that the FDA demanded. [13]

FDA Approval /Newer Data

On October 28, 2016, the FDA of the U.S. granted approval for the Amplatzer PFO occluder for patients with cryptogenic stroke which is determined to have been probably caused by a paradoxical embolism (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm527096.htm). This decision was based, as already mentioned, on the extended follow-up (median 5.9 years) of the RESPECT RCT which evaluated 499 participants aged 18 to 60 years old who were treated with the Amplatzer PFO Occluder plus antithrombotic medications compared to 481 participants who were treated with antithrombotic drugs alone (Table 1). [13] While the rate of new strokes in both treatment groups was very low, the study found a 45% reduction in the rate of new strokes in

participants using the Amplatzer PFO Occluder compared to participants taking only antithrombotic medications (recurrent ischemic stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, resulting in rates of 0.58 events per 100 patient-years and 1.07 events per 100 patient- years, respectively; hazard ratio-HR with PFO closure vs medical therapy, 0.55; P = 0.046 by the log-rank test). Recurrent ischemic stroke of undetermined cause occurred in 10 patients in the PFO closure group and in 23 patients in the medical-therapy group (HR 0.38; P=0.007).

In a pooled analysis of the initial 3 RCTs (CLOSURE I, PC-Trial, RESPECT) employing 2 devices (STARFlex, NMT Medical, Inc., Boston, Massachusetts; and Amplatzer PFO Occluder, AGA Medical/St. Jude Medical, St. Paul, Minnesota) in 2,303 patients, closure was not significantly associated with the primary composite outcome (stroke, TIA, or death). [14] The difference became significant after covariate adjustment (HR: 0.68; p=0.049). For the outcome of stroke, all comparisons were statistically significant, with unadjusted and adjusted HRs of 0.58 (p = 0.043) and 0.58 (p = 0.044), respectively. In analyses limited to the 2-disc occluder device trials, the effect of closure was not significant for the composite outcome, but was for the stroke outcome (unadjusted HR: 0.39; p = 0.013). Atrial fibrillation (AF) was more common among closure patients. The authors concluded that among patients with PFO and cryptogenic stroke, closure reduced recurrent stroke and had a statistically significant effect on the composite of stroke, transient ischemic attack, and death in adjusted but not unadjusted analyses.

Recent RCTs

In 2017, the results of two additional RCTs were reported (Table 1). [15, 16] The CLOSE trial (2017), included 663 patients aged 16 - 60 years who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, randomized to transcatheter PFO closure plus long-term antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group) (randomization group 1). [15] Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative non-contraindicated treatment or to antiplatelet therapy (randomization groups 2 and 3). The primary outcome was occurrence of stroke. Over a mean of 5.3±2.0 years, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet- only group (hazard ratio, 0.03; P<0.001). Procedural complications from PFO closure occurred in 14 patients (5.9%). The rate of AF was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%, P = 0.02). The number of serious adverse events did not differ significantly between the treatment groups (P = 0.56). In the analysis of randomization groups 1 and 3, stroke occurred in 3 of 187 patients assigned to oral anticoagulants and in 7 of 174 patients assigned to antiplatelet therapy alone. The authors concluded that among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone.

The REDUCE trial (2017) enrolled 664 patients (mean age 45.2 years) with cryptogenic stroke, of whom 81% had moderate or large interatrial shunts. [16] Over a median of 3.2 years, ischemic stroke occurred in 6 of 441 patients (1.4%) in the PFO closure group and in 12 of 223 patients (5.4%) in the antiplatelet-only group (hazard ratio, 0.23; P = 0.002). The incidence of new brain infarctions was lower in the PFO closure group than in the antiplatelet-only group (22 patients or 5.7% vs 20 patients or 11.3%; relative risk 0.51; P=0.04), but the incidence of silent brain infarction did not differ significantly between the study groups (P = NS). Serious adverse events occurred in 23.1% in the PFO closure group and in 27.8% in the antiplatelet-only group (P=0.22). Serious device-related adverse events occurred in 6 patients (1.4%) in the PFO closure group, and AF occurred in 29 patients (6.6%) after PFO closure.

Updated Meta-Analysis

A recent updated meta-analysis comprising all 5 RCTs (n = 3,440; mean follow-up 2.9 years) indicated that, compared with medical therapy, risk of recurrent stroke was lower with closure (2.2% vs 4%; RR: 0.54; I^2 = 41%; p = 0.02). [17] Atrial fibrillation risk was higher with closure (4% vs 0.7%; RR: 4.60; I^2 = 28%; p < 0.01). Risk of AF was not different with the Amplatzer PFO occluder (Abbott, Chicago, Illinois) (RR: 2.29; I^2 =0%; p = 0.64) but was significant with the STARFlex (NMT Medical, Boston, Massachusetts) (RR: 7.92; p < 0.01) and Gore (W. L. Gore & Associates, Flagstaff, Arizona) (RR 14.66; p < 0.01) devices. There was no publication bias for both primary outcomes (p = 0.11 and p = 0.14, respectively).

Procedure of PFO Closure

The procedure of PFO closure is relatively simple and in experienced hands it could be performed even without transesophageal echocardiography (TEE) guidance or use of general anesthesia, using only local anesthesia and fluoroscopy guidance.[18, 19] A shared decision-making approach with involvement of patient and patient's family appears to be the most appropriate strategy to follow.

Conclusion

The accumulated evidence is now compelling for the benefit and superiority of PFO closure over medical therapy in patients with cryptogenic strokes for the secondary prevention of stroke. FDA granted approval in 2016 for one type of such closure device to be employed for these procedures and thus it behooves us to apply this therapeutic modality in the most appropriate and prudent strategy in the management of patients with cryptogenic strokes which are deemed secondary to paradoxical embolism. Selecting the appropriate patient is of paramount importance, since there are several competing potential causes of stroke, [20] and only those related to paradoxical embolism are amenable to PFO closure. Risk scores have been proposed which may identify patients with probable paradoxical embolism (e.g. RoPE: risk of paradoxical embolism) and enable the selection of those with a high attributable recurrence risk especially likely to benefit from PFO closure. [21]

Table 1. Studies Supporting PFO Closure over Medical Therapy for Cryptogenic Stroke

Study/Year	Type / Device	No of patients	Outcome
RESPECT, extended / 2016 [13]	RCT / AMPLATZER	980	↓strokes by 45% / NNT: 42 by 5 years
Pooled analysis (3 RCTs)/ 2016 [14]	Pooled analysis / STARFLEX & AMPLATZER	2303	↓strokes by 42%
CLOSE / 2017 [15]	RCT / 11 different devices	663	↓strokes by 99.7% / NNT: 20 by 5 years
REDUCE / 2017 [16]	RCT / HELEX or GORE	664	↓strokes by 77% / NNT: 29 by 2 years
Meta-analysis (5 RCTs) / 2017 [17]	Meta-analysis / Several	3440	↓strokes by 46%

NNT = number needed to treat; PFO = patent foramen ovale; RCTs = randomized controlled trials

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