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Transcatheter Patent Foramen Ovale Closure After Cryptogenic Stroke An Updated Meta-Analysis of Randomized Trials

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time were 108.0 and 19.2 min, respectively. The median diameter of the PmVSDs was 4.24 mm (interquartile range: 3.31 to 5.0 mm). Only 2 patients (1.9%) in the PmVSD cohort had mean pulmonary arterial pressures >25 mm Hg. Clinical characteristics, hemodynamic status, and procedural data are summarized in **Table 1**, on the basis of the subtypes of PmVSD. No mortality was noted. Of the 105 attempts, 5 (4.8%; 4 with perimembranous trabecular-type VSDs) were abandoned after diagnostic catheterization for various reasons (details not shown here). The shape of the VSD was conical in 49 patients (perimembranous trabecular type, 42 patients) and tubular in 51 patients. The median ratio of pulmonary to systemic blood flow and device size implanted were 1.36 and 6 mm, respectively. The median aortic rim was 1.2 mm. Before closure, 72 patients had prolapsed aortic cusp, and 27 had mild or mild to moderate degrees of AR. None of them experienced new-onset AR, except for 1 18-year-old female patient who had a history of infective endocarditis before her VSD closure (**Online Figure 3**). None of patients had worsening tricuspid regurgitation after VSD closure. The 1-month, 6-month, 1-year, and 2-year probabilities of a persistent small residual VSD shunts were 8.7%, 7.2%, 5.9%, and 4.5%, respectively. No mortality or atrioventricular block was reported. One major adverse event was observed in a 15-year-old girl who had an episode of arteriovenous malformation-associated left frontal lobe intracranial hemorrhage 5 months after her transcatheter closure.

To the best of our knowledge, the present study is the first to enroll a large number of patients with PmVSDs and prolapsed aortic valves (72%) or mild AR (27%). Our results included a 100% success rate, no noted atrioventricular blocks, and the development of new-onset mild AR in only 1% of patients. These excellent results might be attributable to the use of a softer device and the conservative size of the device (**Online Figures 3 and 4**).

Traditionally, aortic cusp prolapse has been considered a contraindication to the device closure of PmVSDs because of concerns regarding the worsening of AR (2). In our present cohort, mild and moderate aortic prolapse was noted in 64 and 8 patients, respectively. Although none of them experienced new-onset AR or AR progression during the average 2-year follow-up period, the long-term feasibility of transcatheter closure with duct occluders for the subgroup of patients with PmVSD should be further validated in the future.

The results of surgical VSD repair have been consistently excellent for many years, with percentages of 1-year post-operative residual VSD leakage approaching 1% at many medical centers (1,2). In this

study, we used ADOs, which have less polyester material and may have resulted in slightly delayed complete VSD closure (1-month residual shunt rate 7.2%). How to reduce the risk for residual VSD jets after transcatheter closure remains an important issue.

We demonstrated feasible mid-term results of transcatheter VSD closure in selected patient populations. With a conservative approach, the transcatheter closure of VSDs with ADOs may provide an alternative to open heart surgery.

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APPENDIX For supplemental figures and their legends and a table, please see the online version of this article.

RESEARCH CORRESPONDENCE

Transcatheter Patent Foramen Ovale Closure After Cryptogenic Stroke

An Updated Meta-Analysis of Randomized Trials

Paradoxical embolism from a patent foramen ovale (PFO) mediated right-to-left shunt is a well-described mechanism of ischemic stroke (1). In a patient level



meta-analysis of the earlier 3 randomized trials, percutaneous PFO closure was superior to medical therapy for secondary prevention of cryptogenic stroke, especially in patients with a large shunt or atrial septal aneurysm (2). Recently, the extended follow-up results of the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial (3) and 2 new randomized trials were presented. We performed an updated meta-analysis to evaluate the efficacy and safety of transcatheter PFO closure versus medical therapy for cryptogenic stroke (PROSPERO [International prospective register of systematic reviews] #CRD42017067347).

Electronic databases and scientific conferences were searched for clinical trials that randomized patients with cryptogenic stroke to percutaneous PFO closure versus medical therapy. Two authors (A.Y.E. and I.Y.E.) extracted data on patient characteristics and outcomes at the longest follow-up available. Primary efficacy outcome was recurrent stroke and primary safety endpoint was atrial fibrillation/flutter (AF). Random-effects risk ratios (RRs) were estimated using a DerSimonian and Laird method. Heterogeneity was calculated using the I^2 test and publication bias using Egger's test. Statistical analyses were conducted using STATA 14 (StataCorp, College Station, Texas).

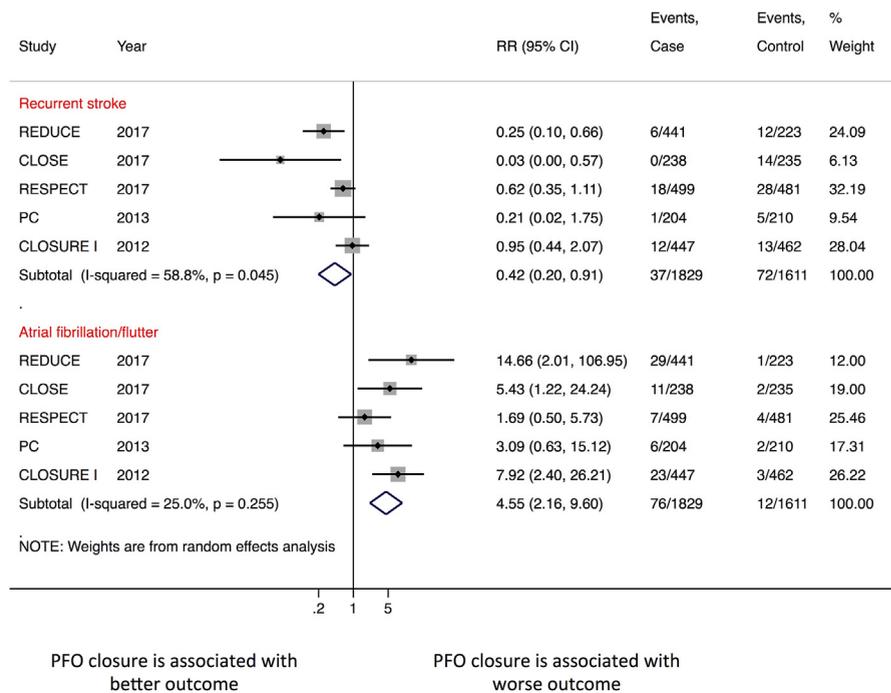
Five trials ($n = 3,440$; mean follow-up 2.9 years) were included. Compared with medical therapy, risk of recurrent stroke was lower with closure (2.0% vs. 4.5%; RR: 0.42; 95% confidence interval [CI]: 0.20 to 0.91; $I^2 = 59\%$; $p = 0.027$). AF risk was higher with closure (4.0% vs. 0.7%; RR: 4.55; 95% CI: 2.16 to 9.60; $I^2 = 25\%$, $p < 0.01$) (Figure 1). Risk of AF was not different with the Amplatzer PFO occluder (Abbott, Chicago, Illinois) (RR: 2.10; 95% CI: 0.80 to 5.56, $I^2 = 0\%$; $p = 0.13$) but was significant with the STARFlex (NMT Medical, Boston Massachusetts) (RR: 7.92; 95% CI: 2.40 to 26.21; $p < 0.01$) and Gore (W.L. Gore & Associates, Flagstaff, Arizona) (RR: 14.66; 95% CI: 2.01 to 106.95; $p < 0.01$) devices. There was no publication bias for both primary outcomes ($p = 0.11$ and $p = 0.14$, respectively).

This updated meta-analysis of 5 multicenter trials demonstrated that in patients with cryptogenic stroke and a PFO, transcatheter closure is superior to medical therapy for secondary prevention of stroke. All included trials suggested that closure is associated with a lower incidence of recurrent stroke except for the 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) trial. The lack of efficacy observed in the CLOSURE I trial has often been attributed to suboptimal effective PFO closure in the device arm, with 14% demonstrating significant residual right-to-left shunting on a 6-month follow-up transesophageal echocardiography (4). The STARFlex device has been associated with more AF and thrombogenesis compared with other devices (5). A patient-level analysis of the CLOSURE I, PC (Percutaneous Closure of PFO Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism), and RESPECT trials demonstrated that transcatheter PFO closure was superior to medical therapy (2), which was further confirmed in this meta-analysis. The enhanced efficacy in the CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) and Gore-REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients With PFO) trials is a reflection of more strict patient selection. The Gore-REDUCE trial had strong exclusion criteria to omit patients with other sources of stroke including AF, coronary disease, or small vessel disease; the CLOSE trial only included those with an atrial septal aneurysm or large shunt.

Although this meta-analysis also demonstrated that AF occurs more frequently with PFO closure, the exact clinical implications of periprocedural AF remains uncertain. Post-implant AF usually occurs early (within 6 months), with almost one-half of these reported as a single paroxysm that resolves spontaneously or with cardioversion; only 3.8% of all post-closure AFs are reported to progress to permanent AF (5). The extended follow-up data from the RESPECT (median 5.9 years) trial continued to show superiority of PFO closure compared with medical therapy despite a higher incidence of AF in the device arm (3).

Risk of major bleeding was similar in the patient-level analysis of the earlier 3 trials and in the newer trials (2,3). Based on this meta-analysis, percutaneous closure should be the treatment of choice in cryptogenic ischemic stroke patients who have a PFO, after aggressive exclusion of other causes of stroke. Patients at high risk of recurrent stroke (i.e., presence of atrial septal aneurysm or a large shunt) receive the greatest benefit from closure. Future guidelines may recommend closure as first line therapy, at least for the subset of patients at highest risk of recurrent paradoxical embolism. However, risk of post-closure AF is relatively high as demonstrated by this

FIGURE 1 Outcomes of Recurrent Stroke and Atrial Fibrillation in Cryptogenic Stroke Patients Randomized to PFO Closure or Medical Therapy

Summary plot for the primary efficacy outcome (recurrent stroke) and primary safety outcome (atrial fibrillation). The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; CLOSE = 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; PC = Percutaneous Closure of PFO Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO = patent foramen ovale; REDUCE = Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients With PFO; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; RR = risk ratio.

meta-analysis and the Gore-REDUCE trial; longer-term outcomes of this event are currently unclear.

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Please note: Dr. Meier has served on the Speakers Bureau for and received speaker fees from Abbott; and has served as a primary investigator of the PC trial. Dr. Tobis has served as a consultant for St. Jude Medical and W.L. Gore; as a co-investigator of the RESPECT trial; and as a proctor for Cardiac Dimensions. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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