ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

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ABSTRACT

BACKGROUND

The efficacy of closure of a patent foramen ovale (PFO) in the prevention of recurrent stroke after cryptogenic stroke is uncertain. We investigated the effect of PFO closure combined with antiplatelet therapy versus antiplatelet therapy alone on the risks of recurrent stroke and new brain infarctions.

METHODS

In this multinational trial involving patients with a PFO who had had a cryptogenic stroke, we randomly assigned patients, in a 2:1 ratio, to undergo PFO closure plus antiplatelet therapy (PFO closure group) or to receive antiplatelet therapy alone (antiplatelet-only group). Imaging of the brain was performed at the baseline screening and at 24 months. The coprimary end points were freedom from clinical evidence of ischemic stroke (reported here as the percentage of patients who had a recurrence of stroke) through at least 24 months after randomization and the 24-month incidence of new brain infarction, which was a composite of clinical ischemic stroke or silent brain infarction detected on imaging.

RESULTS

We enrolled 664 patients (mean age, 45.2 years), of whom 81% had moderate or large interatrial shunts. During a median follow-up of 3.2 years, clinical 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; 95% confidence interval [CI], 0.09 to 0.62; P=0.002). The incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group (22 patients [5.7%] vs. 20 patients [11.3%]; relative risk, 0.51; 95% CI, 0.29 to 0.91; P=0.04), but the incidence of silent brain infarction did not differ significantly between the study groups (P=0.97). Serious adverse events occurred in 23.1% of the patients in the PFO closure group and in 27.8% of the patients 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 atrial fibrillation occurred in 29 patients (6.6%) after PFO closure.

CONCLUSIONS

Among patients with a PFO who had had a cryptogenic stroke, the risk of subsequent ischemic stroke was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone; however, PFO closure was associated with higher rates of device complications and atrial fibrillation. (Funded by W.L. Gore and Associates; Gore REDUCE ClinicalTrials.gov number, NCT00738894.)

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Patent foramen ovale (PFO) is a potential cause of cryptogenic stroke.[1-4] Three previous randomized trials of transcatheter PFO closure did not show a lower risk of recurrent stroke with PFO closure than with medical therapy in their primary intention-to-treat analyses[5-7]; however, secondary analyses suggested a benefit with PFO closure.[8] The goal of the Gore REDUCE Clinical Study was to determine the efficacy and safety of PFO closure (with two versions of a closure device) plus antiplatelet therapy, as compared with antiplatelet therapy alone, for the prevention of recurrent clinical ischemic stroke or new brain infarction in patients with PFO who had had a cryptogenic stroke.

Methods

Trial Design and Oversight

This was a multinational, prospective, randomized, controlled, open-label trial with blinded adjudication of outcome events. The trial was performed at 63 sites in Canada, Denmark, Finland, Norway, Sweden, the United Kingdom, and the United States (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was approved by the institutional review board or ethics committee at each participating site, and all patients provided written informed consent. The trial protocol and final statistical analysis plan, available with the full text of this article at NEJM.org, were designed by the authors in collaboration with the sponsor (W.L. Gore and Associates) and in consultation with the Food and Drug Administration (FDA). The steering committee selected the sites and investigators, assisted the site investigators in assessments of potential eligibility of patients, and communicated with site investigators about the recruitment and retention of patients in the trial. The sponsor was responsible for data management and provided the statistician. The authors were unaware of the study-group assignments and aggregated end-point events throughout the trial, had unrestricted access to the data at the completion of the primary end-point analysis, reviewed the analysis with the trial statistician, and wrote all versions of the manuscript. The sponsor had no role in the writing or approval of the manuscript or in the decision to submit the manuscript for publication but assisted in the creation of the figures and was given the opportunity to review the manuscript. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. Devices and implantation procedures were generally paid for by the patient's insurance or the National Health Service (for the patients from countries other than the United States). In cases in which this was not possible, the sponsor reimbursed the participating site for these costs.

Patient Selection

Patients were eligible if they were 18 to 59 years of age, had had a cryptogenic ischemic stroke within 180 days before randomization, and had a PFO with a right-to-left shunt, as described below. An ischemic stroke was defined as an acute focal neurologic deficit, presumably due to ischemia, that either resulted in clinical symptoms lasting 24 hours or more or was associated with evidence of relevant infarction on magnetic resonance imaging (MRI) or — if MRI could not be performed — computed tomography (CT) of the brain. The index stroke was defined as cryptogenic after other identifiable mechanisms of stroke were ruled out, such as large-artery atherosclerotic disease, established cardioembolic source, small-vessel occlusive disease (lacunar stroke), hypercoagulable disorder requiring anticoagulation, or arterial dissection. To assess whether large-artery atherosclerotic disease was a potential source of stroke, imaging of the intracranial arteries, cervical arteries, and aortic arch was performed in all patients by means of CT angiography, magnetic resonance angiography, ultrasonography, or catheter angiography; patients with stenosis of 50% or more of the diameter of a major vessel or with occlusion of a major vessel were excluded from the trial. Patients were also excluded if they had had a stroke as a result of small-vessel occlusive disease, which was defined as the presence of a small, deep infarction (<1.5 cm in diameter) or a typical clinical lacunar syndrome. Patients were excluded if they had uncontrolled diabetes mellitus, uncontrolled hypertension, autoimmune disease, or a recent history of alcohol or drug abuse, or if they had a specific indication for anticoagulation. (Eligibility criteria are listed in Table S3 in the Supplementary Appendix.) Holter monitoring or prolonged monitoring of cardiac rhythm was not a requirement in the trial protocol.

Right-to-left shunting through a PFO was assessed by means of transesophageal echocardiography with agitated saline while the patient was at rest or while a Valsalva maneuver was being performed. The classification of shunt size was based on the maximum number of microbubbles seen in the left atrium in any single frame during the first three cardiac cycles after detection in the right atrium; the presence of 0 microbubbles was classified as occluded or no shunt, 1 to 5 microbubbles as small, 6 to 25 microbubbles as moderate, and more than 25 microbubbles as large. The presence of an atrial septal aneurysm was determined at the time of the PFO closure procedure and therefore was not assessed before trial entry or among the patients in the antiplatelet-only group.

RANDOMIZATION AND TREATMENTS

Patients were randomly assigned, in a simple, nonstratified 2:1 ratio, to undergo PFO closure plus antiplatelet therapy (PFO closure group) or to receive antiplatelet therapy alone (antiplatelet-only group). Patients assigned to the PFO closure group were required to have a closure attempt within 90 days after randomization with either the Helex Septal Occluder (HELEX; W.L. Gore and Associates) device (implanted through late 2012) or the Cardioform Septal Occluder (GSO; W.L. Gore and Associates) device (implanted from late 2012 onward).

All patients received antiplatelet therapy chosen by the local investigator; however, at each participating site, antiplatelet therapy was mandated to be the same in the two study groups. Antiplatelet therapy could consist of aspirin alone (75 to 325 mg once daily), a combination of aspirin (50 to 100 mg daily) and dipyridamole (225 to 400 mg daily), or clopidogrel (75 mg once daily). Other combinations of antiplatelet drugs and anticoagulants were not permitted. The chosen antiplatelet therapy could be initiated immediately after randomization. Patients in the PFO closure group were treated with one 300-mg dose of clopidogrel before or immediately after the procedure, if they were not already receiving clopidogrel, followed by 75 mg daily for 3 days, and then resumed or started the chosen antiplatelet therapy option. All patients were expected to continue antiplatelet therapy for the duration of follow-up in the trial.

Patients were followed for a minimum of 2 years and a maximum of 5 years. Visits with a trial neurologist occurred at 1, 6, 12, 18, 24, 36, 48, and 60 months and included the administration of a standardized and validated questionnaire (Questionnaire for Verifying Stroke-Free Status) to detect potential stroke or transient ischemic attack.[9] If a transient ischemic attack or stroke was suspected on clinical grounds at any time, an evaluation was performed by a neurologist, who was aware of the treatment assignments, and brain imaging was performed at that time, as required by the protocol. Follow-up echocardiography with agitated saline was performed in patients in the PFO closure group at 1, 12, and 24 months. Follow-up MRI was performed in all patients at 24 months, if it had not already been performed to assess an end-point event.

TRIAL END POINTS

The trial had two coprimary end points. The first coprimary end point was freedom from clinical evidence of an ischemic stroke (clinical ischemic stroke) through at least 24 months, reported here as the rate of recurrence of stroke. A recurrent ischemic stroke event was defined as a focal neurologic deficit, presumably due to ischemia, lasting more than 24 hours or until death, or a deficit associated with MRI or CT evidence of a new brain infarction. Deaths and suspected recurrent stroke or transient ischemic attack events were reviewed and adjudicated by the clinical events committee. The second coprimary end point was the incidence of new brain infarction, which was a composite of clinical ischemic stroke or silent brain infarction detected by the presence of at least one new hyperintense lesion of 3 mm or greater in diameter[10] on T_2-weighted MRI between the screening MRI and the 24-month MRI, as determined by the MRI core laboratory. The second coprimary end point was changed from a secondary end point after 467 patients were enrolled, because other trials of PFO closure that were completed during the early phase of the current trial (but before the analysis of the outcome data) had a lower-than-expected event rate. The clinical events committee and MRI core laboratory were unaware of the study-group assignments, of the participating center, and of each other's assessments. The secondary end points were success of PFO closure (as assessed by means of echocardiography) and adverse events, which were classified by the local investigators

as serious or not serious and as related or not related to device, procedure, or antiplatelet therapy.

STATISTICAL ANALYSIS

Our initial statistical analysis plan was to use one-sided hypothesis testing, but we report two-sided results for consistency with previous trials of PFO closure. Two sided P values of 0.05 or less were considered to indicate statistical significance and were unadjusted for multiple testing unless otherwise noted.

The initial expected percentage of patients who would be free from events in the antiplatelet-only group at 24 months was 92%.[1,11] The protocol specified that PFO closure plus antiplatelet therapy would be considered superior to antiplatelet therapy alone if there was a 55% lower risk of recurrent stroke in the PFO closure group than in the antiplatelet-only group. We estimated that a sample size of 664 patients (randomly assigned in a 2:1 ratio to PFO closure plus antiplatelet therapy or antiplatelet therapy alone) would provide 80% power to detect the superiority of PFO closure plus antiplatelet therapy, assuming a 15% rate of incomplete follow-up, at a two-sided alpha level of 0.048 to allow for interim analysis. An initial secondary end point was the incidence of new lesions detected on neuroimaging from the imaging performed at screening through 24 months after randomization.

During the course of the current trial, other trials of PFO closure[5-7] reported lower-than-expected risks of stroke in medically treated patients. On the basis of this information and without knowledge of the event rates in the study groups in the current trial, we modified the statistical analysis plan — after consulting with the FDA — to include the neuroimaging end point as a coprimary end point and to rescind the interim analysis. For this new end point, we specified that PFO closure plus antiplatelet therapy would be considered superior to antiplatelet therapy alone if there was a 55% lower risk of new lesions in the PFO closure group than in the antiplatelet-only group. The adequacy of sample size for the new coprimary end point was assessed on the basis of an expected rate of brain infarction that was five times the rate of recurrent clinical stroke,[12] a rate of recurrent stroke of 2.9% in the antiplatelet-only group at 24 months,[5] and an attrition rate of 10%. Under these assumptions, we calculated that the trial would have 73% power to test the new brain infarction end-point hypothesis.

The coprimary end points were each analyzed in the intention-to-treat population, which included all patients who underwent randomization. For the first coprimary end point, the rate of recurrent stroke was compared with the use of the log-rank test and plotted with the use of the Kaplan–Meier method. Statistical testing of the two coprimary end points was performed with the use of P values that were adjusted for multiplicity according to the Dubey and Armitage–Parmar procedure (see the Supplementary Appendix).[13] If a multiplicity-adjusted P value of 0.05 or less or an observed hazard ratio of 0.60 or less was shown for the recurrent stroke end point, a two-sample binomial test would then be performed to compare the percentage of patients with new brain infarctions between the two study groups. In the analysis of recurrent clinical stroke, the data from all patients in whom data were censored were analyzed up to the time of censoring. In the analysis of new brain infarction, no method of imputation of missing data was used for patients who could not be evaluated, and they were excluded from the analysis.

Exploratory analyses were performed in the per-protocol cohort and in the as-treated cohort (see the Supplementary Appendix). We performed prespecified subgroup analyses to compare sites in the United States with sites elsewhere and also performed post hoc exploratory analyses of subgroups of patients defined according to age (18 to 45 years or 46 to 59 years), sex, and PFO shunt size (small or moderate-to-large). Subgroup analyses were performed with the use of Cox regression (with study-group assignment, subgroup, and the corresponding interaction as terms in the model to obtain hazard ratios) and log-rank tests. Final adjudication of clinical events was performed on April 17, 2017, and core laboratory review of the MRIs was completed on April 24, 2017. Analysis of primary end-point data was performed on April 24, 2017.

RESULTS

TRIAL PATIENTS

A total of 664 patients (mean age, 45.2 years; 81% with moderate or large interatrial shunts) were enrolled from December 2008 through February 2015 and were randomly assigned to

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PFO Closure Group (N=441)	Antiplatelet-Only Group (N=223)
Age — yr	45.4±9.3	44.8±9.6
Days from qualifying event to randomization	100±52	101±53
Male sex — no. (%)	261 (59.2)	138 (61.9)
Medical history — no. (%)		
Current smoking	63 (14.3)	25 (11.2)
Hypertension	112 (25.4)	58 (26.0)
Diabetes mellitus	18 (4.1)	10 (4.5)
Stroke or TIA before the index event	62 (14.1)	23 (10.3)
Previous stroke	42 (9.5)	13 (5.8)
Previous TIA	26 (5.9)	11 (4.9)
Index event — no. (%)		
Ischemic stroke with symptoms lasting ≥24 hr	402 (91.2)	199 (89.2)
Ischemic stroke symptoms lasting <24 hr, with imaging confirmation of infarct	39 (8.8)	24 (10.8)
Patent foramen ovale shunt size — no./total no. (%)†		
Small	77/425 (18.1)	43/216 (19.9)
Moderate	166/425 (39.1)	94/216 (43.5)
Large	182/425 (42.8)	79/216 (36.6)
Atrial septal aneurysm — no./total no. (%)	86/422 (20.4)	NA‡

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. NA denotes not applicable, and TIA transient ischemic attack.

† Shunt size was classified on the basis of the estimated number of microbubbles detected in the left atrium within three cardiac cycles after appearance in the right atrium, as observed on transesophageal echocardiography while the patient was at rest or while a Valsalva maneuver was being performed. The presence of 0 microbubbles was classified as occluded or no shunt, 1 to 5 microbubbles as small, 6 to 25 microbubbles as moderate, and more than 25 microbubbles as large.

‡ The presence of an atrial septal aneurysm was determined at the time of the PFO closure procedure and therefore was not recorded before trial entry or among the patients in the antiplatelet-only group.

the PFO closure group (441 patients) or to the antiplatelet-only group (223 patients). Baseline characteristics were similar in the two study groups (Table 1). The median time from the index stroke to randomization was 102 days (interquartile range, 56 to 148). The median duration of follow-up was 3.2 years (interquartile range, 2.2 to 4.8), with 1529 patient-years of follow-up in the PFO closure group and 703 patient-years of follow-up in the antiplatelet-only group. A total of 8.8% of the patients in the PFO closure group and 14.8% in the antiplatelet-only group discontinued the trial prematurely (Fig. S1 in the Supplementary Appendix).

At baseline, brain imaging was performed in 99.8% of the patients — MRI was performed in 649 patients (97.7%), CT in 14 patients (2.1%), and neither imaging study in 1 patient (0.2%). Final neuroimaging results were available for 383 patients in the PFO closure group and for 177 patients in the antiplatelet-only group. Antiplatelet therapy regimens were similar in the two study groups. Information on randomization, treatment, and follow-up of patients and on antiplatelet regimens are summarized in Figures S1 through S3 and Table S4 in the Supplementary Appendix.

PROCEDURAL OUTCOMES

PFO closure with a study device was attempted in 413 of 441 patients (93.7%) in the PFO closure group at a median of 28 days (interquartile range, 14 to 52) after randomization. Implantation and retention of a study device were suc-

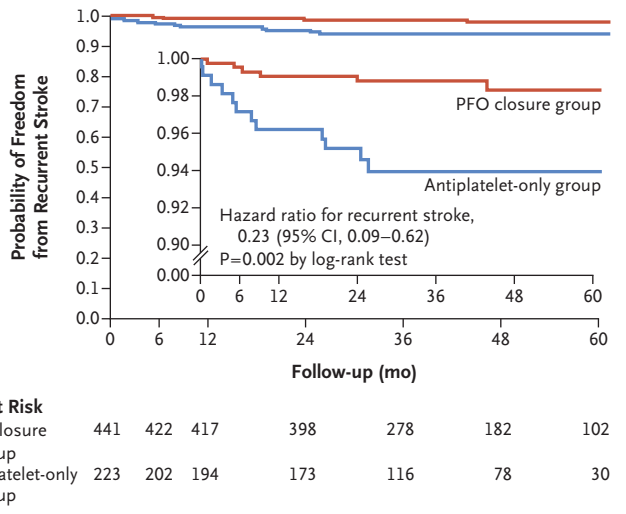

Figure 1. Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.

Shown are Kaplan–Meier plots of the estimate of the probability of freedom from clinical evidence of recurrent ischemic stroke in the intention-to-treat population (all patients who were randomly assigned to undergo PFO closure followed by antiplatelet therapy [PFO closure group] or to receive antiplatelet therapy alone [antiplatelet-only group]). During a median follow-up of 3.2 years, clinical ischemic strokes 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 for recurrent stroke equates with 1 minus the rate of freedom from stroke. The inset shows the same data on an enlarged y axis.

cessful in 408 patients (158 patients received a HELEX device and 250 patients a GSO device), representing a rate of successful device retention of 98.8%. A nonstudy PFO closure device was implanted in 6 patients. Patient characteristics and technical success of PFO closure were similar with respect to the two study devices (Tables S5 and S6 in the Supplementary Appendix). Complete PFO closure with a study device was observed in 73.2% of the patients immediately after the procedure and in 75.6% of the patients at 12 months.

A study device was not placed in 32 patients (7.3%) in the PFO closure group; an attempt to implant a study device was not made in 28 patients, and 4 of the 5 patients in whom an initial attempt was unsuccessful had no successful reattempt to implant a study device. A total of 14 patients (6.3%) in the antiplatelet-only group underwent PFO closure during the course of the trial (Fig. S3 in the Supplementary Appendix).

PRIMARY END POINTS

With respect to the first coprimary end point, recurrent clinical ischemic stroke occurred in 6 patients (1.4%) in the PFO closure group (0.39 strokes per 100 patient-years) and in 12 patients (5.4%) in the antiplatelet-only group (1.71 strokes per 100 patient-years) (hazard ratio for recurrent stroke, 0.23; 95% confidence interval [CI], 0.09 to 0.62; P=0.002) (Fig. 1). With respect to the second coprimary end point, new brain infarction (clinical ischemic stroke or silent brain infarction) occurred in 22 patients (5.7%) in the PFO closure group and in 20 patients (11.3%) in the antiplatelet-only group (absolute difference, 5.6 percentage points [95% CI, 0.3 to 10.8]; relative risk, 0.51 [95% CI, 0.29 to 0.91]; P=0.04) (Table 2). In the coprimary end-point analysis that incorporated an adjustment for multiple testing, the P values were 0.002 for the recurrent stroke end point and 0.048 for the new brain infarction end point.

Sensitivity analyses to assess the effect of missing data are summarized in the Supplementary Appendix. In the per-protocol and as-treated cohorts, the results favored the PFO closure group with respect to both coprimary end points (Table S7 in the Supplementary Appendix). Exploratory analyses to evaluate heterogeneity in relation to baseline covariates indicated no interactions across strata of age, sex, shunt size, or geographic region (Fig. 2).

SAFETY

Adverse events are summarized in Table 3. Serious adverse events occurred in 164 patients: 102 patients (23.1%) in the PFO closure group and 62 patients (27.8%) in the antiplatelet-only group (P=0.22). Two deaths occurred in the PFO closure group (one suicide and one fatal myocardial infarction), and no deaths occurred in the antiplatelet-only group. In the PFO closure group, procedure-related serious adverse events occurred in 2.5% of the patients, and device-related serious adverse events in 1.4%.

The risks of major bleeding, deep-vein thrombosis, and pulmonary embolism did not differ significantly between study groups. Atrial fibrillation or flutter occurred in significantly more patients in the PFO closure group than in the antiplatelet-only group (6.6% vs. 0.4%, P<0.001); 83% of the cases of atrial fibrillation or flutter

Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	no. of patients/total no. (%)			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)‖	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)‖	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)‖	0.97**

* Freedom from clinical ischemic stroke is reported here as the number of recurrent strokes through at least 24 months. New brain infarction was a composite of clinical ischemic stroke or silent brain infarction detected on imaging at 24 months.
† Clinical evidence of ischemic stroke was reported through the time of available follow-up, with a minimum of 2 years, maximum of 5 years, and median of 3.2 years.
‡ Data are presented as a hazard ratio with a 95% confidence interval in the PFO closure group as compared with the antiplatelet-alone group.
§ The P value was calculated with the use of a log-rank test.
¶ One additional clinical stroke occurred in the PFO closure group after 2 years and therefore was not included in the composite new brain infarction end point at 24 months. Recurrent clinical ischemic stroke and silent brain infarction are the two components of the second coprimary end point.
‖ Data are presented as a relative risk with a 95% confidence interval in the PFO closure group as compared with the antiplatelet-alone group.
** The P value was calculated with the use of a binomial proportions test.

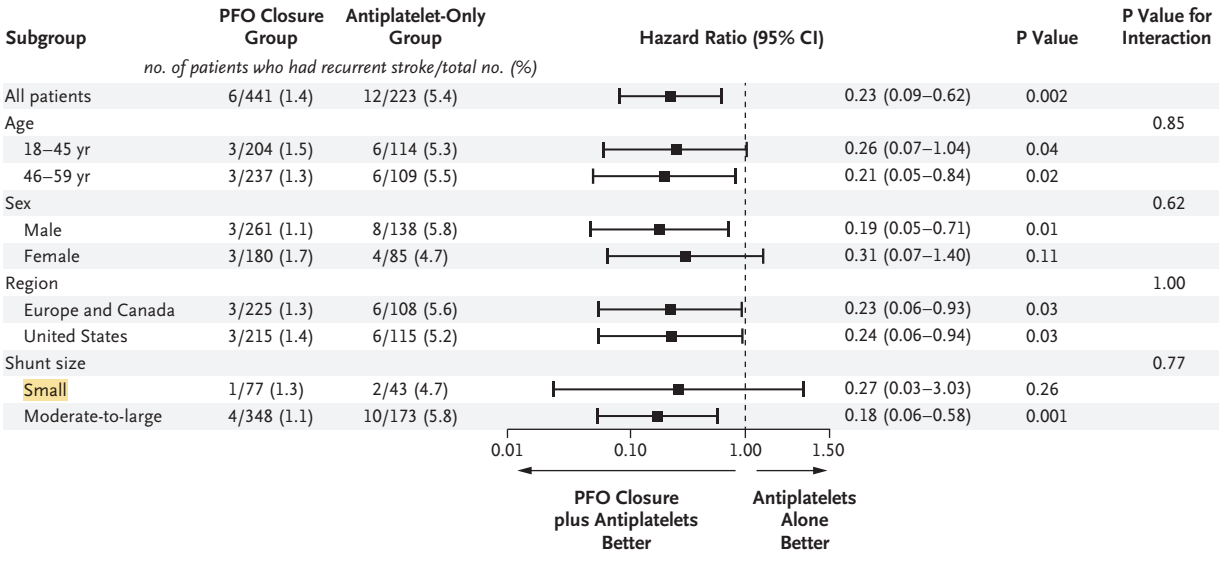

Figure 2. Exploratory Analyses to Evaluate Heterogeneity in Relation to Baseline Covariates.

Subgroup analyses were performed in the intention-to-treat population. The classification of shunt size was based on the maximum number of microbubbles seen in the left atrium in any single frame during the first three cardiac cycles after detection in the right atrium; the presence of 0 microbubbles was classified as occluded or no shunt, 1 to 5 microbubbles as small, 6 to 25 microbubbles as moderate, and more than 25 microbubbles as large. In one patient in the PFO closure group, the baseline shunt size was unknown according to the site assessment that was used for the analysis.

Table 3. Adverse Events.

Adverse Event	PFO Closure Group (N=441)	Antiplatelet-Only Group (N=223)	P Value*
	no. of patients (%)		
Any serious adverse event	102 (23.1)	62 (27.8)	0.22
Device related	6 (1.4)	NA	NA
Procedure related	11 (2.5)	NA	NA
Death†	2 (0.5)	0	0.55
Serious bleeding adverse event	8 (1.8)	6 (2.7)	0.57
Procedure associated‡	4 (0.9)	NA	NA
Other§	4 (0.9)	6 (2.7)	0.09
Any atrial fibrillation or flutter	29 (6.6)	1 (0.4)	<0.001
Serious atrial fibrillation or flutter¶	10 (2.3)	1 (0.4)	0.11
Serious device-related adverse event‖	6 (1.4)	NA	NA
Device dislocation	3 (0.7)		
Device-related thrombosis	2 (0.5)		
Aortic dissection	1 (0.2)		
Any deep-vein thrombosis or pulmonary embolism	3 (0.7)	2 (0.9)	1.00

* P values were calculated with the use of Fisher's exact test.
† One suicide related to depression occurred 131 days after randomization, and one fatal myocardial infarction occurred 1045 days after randomization.
‡ Procedure-associated serious bleeding adverse events were events of bleeding within 30 days after the procedure at the vascular access site (three patients) or cardiac tamponade (one patient).
§ Other serious bleeding adverse events were events of bleeding in the reproductive, visual, gastrointestinal, and musculoskeletal systems.
¶ Atrial fibrillation or flutter was classified as a serious adverse event by the local investigator.
‖ A serious device-related adverse event was any adverse event that involved or was related to the device, with the exclusion of arrhythmia.

were detected within 45 days after the procedure, and 59% resolved within 2 weeks after onset. Of the 29 patients who had atrial fibrillation or flutter in the PFO closure group, 1 had a recurrent stroke. (Additional safety data are provided in Table S8 in the Supplementary Appendix.)

DISCUSSION

In this trial involving patients with cryptogenic ischemic stroke, the risk of recurrent stroke, including clinical ischemic stroke and a composite of clinical and silent brain infarctions, was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone. The number of patients who needed to be treated to prevent one stroke in 24 months was approximately 28 patients. The efficacy of PFO closure was similar in the primary intention-to-treat analysis and in the analysis of the per-protocol and as-treated populations.

Previous trials of PFO closure did not show efficacy in their primary intention-to-treat analyses; however, analyses based on the as-treated populations, follow-up studies, and meta-analyses have suggested that there is a possible benefit from the procedure in lowering the risk of stroke.[5-8] Unlike those previous trials, the current trial was designed to determine the efficacy and safety of PFO closure followed by antiplatelet therapy, as compared with antiplatelet therapy alone. We required antiplatelet agents to be used as the medical therapy, in accordance with established guidelines and current practice,[2,14,15] whereas the previous trials allowed the use of anticoagulants in the medical-therapy group at the discretion of treating or trial physicians — a design that may have led to confounding of

results and bias within the medical-therapy groups. Two previous trials reported subgroup analyses according to the type of antithrombotic treatment. In the CLOSURE-1 trial (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),[6] PFO closure was not shown to be superior to antiplatelet therapy. In the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment),[5] the risk of stroke may have been lower with PFO closure than with antiplatelet therapy, but the interaction of outcome with antithrombotic treatment was not significant. Furthermore, discontinuation of antithrombotic therapy was permitted after PFO closure in the previous trials, which may have increased the risk of stroke due to causes other than PFO.

In the current trial, we selected patients who were likely to have strokes attributable to PFO. We excluded patients who had had lacunar strokes, patients who had uncontrolled vascular risk factors, and patients who were 60 years of age or older, as well as patients with overt alternative causes of their strokes. This approach enhanced the likelihood that the index stroke was caused by the PFO and consequently increased the likelihood that PFO closure would be effective. This approach to patient selection was supported by the findings from the Risk of Paradoxical Embolization meta-analysis, which suggested that a PFO is the most likely cause of cryptogenic stroke among relatively young patients who have few other risk factors.[16,17] The risk of stroke in the antiplatelet-only group in our trial was numerically greater than in previous trials. This could have been related to the enrollment of patients at greater risk of stroke, earlier enrollment after the index stroke, or the absence of anticoagulation as a treatment option in our trial.

The current trial required that patients have neuroimaging performed at the baseline screening and at 24 months after randomization or after a stroke event. This requirement allowed for a more systematic evaluation of the composite end point of new brain infarction than was possible in other trials. Our definition of new brain infarction included clinically silent infarction, which is often associated with subtle neurologic deficits,[18] particularly cognitive impairment,[19,20] and is associated with an increased risk of subsequent clinical stroke.[21-23] Although the rate of composite events of new brain infarction was lower in the PFO closure group, we did not observe a significant between-group difference in the rate of silent cerebral ischemic events. One possible reason is that our approach to detecting silent brain infarctions may have been insensitive, because it was based on the appearance of new lesions 3 mm or larger in diameter on T_2-weighted sequence MRI. The diagnostic evaluation of stroke has evolved since the design of this trial and now includes higher MRI field strength, multiple acquisition sequences, and varying criteria with respect to the size of ischemic lesions, modified according to their location.[21,24] Another possible explanation for the lack of a significant between-group difference in the rate of silent cerebral ischemic events is bias in assessment and referral for end-point adjudication of new neurologic symptoms over the course of the trial,[25] because the treating physicians were aware of the study-group assignments. This criticism has been raised regarding other trials of PFO closure. We found that the referral for adjudication of events was proportionate to the number of confirmed clinical strokes (Table S8 in the Supplementary Appendix), but referral bias was still possible.

Complete closure of the PFO was attained at 12 months in 75.6% of the procedures in the current trial; the risk of device-related thrombosis was 0.5%, but there were no instances of erosion of the device into the atrial wall or aorta. Effective closure (defined post hoc as freedom from large shunt), which was assessed for the purpose of comparison with other trials of PFO closure, was observed in 94.5% of the patients at 12 months. Atrial fibrillation was more commonly reported in the PFO closure group, but it was usually transient. The clinical relevance of atrial fibrillation related to closure and overall risk of stroke requires further investigation.

The generalizability of the results of the current trial may have been affected by the opportunity for patients to have PFO closure performed outside the trial. A total of 14 patients who were assigned to the antiplatelet-only group underwent PFO closure outside the trial. Other potential limitations of the current trial were the

differential dropout rate between the two study groups, which could have created misclassification bias toward or away from a null result, and the relatively low number of total events, which hampers subgroup analysis.

In conclusion, among patients who had had cryptogenic stroke most likely attributable to PFO, the risks of recurrent stroke and new brain infarction were significantly lower with closure of the PFO plus antiplatelet therapy than with antiplatelet therapy alone.

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