ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

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ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale reduces the risk of recurrence of ischemic stroke in patients who have had a cryptogenic ischemic stroke is unknown.

METHODS

In a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events, we randomly assigned patients 18 to 60 years of age who had a patent foramen ovale (PFO) and had had a cryptogenic ischemic stroke to undergo closure of the PFO (PFO closure group) or to receive medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole; medical-therapy group). The primary efficacy end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The results of the analysis of the primary outcome from the original trial period have been reported previously; the current analysis of data from the extended follow-up period was considered to be exploratory.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. Patients were followed for a median of 5.9 years. Treatment exposure in the two groups was unequal (3141 patient-years in the PFO closure group vs. 2669 patient-years in the medical-therapy group), owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat population, 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 with PFO closure vs. medical therapy, 0.55; 95% confidence interval [CI], 0.31 to 0.999; 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 (hazard ratio, 0.38; 95% CI, 0.18 to 0.79; P=0.007). Venous thromboembolism (which comprised events of pulmonary embolism and deep-vein thrombosis) was more common in the PFO closure group than in the medical-therapy group.

CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

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Between 20 and 30% of ischemic strokes are cryptogenic.[1] A strong association between cryptogenic strokes and the presence of patent foramen ovale (PFO) suggests that paradoxical embolism through a PFO may be one important cause of otherwise unexplained infarcts.[2] Percutaneous devices for closure of a PFO have been studied to assess their effectiveness in preventing a recurrence of stroke after cryptogenic stroke, with more recently developed devices showing superiority over earlier technology.[3] Three randomized trials individually did not show a significantly lower risk of recurrent stroke with PFO closure than with medical therapy alone.[4-6] However, in a pooled individual-patient meta-analysis and a study-level network meta-analysis of randomized trials, closure of the PFO with the Amplatzer PFO Occluder was found to result in a lower risk of recurrence of ischemic stroke than medical therapy.[7,8]

The primary analyses of the randomized trials of PFO closure were based on moderate durations of follow-up, averaging 2 to 4 years. Outcomes over the course of more extended periods have been reported in observational series, but without randomized comparisons.[9,10] In the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, the results from the original trial period were reported with a median of 2.1 years of follow-up.[5] To provide insight into the long-term effects of PFO closure, we now report the results from the extended follow-up period.

Methods

Trial Design and Oversight

The RESPECT trial was a multicenter, randomized, open-label, controlled clinical trial with blinded adjudication of end-point events.[5] The trial was performed at 69 sites in the United States and Canada (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The trial was approved by the institutional review board at each site, and all the patients provided written informed consent. The trial was designed by the sponsor (St. Jude Medical) and physician advisors, in consultation with the Food and Drug Administration (FDA). The steering committee (Table S2 in the Supplementary Appendix) and other coauthors had unrestricted access to the data, wrote the first and subsequent drafts of the manuscript, and attest to the integrity of the trial, the completeness and accuracy of the reported data, and the fidelity of the trial to the protocol, available at NEJM.org.

The primary analysis of the original trial period was conducted when the prespecified target of 25 adjudicated end-point events had been reached.[5] All the patients in the trial were requested to consent to participate in a long-term follow-up period that would extend until the time of a regulatory decision. The results reported in this article reflect the final database lock that was performed for regulatory submission.

Patient Selection

Patients who had had a cryptogenic ischemic stroke were eligible for participation in the trial if they were 18 to 60 years of age, had a PFO that was confirmed by transesophageal echocardiography, and could undergo randomization within 270 days after the index stroke. Patients were excluded from participation if a mechanism for the qualifying stroke other than presumed paradoxical embolization could be identified, such as large-vessel arteriopathy, a cardiac source of embolism, intrinsic small-vessel disease, or an arterial hypercoagulable state (as indicated by the presence of antiphospholipid antibodies or hyperhomocysteinemia). Complete enrollment criteria are provided in Table S3 in the Supplementary Appendix.

Randomization and Trial Treatment

Patients were randomly assigned, in a 1:1 ratio, to receive medical therapy alone (medical-therapy group) or to undergo closure of the PFO (PFO closure group). Randomization was stratified according to site, planned antithrombotic medication regimen should the patient be assigned to medical therapy, and the presence or absence of an atrial septal aneurysm.

Patients assigned to the PFO closure group underwent a procedure in which the Amplatzer PFO Occluder was inserted with fluoroscopic and echocardiographic guidance. The procedure was performed within 21 days after randomization; patients continued their prerandomization antithrombotic regimen until the time of placement of the device. After the device was implanted, patients received 81 to 325 mg of aspirin plus clopidogrel daily for 1 month, followed by aspirin monotherapy for 5 months. Subsequently, antithrombotic therapy was at the discretion of the site investigator.

In the medical-therapy group, four medical therapies were allowed throughout the trial: aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole. Aspirin with clopidogrel was also permitted initially, but this regimen was eliminated in 2006 (3 years after trial enrollment began) to conform to a change in guidelines.[11]

TRIAL END POINTS

For ascertainment of trial outcomes, patients were evaluated at 1, 6, 12, 18, and 24 months and annually thereafter. Methods for the detection and adjudication of strokes and transient ischemic attacks are detailed in Text Section S1 in the Supplementary Appendix.

The primary efficacy end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. In the PFO closure group, early death after randomization was defined as death from any cause within 30 days after placement of the device or within 45 days after randomization, whichever occurred later; in the medical-therapy group, it was defined as death from any cause within 45 days after randomization.

Recurrent strokes were adjudicated as being of "determined" or "undetermined" mechanism with the use of the ASCOD (atherosclerosis [A], small-vessel disease [S], cardiac pathology [C], other causes [O], dissection [D]) classification algorithm[12]; adjudication was performed by the stroke etiology adjudication committee, whose members were unaware of the treatment assignments. In addition, events were adjudicated as being of "cryptogenic" or "noncryptogenic" mechanism with the use of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification algorithm,[13] which identifies five subtypes of ischemic stroke; this adjudication was performed by members of the clinical events committee, who were also unaware of the treatment assignments. The ASCOD system, as compared with the older TOAST system, avoids conflation of etiologic factors when more than one defined etiologic factor is present, gives clearer guidance on the use of recently developed diagnostic tests, and provides useful mechanistic classification in patients who had less stringent repeat etiologic workups as well as in patients who had stringent repeat etiologic workups. Details are provided in Text Section S1 in the Supplementary Appendix. We also analyzed both of the clinical secondary efficacy end points that were evaluated in the original trial period: the absence of recurrent symptomatic cryptogenic nonfatal ischemic stroke or early cardiovascular death, and the absence of transient ischemic attack.

STATISTICAL ANALYSIS

The outcome analysis of the extended follow-up period was performed in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned. Log-rank tests were used to compare Kaplan–Meier estimates for survival curves in the two treatment groups in a time-to-first-event analysis. Hazard ratios and 95% confidence intervals were estimated with the use of a Cox proportional-hazards model. For between-group comparisons, nominal two-sided P values of 0.05 or less were considered to indicate statistical significance. For the primary end point, we performed an unadjusted analysis (the main analysis), as well as an analysis that adjusted for the three baseline variables that were used to stratify randomization (sensitivity analysis). Statistical testing for effect modification (interactions) was conducted for the same baseline variables as those tested in the analysis of the primary outcome from the original trial period; P values for interaction of 0.10 or less were considered to indicate statistical significance.

The outcome data that were collected during the extended follow-up period were analyzed at three time points, according to procedures and requests specified by the FDA. The results reported here, which are based on data from the final data analysis for regulatory submission, were selected for reporting by members of the steering committee because they represent the most complete data set. The analyses of data from the extended follow-up period were considered to be exploratory, so no adjustment for alpha spending was made in the calculation of nominal P values for the primary end point in the intention-to-treat population. If we had used a group sequential design to manage alpha spending over the four sequential analyses undertaken, with the use of the Lan–DeMets alpha-spending function, the threshold for statistical significance for the final data analysis would have been 0.043 (see Text Section S2 in the Supplementary Appendix). Two sensitivity analyses were performed to assess the effect of missing data on the analysis of the primary end-point

composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization (see Text Section S4 in the Supplementary Appendix): a multiple imputation analysis with covariate adjustment[14] and a multiple imputation analysis with systematic variation of the hazard ratio for patients who withdrew from the trial versus patients who continued in the trial.[15] To maximize the collection of safety data, patients were encouraged to continue in follow-up after the occurrence of a primary efficacy end-point event during the original trial period; therefore, the duration of safety observation exceeded the duration of efficacy observation.

RESULTS

TRIAL PATIENTS

From August 23, 2003, through December 28, 2011, a total of 980 patients (mean age, 45.9 years) were enrolled in the original trial; 499 were randomly assigned to the PFO closure group and 481 to the medical-therapy group (Fig. S1 in the Supplementary Appendix). At the time of the extended follow-up database lock on May 31, 2016, a total of 5688 patient-years of efficacy follow-up and 5810 patient-years of safety follow-up had accumulated, during a median follow-up of 5.9 years (interquartile range, 4.2 to 8.0); 716 patients (73.1%) remained in active follow-up, as compared with 851 patients (86.8%) at the end of the original trial period. The dropout rate was 33.3% in the medical-therapy group and 20.8% in the PFO closure group, resulting in a significant between-group difference in the median duration of safety follow-up (2669 patient-years in the medical-therapy group vs. 3141 patient-years in the PFO closure group, P<0.001).

The demographic and clinical characteristics of the two treatment groups were well balanced at baseline (Table 1). The baseline characteristics of the patients who had dropped out of the trial

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PFO Closure Group (N=499)	Medical-Therapy Group (N=481)	All Patients (N=980)
Age — yr	45.7±9.7	46.2±10.0	45.9±9.9
Male sex — no. (%)	268 (53.7)	268 (55.7)	536 (54.7)
Time from index stroke to randomization — days	130±70	130±69	130±70
Medical history — no./total no. (%)			
Diabetes mellitus	33/499 (6.6)	41/481 (8.5)	74/980 (7.6)
Hypertension	160/499 (32.1)	153/481 (31.8)	313/980 (31.9)
Smoking status			
Current smoker	75/499 (15.0)	55/481 (11.4)	130/980 (13.3)
Former smoker	134/499 (26.9)	143/481 (29.7)	277/980 (28.3)
Hypercholesterolemia	196/499 (39.3)	195/481 (40.5)	391/980 (39.9)
Coronary artery disease	19/499 (3.8)	9/481 (1.9)	28/980 (2.9)
Myocardial infarction	5/499 (1.0)	2/481 (0.4)	7/980 (0.7)
Peripheral vascular disease	5/499 (1.0)	1/481 (0.2)	6/980 (0.6)
Previous transient ischemic attack	58/499 (11.6)	61/481 (12.7)	119/980 (12.1)
Previous stroke	53/498 (10.6)	51/481 (10.6)	104/979 (10.6)
Family history of stroke	136/495 (27.5)	109/480 (22.7)	245/975 (25.1)
Migraine	195/499 (39.1)	186/481 (38.7)	381/980 (38.9)
Deep-vein thrombosis	20/499 (4.0)	15/481 (3.1)	35/980 (3.6)
Congestive heart failure	3/499 (0.6)	0	3/980 (0.3)
Chronic obstructive pulmonary disease	4/499 (0.8)	7/481 (1.5)	11/980 (1.1)
Birth control or hormone-replacement medications	41/499 (8.2)	51/481 (10.6)	92/980 (9.4)
Substantial right-to-left shunt — no./total no. (%)†	247/499 (49.5)	231/481 (48.0)	478/980 (48.8)
Atrial septal aneurysm — no./total no. (%)	180/499 (36.1)	170/481 (35.3)	350/980 (35.7)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any of the characteristics listed.
† A substantial shunt refers to a shunt size of grade 3. Grades ranged from 1 to 3, with higher grades indicating a larger size.

Table 2. Long-Term Efficacy End Points.*

End Point	PFO Closure Group (N=499)		Medical-Therapy Group (N=481)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate per 100 Patient-Yr	Patients with Event	Event Rate per 100 Patient-Yr		
	no. (%)		*no. (%)*			
Recurrent ischemic stroke	18 (3.6)	0.58	28 (5.8)	1.07	0.55 (0.31–0.999)	0.046
Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD	10 (2.0)	0.32	23 (4.8)	0.86	0.38 (0.18–0.79)	0.007
Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST	1 (0.2)	0.03	11 (2.3)	0.41	0.08 (0.01–0.58)	0.01
Transient ischemic attack	17 (3.4)	0.54	23 (4.8)	0.86	0.64 (0.34–1.20)	0.16

* The end points shown are the first such event that occurred in a patient, not second or later recurrences. ASCOD denotes atherosclerosis (A), small-vessel disease (S), cardiac pathology (C), other causes (O), dissection (D),[12] and TOAST Trial of ORG 10172 in Acute Stroke Treatment.[13]

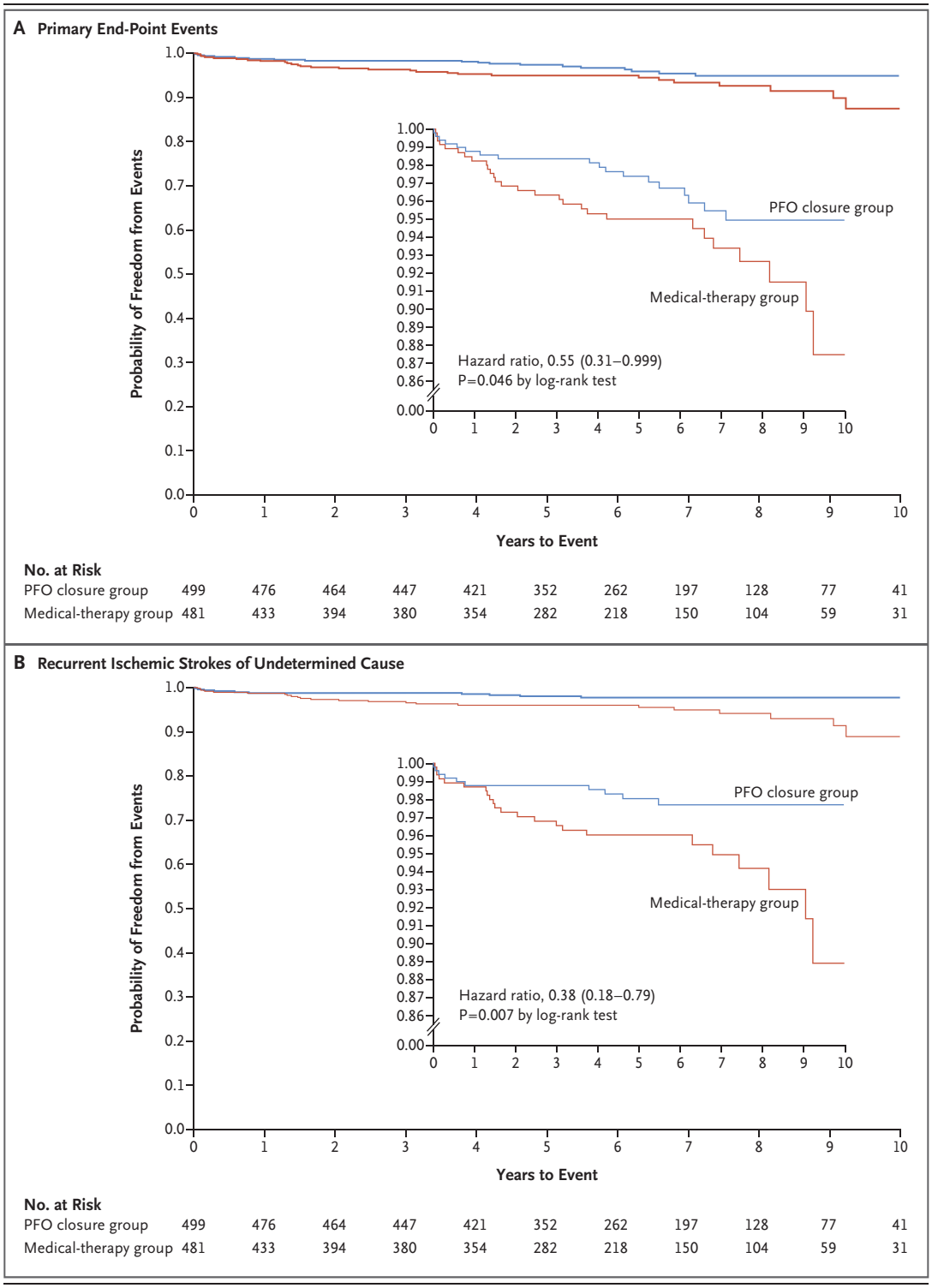
were generally similar to those of the patients who were being actively followed at the time the extended follow-up database was locked; however, nominal differences in some baseline features were noted, including both a higher percentage of current smokers and a higher percentage of patients who had had a stroke that preceded the qualifying stroke among the patients who had dropped out than among the patients who remained in active follow-up. Of the 499 patients who were assigned to the PFO closure group, 467 (93.6%) underwent the procedure, and the Amplatzer PFO Occluder was implanted in 465 of these patients. The medical-therapy group had greater intensity of antithrombotic therapy during the course of the trial than the PFO closure group, including more common use of anticoagulant agents (percentage of patient-years of follow-up in which anticoagulant therapy was used, 21.6 vs. 3.3). Additional information on trial patients is available in Table S4 and Figures S1 and S2 in the Supplementary Appendix.

EFFICACY END POINTS

Efficacy analyses included a total observation period of 3080 patient-years in the PFO closure group and 2608 patient-years in the medical-therapy group. Overall, 46 patients had a primary end-point event (a summary of the ascertainment of these events is provided in Table S5 in the Supplementary Appendix), all of which were recurrent nonfatal ischemic strokes. Recurrent ischemic stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, yielding rates of 0.58 events per 100 patient-years and 1.07 events per 100 patient-years, respectively (hazard ratio with PFO closure vs. medical therapy, 0.55; 95% confidence interval [CI], 0.31 to 0.999; P=0.046) (Table 2 and Fig. 1A). In a time-dependent covariate analysis, the interaction between time and treatment effect was not significant (P=0.64),

Figure 1 (facing page). Primary End-Point Events and Recurrent Ischemic Strokes of Undetermined Cause.

The primary efficacy end point (Panel A) was the composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, and early death after randomization. In the intention-to-treat population, there were 46 primary end-point events, all of which were recurrent nonfatal ischemic strokes; 18 occurred in the group of patients assigned to closure of the patent foramen ovale (PFO) and 28 in the group of patients assigned to medical therapy. In the analysis of recurrent ischemic strokes of undetermined cause (no identified non-PFO cause; Panel B), there were 33 events in the intention-to-treat population; 10 occurred in patients who were assigned to the PFO closure group and 23 in patients assigned to the medical-therapy group. The inset in each panel shows the same data on an enlarged y axis.



which indicated that the proportional-hazards assumption was valid. Results of the analyses of the primary end point that were based on the data available at the time of each individual database lock of the trial are summarized in Table S6 in the Supplementary Appendix.

The analysis that adjusted for the three baseline variables that were used to stratify randomization (trial site, planned antithrombotic regimen if a patient was to be randomly assigned to the medical-therapy group, and presence or absence of an atrial septal aneurysm) showed results similar to those of the unadjusted analysis (hazard ratio, 0.51; 95% CI, 0.27 to 0.96; P=0.04). In the multiple imputation analysis with covariate adjustment, the hazard ratio for ischemic stroke with PFO closure versus medical therapy was 0.50 (95% CI, 0.28 to 0.87; P=0.02). In the multiple imputation analysis with systematic variation of the hazard ratio for patients who withdrew from the trial versus patients who continued in the trial, when the event rate in the medical-therapy group during censored periods was projected to be equal to that during observed periods, the event rate in the PFO closure group during censored periods had to be more than 1.5 times as high as the event rate during observed periods for nominal statistical significance to be lost (Text Section S4 in the Supplementary Appendix).

When the ASCOD algorithm was applied to classify recurrent ischemic strokes, 13 of the 46 patients (28.3%) who had a recurrent ischemic stroke had a stroke that was associated with a mechanism that was determined to be unrelated to the PFO and 33 (71.7%) had a stroke of undetermined cause (see Table S7 in the Supplementary Appendix for a complete listing of the determined mechanisms of stroke). The percentages of patients who underwent various types of repeated diagnostic evaluation for recurrent ischemic stroke did not differ significantly between the PFO closure group and the medical-therapy group (Table S8 in the Supplementary Appendix). Recurrent ischemic stroke of undetermined mechanism occurred in 10 patients in the PFO closure group as compared with 23 patients in the medical-therapy group, yielding corresponding rates of 0.32 events per 100 patient-years and 0.86 events per 100 patient-years (hazard ratio, 0.38; 95% CI, 0.18 to 0.79; P=0.007) (Fig. 1B). In contrast, the rate of recurrent ischemic strokes of determined mechanism was 0.25 events per 100 patient-years in the PFO closure group and 0.19 events per 100 patient-years in the medical-therapy group (hazard ratio, 1.34; 95% CI, 0.44 to 4.11; P=0.60).

Both of the prespecified secondary clinical end points of the original trial period were also analyzed for the extended follow-up period. In the analysis of the incidence of recurrent cryptogenic ischemic stroke or early death from cardiovascular causes, a total of 12 such events occurred in the intention-to-treat population during this period; all were ischemic strokes that, after extensive repeat testing, were deemed to be cryptogenic on the basis of the TOAST classification: 1 event occurred in the PFO closure group, and 11 events occurred in the medical-therapy group (hazard ratio, 0.08; 95% CI, 0.01 to 0.58; P=0.01). In the analysis of the incidence of transient ischemic attack, the difference between the two groups was not significant (hazard ratio, 0.64; 95% CI, 0.34 to 1.20; P=0.16).

The results of subgroup analyses to determine the potential heterogeneity of the treatment effect according to baseline covariates suggested that the benefit of PFO closure as compared with medical therapy may have been greater among patients with an atrial septal aneurysm than among those without an atrial septal aneurysm, among patients with a substantial (grade 3) right-to-left shunt than among those with no shunt or a trace or moderate shunt, and among patients whose planned medical regimen (if they were to be assigned to the medical-therapy group) included antiplatelets than among those whose planned regimen included anticoagulants. (Fig. 2).

SAFETY

The safety analyses included a total observation period of 3141 patient-years in the PFO closure group and 2669 patient-years in the medical-therapy group. The overall rate of serious adverse events was 40.3% in the PFO closure group and 36.0% in the medical-therapy group (P=0.17) (Table S9 in the Supplementary Appendix). Among the individual serious adverse events reported, the rate of pulmonary embolism was 0.41 per 100 patient-years in the PFO closure group and 0.11 per 100 patient-years in the medical-therapy group (hazard ratio, 3.48; 95% CI, 0.98 to 12.34; P=0.04), and the rate of deep-vein thrombosis was 0.16 per 100 patient-years

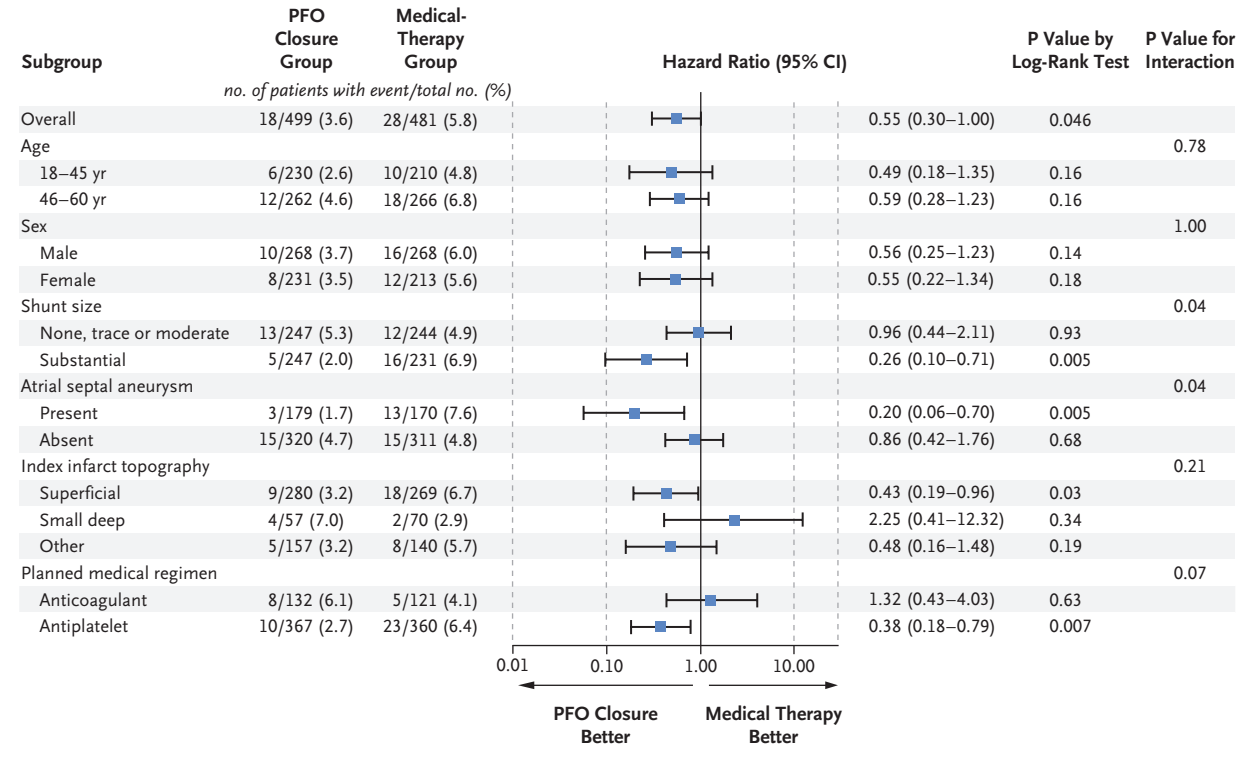


Figure 2. Rate of Recurrent Ischemic Stroke According to Subgroup.

Potential heterogeneity of the treatment effect was noted with respect to three baseline characteristics (threshold for significant interaction, P=0.10), with a suggestion of greater risk reductions with PFO closure than with medical therapy alone among patients with an atrial septal aneurysm, among patients with a substantial shunt size, and among patients whose planned medical regimen was antiplatelet therapy rather than anticoagulant therapy if they were to be randomly assigned to the medical-therapy group. A substantial shunt refers to a shunt size of grade 3. Grades ranged from 1 to 3, with higher grades indicating a larger size.

and 0.04 per 100 patient-years, respectively (hazard ratio, 4.44; 95% CI, 0.52 to 38.05; P=0.14). Among the patients in the PFO closure group, the subgroup of patients who had a history of overt deep-vein thrombosis had a higher incidence of venous thromboembolic events than did the subgroup of patients without such a history (Table S10 in the Supplementary Appendix).

There were 7 deaths in the PFO closure group and 11 in the medical-therapy group. All these deaths occurred after the early postrandomization period (which was defined in the medical-therapy group as the 45-day period after randomization and in the PFO closure group as either the 45-day period after randomization or the 30-day period after placement of the device, whichever occurred later) and were adjudicated as being unrelated to the trial (Table S11 in the Supplementary Appendix).

A total of 25 serious adverse events in the PFO closure group were adjudicated as being device-related or procedure-related (Table 3). Seven periprocedural events (including serious and nonserious events) of atrial fibrillation occurred in the PFO closure group; all these events resolved before the patients' discharge from the hospital. The rate of serious and nonserious events of atrial fibrillation reported after the periprocedural period did not differ significantly between the PFO closure group and the medical-therapy group (0.48 per 100 patient-years and 0.34 per 100 patient-years, respectively; hazard ratio, 1.47; 95% CI, 0.64 to 3.37; P=0.36).

DISCUSSION

In this exploratory analysis of long-term follow-up data from patients 18 to 60 years of age who

Table 3. Serious Adverse Events Related to the Procedure or Device among the 499 Patients in the PFO Closure Group.*

Serious Adverse Event	Patients with Event	Total No. of Events	Procedure-Related Events	Device-Related Events
	no. (%)		*no. (%)*	
Allergic drug reaction	1 (0.2)	1	1 (0.2)	0
Atrial fibrillation	2 (0.4)	2	1 (0.2)	1 (0.2)
Atrial flutter	1 (0.2)	1	0	1 (0.2)
Cardiac perforation	1 (0.2)	1	1 (0.2)	0
Cardiac thrombus	2 (0.4)	2	1 (0.2)	1 (0.2)
Chest tightness	1 (0.2)	1	0	1 (0.2)
Deep-vein thrombosis	1 (0.2)	1	1 (0.2)	0
Infective endocarditis	1 (0.2)	1	0	1 (0.2)
Ischemic stroke	2 (0.4)	2	0	2 (0.4)
Pericardial effusion	1 (0.2)	1	1 (0.2)	0
Pericardial tamponade	2 (0.4)	2	2 (0.4)	0
Pulmonary embolism	2 (0.4)	2	0	2 (0.4)
Residual shunt requiring closure	2 (0.4)	2	0	2 (0.4)
Sepsis	1 (0.2)	1	0	1 (0.2)
Nonsustained ventricular tachycardia	1 (0.2)	1	0	1 (0.2)
Major vascular complications				
Bleeding	2 (0.4)	2	2 (0.4)	0
Hematoma	1 (0.2)	1	1 (0.2)	0
Vasovagal reaction	1 (0.2)	1	1 (0.2)	0
Total	21 (4.2)	25	12 (2.4)	13 (2.6)

* The serious adverse events listed here were adjudicated by the data and safety monitoring committee as having been related to the device or procedure. All the adjudicated serious adverse events that occurred in the two groups are listed in Table S9 in the Supplementary Appendix.

had a PFO and had had an initial cryptogenic ischemic stroke, closure of the PFO with the Amplatzer PFO Occluder was associated with a lower rate of recurrent ischemic strokes than medical therapy. The association of PFO closure with lower rates of recurrent ischemic strokes was particularly apparent in cases that involved strokes that had no identified non-PFO mechanisms. This association was apparent both when events of recurrent stroke were adjudicated as having an undetermined cause on the basis of a flexible or extensive repeat workup (ASCOD classification)[12] and when they were adjudicated as having a cryptogenic cause only after an extensive repeat workup (TOAST classification).[13]

The relative difference in the rate of recurrent ischemic stroke between PFO closure and medical therapy alone was large (45% lower with PFO closure), but the absolute difference was small (0.49 fewer events per 100 patient-years with PFO closure). Nonetheless, the cumulative absolute benefit had clinical relevance, since patients in this trial were younger (18 to 60 years of age) than the general population of patients who have strokes and thus faced a longer period of risk for recurrent stroke. On the basis of the results of the current trial, the number of persons in a population similar to that assessed in our trial who would need to be treated with PFO closure rather than with medical therapy to prevent one stroke over a period of 5 years is estimated to be 42.

The rate of venous thromboembolism (which comprised events of pulmonary embolism and

deep-vein thrombosis) was higher in the PFO closure group than in the medical-therapy group. The rate of venous thromboembolism in both groups exceeded that in healthy populations,[16] which suggests that persons who have had a cryptogenic stroke and also have a PFO have a mildly elevated long-term risk of venous thromboemboli. In our trial, the lower intensity of antithrombotic therapy, including the less common use of anticoagulant agents, in the PFO closure group than in the medical-therapy group may have contributed to the higher rate of venous thromboembolism in the PFO closure group. Among the patients in the PFO closure group, the propensity to venous thromboembolic events was particularly strong in the subgroup of patients who had previous, clinically manifest, unprovoked deep-vein thrombosis. Although this subgroup of patients represented only 4% of patients in the PFO closure group, they accounted for 25% of the venous thromboembolic events that occurred during the trial. These findings provide indirect support for the recent revision in national management guidelines that endorsed lifelong anticoagulation therapy in patients with overt deep-vein thrombosis.[17]

Differences between the two treatment groups in the percentage of patients who remained in active follow-up resulted in an unequal duration of exposure to the risk of recurrent ischemic stroke. Some patients in the medical-therapy group may have been lost to follow-up after undergoing PFO closure with the off-label use of devices approved by the FDA for other indications. Retention rates in the medical-therapy group were higher than, or similar to, those in other trials involving patients with diverse cardiovascular conditions in which intervention with a device was compared with medical therapy[4,6,18,19]; nonetheless, differential retention is an important consideration in the interpretation of our trial findings. Since patients who left the trial tended to have some baseline features that were associated with an increased risk of stroke (having a history of stroke or being a current smoker), differential follow-up may have biased the trial conservatively, toward underestimation of the treatment effect. Sensitivity analyses that were conducted to assess the effect of missing data were consistent with such an effect; PFO closure was more strongly associated with a lower risk of recurrent stroke than was medical therapy in a covariate-adjusted multiple imputation analysis and in the preponderance of multiple imputation analyses with systematic variation of hazard rates.

This trial has additional limitations. The trial protocol did not require prolonged cardiac monitoring before enrollment to exclude patients with occult, low-burden atrial fibrillation. However, occult atrial fibrillation is an uncommon cause of otherwise cryptogenic ischemic stroke among patients 18 to 60 years of age,[20] and the rate of new-onset atrial fibrillation over the course of the prolonged follow-up period was low. Formal approaches to classifying potential mechanisms of ischemic stroke have become more nuanced since the trial was designed.[12,21] However, the benefit of closure in reducing the risk of recurrent strokes that did not have an identified non-PFO mechanism was seen when events of stroke were adjudicated with the use of both newer, more flexible (ASCOD) criteria as well as older, more rigid (TOAST) criteria.[12,13]

Workup of the etiologic factors of recurrent ischemic stroke was performed in a clinically indicated manner rather than a protocol-mandated manner. In clinical practice, causal workup for repeat strokes is sometimes not as extensive as it is for first strokes. Although the possibility exists that the extensiveness of workup of recurrent stroke was influenced by the clinician's knowledge of a patient's treatment assignment, the percentages of patients who underwent various types of repeated diagnostic tests did not differ significantly between the PFO closure group and the medical-therapy group.

In conclusion, in an exploratory analysis, among patients with a PFO who were 18 to 60 years of age at the time of an index cryptogenic ischemic stroke, PFO closure with the use of the Amplatzer PFO Occluder was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during an extended follow-up period. PFO closure was associated with a higher rate of venous thromboembolism than medical therapy alone.

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