ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

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ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale is effective in the prevention of recurrent ischemic stroke in patients who have had a cryptogenic stroke is unknown. We conducted a trial to evaluate whether closure is superior to medical therapy alone in preventing recurrent ischemic stroke or early death in patients 18 to 60 years of age.

METHODS

In this prospective, multicenter, randomized, event-driven trial, we randomly assigned patients, in a 1:1 ratio, to medical therapy alone or closure of the patent foramen ovale. The primary results of the trial were analyzed when the target of 25 primary end-point events had been observed and adjudicated.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The medical-therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%). Treatment exposure between the two groups was unequal (1375 patient-years in the closure group vs. 1184 patient-years in the medical-therapy group, P=0.009) owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat cohort, 9 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P=0.08). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the closure group vs. 14 events in the medical-therapy group; hazard ratio, 0.37; 95% CI, 0.14 to 0.96; P=0.03) and in the as-treated cohort (5 events vs. 16 events; hazard ratio, 0.27; 95% CI, 0.10 to 0.75; P=0.007). Serious adverse events occurred in 23.0% of the patients in the closure group and in 21.6% in the medical-therapy group (P=0.65). Procedure-related or device-related serious adverse events occurred in 21 of 499 patients in the closure group (4.2%), but the rate of atrial fibrillation or device thrombus was not increased.

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

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It is unknown whether closure of a patent foramen ovale is effective in the prevention of recurrent stroke after a cryptogenic ischemic stroke. Observational studies and meta-analyses have suggested that closure is associated with a benefit; however, a randomized 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 (CLOSURE I), failed to show the superiority of closure over medical therapy alone.[1-3] In observational studies, the Amplatzer PFO Occluder has been shown to have advantageous safety features as a closure device.[4-7] We report the results of closure with the use of this device in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT).

Methods

Study Design and Oversight

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

The trial was approved by the institutional review board at each site, and all 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 sponsor selected and monitored the sites and was responsible for data management. The steering committee (Table S2 in the Supplementary Appendix) and other coauthors had unrestricted access to the data, reviewed the analysis with the independent primary study statistician, wrote the first and subsequent drafts of the manuscript, and attest to the integrity of the trial and the completeness and accuracy of the reported data.

Patient Selection

Patients were eligible for participation in RESPECT if they were between 18 and 60 years of age, had had a cryptogenic ischemic stroke, and had a patent foramen ovale identified by means of transesophageal echocardiography. Randomization had to occur within 270 days after the stroke.

Ischemic stroke was defined as an acute focal neurologic deficit, which was presumed to be due to focal ischemia, and either symptoms that persisted for 24 hours or longer or symptoms that persisted for less than 24 hours but were associated with findings of a new, neuroanatomically relevant, cerebral infarct on magnetic resonance imaging (MRI) or computed tomography (CT).

Patent foramen ovale was defined as transesophageal echocardiographic evidence of infused microbubbles in the left atrium within three cardiac cycles after their appearance in the right atrium, at rest or during Valsalva release. The shunt size was graded on a standard scale,[8,9] with grade 0 indicating no microbubbles; grade 1, 1 to 9 microbubbles; grade 2, 10 to 20 microbubbles; and grade 3, more than 20 microbubbles. An atrial septal aneurysm was defined as a septum primum excursion of 10 mm or more.[10]

Patients were excluded from the trial if a mechanism for the index stroke other than paradoxical embolization could be identified, such as large-vessel disease, any cardioembolic source, a lacunar infarct that was probably due to intrinsic small-vessel disease, or an arterial hypercoagulable state (as indicated by the presence of anticardiolipin antibody, lupus anticoagulant, or hyperhomocysteinemia) (Table S3 in the Supplementary Appendix).

Randomization and Study Treatment

Patients were randomly assigned, in a 1:1 ratio, to medical therapy alone or to closure of the patent foramen ovale. Randomization was stratified according to site, recommended medical treatment before randomization, and presence or absence of an atrial septal aneurysm. Patients who were assigned to the closure group underwent the procedure within 21 days after randomization and continued their prerandomization antithrombotic regimen until placement of the device.

In the medical-therapy group, four medical therapies were allowed throughout the study: aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole. Aspirin with clopidogrel was also permitted initially but was eliminated in 2006 to conform to a change in guidelines.[11]

Patients in the closure group underwent a

procedure in which the Amplatzer PFO Occluder was inserted with fluoroscopic and echocardiographic guidance (Fig. S1 in the Supplementary Appendix). Transesophageal echocardiography was performed 6 months after the procedure. Complete closure of the patent foramen ovale was defined as a shunt grade of 0, and effective closure as a shunt grade of 0 or 1.

After placement of the device, patients received 81 to 325 mg of aspirin plus clopidogrel for 1 month, followed by aspirin monotherapy for 5 months. Subsequently, antiplatelet therapy was administered at the discretion of the site investigator. All patients were evaluated at 1, 6, 12, 18, and 24 months and annually thereafter. At each visit, patients were interviewed with the use of a validated questionnaire[12,13] to identify symptoms of potential stroke or transient ischemic attack.

For patients with a suspected end-point event, a history was obtained, neurologic examination was performed by the site neurologist, and imaging studies were obtained. If a new infarction was present on either a CT or MRI scan, the largest linear diameter was measured.

STUDY END POINTS

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

The secondary efficacy end points were complete closure of the patent foramen ovale on the 6-month follow-up transesophageal echocardiogram, the absence of recurrent symptomatic nonfatal ischemic stroke or cardiovascular death, and the absence of a transient ischemic attack.

An independent clinical events committee, whose members were unaware of the identities of the patients, the treatment assignments, and the site at which the patients were enrolled, adjudicated end-point events. An independent data and safety monitoring board, whose members were unaware of the site at which the patients were enrolled, adjudicated reported adverse events and assessed the severity, expectedness, and relatedness of the event to the device, procedure, delivery system, and study protocol.

STATISTICAL ANALYSIS

The primary analysis specified in the protocol was a between-group comparison of the raw counts of events. The primary analysis was conducted in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned. Decision rules for stopping the trial were based on raw counts of events and the projected equal length of follow-up in the two groups. We estimated that the study would have 80% power to show a reduction in risk with closure of approximately 75%, assuming that the rate of primary events at 2 years of follow-up would be 4.3% in the medical-therapy group and 1.05% in the closure group, at a two-sided type 1 error rate of 0.05.

The protocol prespecified that if the dropout rates differed significantly between the two groups, survival functions for the time to the end-point event for each treatment would be used to provide an exposure-stratified comparison; survival analysis methods would be used at a two-sided significance level of 0.05 with the use of the log-rank statistic. Hazard ratios were calculated with the use of a Cox proportional-hazards model.

Two additional populations were prespecified for analyses. The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation. The as-treated cohort included patients who received a protocol-approved treatment, adhered to the protocol-mandated medical treatment, and were classified according to the treatment actually received. A post hoc analysis of the intention-to-treat cohort assessed whether baseline covariates modified the effectiveness of closure of a patent foramen ovale. Statistical testing for effect modification (interactions) was performed with the use of Cox proportional-hazards regression; if the two-sided chi-square statistic was associated with a P value for interaction of 0.10 or less, the interaction was considered to be significant. The results reported here include data from visits or adverse-events that occurred on or before the adjudication of the 25th primary end-point event.

RESULTS

STUDY PATIENTS

From August 23, 2003, through December 28, 2011, a total of 980 patients were enrolled; 499 were randomly assigned to the closure group and 481 to the medical-therapy group (Fig. S2 in the Supplementary Appendix). The median time from the index stroke to randomization was 120 days (interquartile range, 74 to 179). A total of 2559 patient-years of follow-up were accumulated, with a mean (±SD) follow-up period of 2.6±2.0 years, a median of 2.1 years (interquartile range, 1.0 to 4.1), and a range of 0 to 8.1 years. At the time the database was locked, 851 patients (86.8%) remained in active follow-up. The dropout rate was 17.2% in the medical-therapy group and 9.2% in the closure group, resulting in a significant between-group difference in follow-up observation (1375 years in the closure group vs. 1184 years in the medical-therapy group, P=0.009). The baseline characteristics were well balanced between the two treatment groups (Table 1) and were also similar between patients who were being actively followed at the time the database was locked and those who had dropped out of the study (Table S4 in the Supplementary Appendix). The assigned antithrombotic regimen for the 480 patients in the medical-therapy group for whom a medical regimen was recommended at randomization was aspirin alone in 223 patients (46.5%), warfarin alone in 121 patients (25.2%), clopidogrel alone in 67 patients (14.0%), aspirin with extended-release dipyridamole in 39 patients (8.1%), and aspirin with clopidogrel in 30 patients (6.2%).

PROCEDURAL OUTCOMES

Of the 499 patients who were assigned to the closure group, 464 (93.0%) underwent the procedure, and the Amplatzer PFO Occluder was implanted in 462 of them. The rate of technical success (delivery and release of the device) was 99.1%. The rate of procedural success (implantation with no in-hospital serious adverse events) was 96.1%. The mean procedure time was 51.9±28.6 minutes, and the mean fluoroscopy time was 11.8±8.9 minutes.

PRIMARY END POINT

A total of 25 primary end-point events occurred, all of which were nonfatal ischemic strokes. In the intention-to-treat cohort, 9 events occurred in patients in the closure group, and 16 in patients in the medical-therapy group. The difference between the two groups in the number of patient-years of follow-up met the criteria for considering the raw-count analysis of the intention-to-treat cohort invalid. In the primary time-to-event analysis of the 980 patients in the intention-to-treat cohort (499 in the closure group and 481 in the medical-therapy group) with 25 primary end-point events (9 in the closure group and 16 in the medical-therapy group), the rate of the primary end point was 0.66 events per 100 patient-years in the closure group as compared with 1.38 events per 100 patient-years in the medical-therapy group (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P=0.08) (Fig. 1A).

The per-protocol cohort consisted of 944 patients (471 in the closure group and 473 in the medical-therapy group) with 20 primary end-point events (6 in the closure group and 14 in the medical-therapy group) (Fig. S4 in the Supplementary Appendix). The rate of the primary end point was 0.46 events per 100 patient-years in the closure group as compared with 1.30 events per 100 patient-years in the medical-therapy group (hazard ratio, 0.37; 95% CI, 0.14 to 0.96; P=0.03) (Fig. S3 in the Supplementary Appendix).

The as-treated cohort consisted of 958 patients (474 in the closure group and 484 in the medical-therapy group) with 21 primary end-point events (5 in the closure group and 16 in the medical-therapy group) (Fig. S5 in the Supplementary Appendix). The rate of the primary end point was 0.39 events per 100 patient-years in the closure group as compared with 1.45 events per 100 patient-years in the medical-therapy group (hazard ratio, 0.27; 95% CI, 0.10 to 0.75; P=0.007) (Fig. 1B).

The event-rate point estimates for recurrent ischemic stroke in the intention-to-treat cohort were 1.3% in the closure group as compared with 1.7% in the medical-therapy group at 1 year, 1.6% as compared with 3.0% at 2 years, and 2.2% as compared with 6.4% at 5 years. Analyses to determine the potential heterogeneity of the treatment effect according to baseline covariates suggested that closure may have provided a greater benefit in patients with a substantial (grade 3) right-to-left shunt and in those with an atrial septal aneurysm (Fig. 2). The size of recurrent ischemic strokes differed between the treatment

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closure Group (N=499)	Medical 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)
Medical history — no./total no. (%)			
Diabetes mellitus	33/499 (6.6)	40/481 (8.3)	73/980 (7.4)
Systemic hypertension	158/499 (31.7)	150/481 (31.2)	308/980 (31.4)
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	194/499 (38.9)	193/481 (40.1)	387/980 (39.5)
Coronary artery disease	19/499 (3.8)	9/481 (1.9)	28/980 (2.9)
Previous 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	135/495 (27.3)	108/480 (22.5)	243/975 (24.9)
Migraine	195/499 (39.1)	185/481 (38.5)	380/980 (38.8)
Deep-vein thrombosis	20/499 (4.0)	15/481 (3.1)	35/980 (3.6)
Congestive heart failure	3/499 (0.6)	0/481 (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 therapy	41/499 (8.2)	52/481 (10.8)	93/980 (9.5)
Patent foramen ovale — no. (%)			
Maximum right-to-left shunt grade at rest or during Valsalva release†			
Grade 1	108 (21.6)	114 (23.7)	222 (22.7)
Grade 2	138 (27.7)	121 (25.2)	259 (26.4)
Grade 3	247 (49.5)	231 (48.0)	478 (48.8)
Atrial septal aneurysm	180 (36.1)	169 (35.1)	349 (35.6)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any of the characteristics listed.

† The shunt size was graded according to the number of infused microbubbles in the left atrium within three cardiac cycles after their appearance in the right atrium at rest or during Valsalva release, as seen on a transesophageal echocardiogram. Grade 1 indicated 1 to 9 bubbles; grade 2, 10 to 20 bubbles; and grade 3, more than 20 bubbles.

groups, with moderate, large, or massive infarcts occurring in 69% of the patients (9 of 13 patients) in the medical-therapy group as compared with 14% of the patients (1 of 7) in the closure group (P=0.06).

SECONDARY END POINTS

At 6 months, 72.7% of the patients in the closure group met the criteria for complete closure of the patent foramen ovale and 93.5% met the criteria for effective closure. In time-to-event analyses of the intention-to-treat cohort, the composite end point of recurrent symptomatic nonfatal ischemic stroke or cardiovascular death occurred less frequently in the closure group than in the medical-therapy group (hazard ratio, 0.17; 95% CI, 0.02 to 1.47; P=0.07). There was no significant difference between the two groups in the incidence of transient ischemic attack (hazard ratio, 0.89; 95% CI, 0.31 to 2.54; P=0.83).

SAFETY

The rate of serious adverse events did not differ significantly between the closure group and the medical-therapy group (23.0% and 21.6%, respectively; P=0.65) (Table S5 in the Supplementary

Appendix). None of the study-related serious adverse events resulted in death or permanent disability. No unanticipated adverse effects of the device were reported.

There were 22 serious adverse events in the closure group that were adjudicated as device-related or procedure-related (Table 2). Pericardial tamponade occurred in two patients and was treated during the course of the procedure. The rate of atrial fibrillation classified as a serious adverse event was identical in the closure group and the medical-therapy group, and the total incidence of atrial fibrillation did not differ significantly between the two groups (3.0% and 1.5%, respectively; P=0.13).

A procedure-related cardiac thrombus, detected in the right atrium, developed in one patient and resulted in abandonment of the procedure, with no device implanted. Another cardiac thrombus was adjudicated as device-related: a right atrial thrombus not attached to the device was detected in a patient 4 months after the procedure, together with a pulmonary embolism and a deep-vein thrombosis. A pulmonary embolism developed in six patients (1.2%) in the closure group and one patient (0.2%) in the medical-therapy group (P=0.12); the incidence of pulmonary embolism continues to be monitored. Three deaths in the device group and six in the medical-therapy group occurred after the early postrandomization period and were adjudicated as not study-related (Table S6 in the Supplementary Appendix).

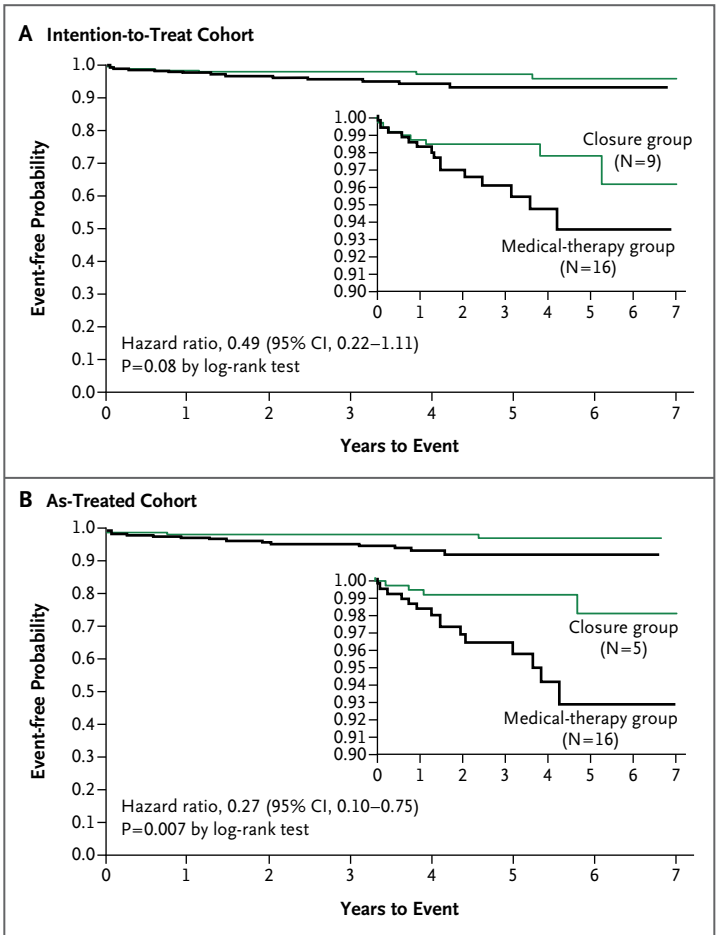

Figure 1. Primary End-Point Events in the Intention-to-Treat and As-Treated Cohorts.

In the intention-to-treat cohort (Panel A), there were 25 primary end-point events, all of which were recurrent nonfatal ischemic strokes; 9 occurred in patients who were assigned to the closure group and 16 in patients assigned to the medical-therapy group. Three patients with recurrent ischemic stroke who had been randomly assigned to the closure group did not have a device in place at the time of the recurrent stroke. The as-treated cohort (Panel B) included all patients who received a protocol-approved treatment and adhered to the protocol-mandated medical treatment; in this cohort, patients were classified according to the treatment they actually received, regardless of the randomization assignment. The insets show the same data on an enlarged y axis.

DISCUSSION

In this study of patients who had had a cryptogenic ischemic stroke, closure of a patent foramen ovale with the Amplatzer PFO Occluder was compared with medical therapy alone. No significant benefit of closure of the patent foramen ovale was shown in the primary (intention-to-treat) analysis. The primary analysis of the intention-to-treat cohort showed a nominal 51% hazard-rate reduction with closure, but the reduction did not reach significance. However, closure of a patent foramen ovale with the Amplatzer PFO Occluder was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.

Implantation of the Amplatzer PFO Occluder was associated with a high rate of procedural success (96.1%), with minimal or no residual shunting in 93.5% of treated patients. The procedure-related and device-related complications included 22 serious events in 21 of the 499 patients, but no recurrent strokes from atrial fibrillation or device thrombosis occurred, and the overall frequency of serious adverse events did not differ significantly between the closure group and the medical-therapy group.

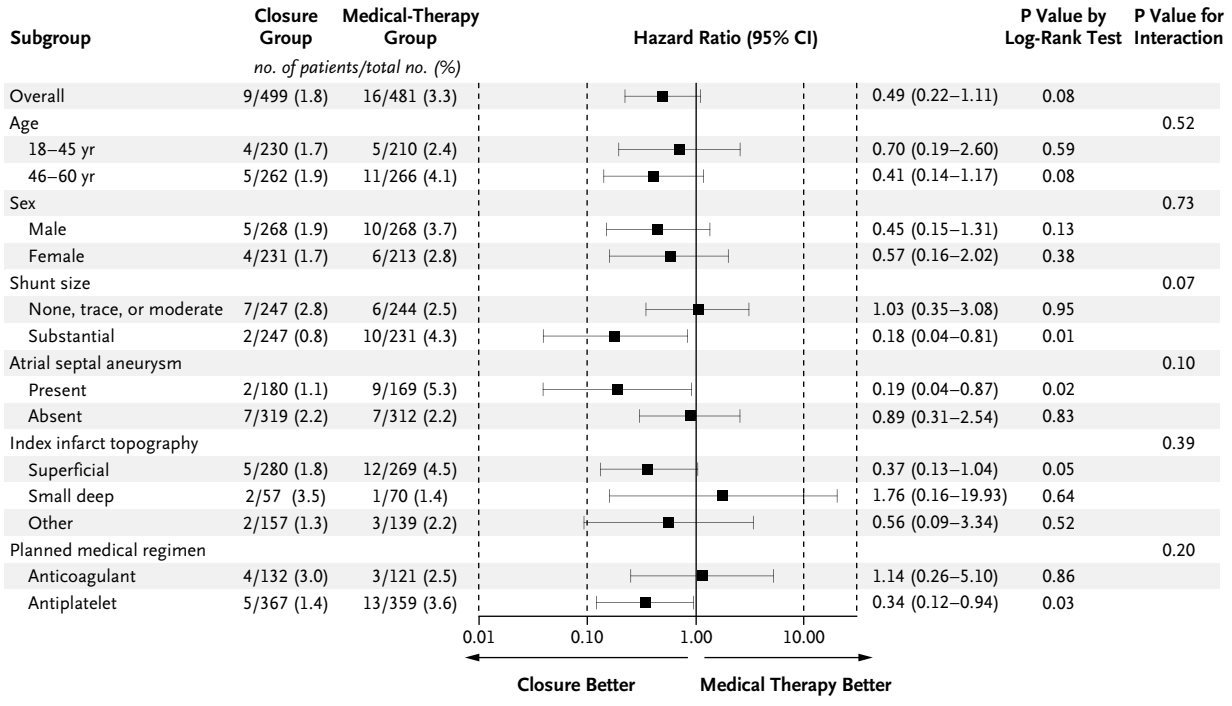

Figure 2. Analysis of the Primary End-Point According to Subgroup, in the Intention-to-Treat Cohort.

Potential heterogeneity of the treatment effect was noted with respect to two baseline characteristics, with a suggestion of greater risk reductions with closure than with medical therapy alone in patients with an atrial septal aneurysm or a substantial shunt size. The percentages are Kaplan–Meier estimates of the event rates.

The strengths of RESPECT include the randomized design; the frequency of monitoring at all sites; the adjudication of end-point events by an independent, expert clinical events committee, whose members were unaware of the identities of the patients, the treatment assignments, and the site at which the patients were enrolled; an independent evaluation of all end-point events and adverse events by a data and safety monitoring board; and a study design that allowed long-term ascertainment of outcomes in many patients.

An exploratory subgroup analysis suggested heterogeneity of the treatment effect in favor of closure in subgroups defined according to two baseline characteristics: the presence of an atrial septal aneurysm and a substantial shunt size. These characteristics have been shown in epidemiologic studies to be associated with an increased likelihood that a stroke is related to a patent foramen ovale and therefore provide supportive evidence of a true biologic effect and rationale for closure of a patent foramen ovale.

Point estimates for the relative reduction in recurrent ischemic strokes with closure versus medical therapy alone were large, but the absolute reduction was modest. Nonetheless, if in fact there is a long-lasting protective benefit of closure, the clinical benefit may be substantial, since patients 18 to 60 years of age are at risk over an extended period. The magnitude of the absolute reduction in events exceeds that of several well-established pharmacologic treatments for the prevention of secondary strokes.[14,15] In addition, closure of a patent foramen ovale was associated with a reduction in moderate, large, and massive infarcts in a post hoc analysis.

In both RESPECT and CLOSURE I,[3] the intention-to-treat analysis did not show the superiority of closure of a patent foramen ovale over medical therapy alone. However, our secondary analysis did show the superiority of closure, unlike the secondary analysis in CLOSURE I. There were important differences between the two trials with respect to study design, the population in-

Table 2. Serious Adverse Events Related to the Procedure or Device among the 499 Patients in the 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)	—
Atrial fibrillation	1 (0.2)	1	1 (0.2)	—
Atrial flutter	1 (0.2)	1	—	1 (0.2)
Cardiac perforation	1 (0.2)	1	1 (0.2)	—
Cardiac thrombus	2 (0.4)	2	1 (0.2)	1 (0.2)
Chest tightness	1 (0.2)	1	—	1 (0.2)
Deep-vein thrombosis	1 (0.2)	1	1 (0.2)	—
Infective or bacterial endocarditis	1 (0.2)	1	—	1 (0.2)
Ischemic stroke	2 (0.4)	2	—	2 (0.4)
Pericardial effusion	1 (0.2)	1	1 (0.2)	—
Pericardial tamponade	2 (0.4)	2	2 (0.4)	—
Pulmonary embolism	1 (0.2)	1	—	1 (0.2)
Residual shunt requiring closure	1 (0.2)	1	—	1 (0.2)
Sepsis	1 (0.2)	1	—	1 (0.2)
Nonsustained ventricular tachycardia	1 (0.2)	1	—	1 (0.2)
Major vascular complications				
Bleeding	2 (0.4)	2	2 (0.4)	—
Hematoma	1 (0.2)	1	1 (0.2)	—
Vasovagal reaction	1 (0.2)	1	1 (0.2)	—
Total	21 (4.2)	22	12 (2.4)	10 (2.0)

* 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 S5 in the Supplementary Appendix.

cluded, and the device tested.[16] The follow-up period was longer in RESPECT than in CLOSURE I, which had a fixed 2-year observation period. In addition, the enrollment criteria in RESPECT were more stringent than were those in CLOSURE I. Patients who had had only a transient ischemic attack did not meet the enrollment criteria for RESPECT, and patients with a lacunar stroke that was probably due to intrinsic cerebral small-vessel disease were excluded from RESPECT. Moreover, the Amplatzer PFO Occluder, as compared with the STARFlex device used in CLOSURE I, was associated with higher effective closure rates, without provoking events that could lead to recurrent stroke, such as device thrombosis and atrial fibrillation.

The PC Trial, which is reported elsewhere in this issue of the *Journal*, studied the same closure device, the Amplatzer PFO Occluder.[17] Both the PC Trial and RESPECT showed excellent safety-related results with respect to the device and the procedure and a high rate of closure of the patent foramen ovale, but neither study individually showed the superiority of closure over medical therapy alone in the intention-to-treat cohort. Combining RESPECT and PC Trial data, including patient-level pooling of the results, is needed to report the totality of evidence.

There are several limitations of this study. First, the difference in the dropout rate between the medical-therapy group and the device group, which resulted in unequal duration of exposure to the risk of recurrence, complicates the interpretation of the results. Loss of some patients from the medical-therapy group may have been due to the availability of off-label procedures for closure of a patent foramen ovale with the use of FDA-approved devices that are not specified for

that use and to patients' declining motivation to remain in long-term follow-up when the only therapy being received was medication. Second, entry and retention biases could have been introduced by the possibility that high-risk patients were preferentially treated outside the trial.[18]

Third, the results of the per-protocol and as-treated analyses need to be interpreted with caution, owing to potential bias arising from nonrandom factors that may have accounted for nonadherence to the protocol (Fig. S4 and S5 in the Supplementary Appendix). On the other hand, the results of these analyses are important to consider because some patients did not receive the randomly assigned treatment.[19] Of the nine primary events of recurrent ischemic stroke that occurred in the closure group of the intention-to-treat population, three occurred in patients who did not have a device in place at the time of the recurrent stroke. In one case, the stroke occurred after randomization but before the closure procedure; in the second case, the stroke occurred in a patient who decided not to undergo the procedure; and in the third case, the stroke occurred after the patient underwent unanticipated coronary-artery bypass surgery during which the patent foramen ovale was closed with a surgical patch rather than with the assigned device.

In conclusion, in patients between 18 and 60 years of age who had had a cryptogenic ischemic stroke, there was no significant benefit of closure of a patent foramen ovale over medical therapy alone in the intention-to-treat analysis. The superiority of closure with the use of the Amplatzer PFO Occluder was shown in two prespecified secondary analyses, with a low rate of associated risks.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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