The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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ABSTRACT

BACKGROUND

Trials of patent foramen ovale (PFO) closure to prevent recurrent stroke have been inconclusive. We investigated whether patients with cryptogenic stroke and echocardiographic features representing risk of stroke would benefit from PFO closure or anticoagulation, as compared with antiplatelet therapy.

METHODS

In a multicenter, randomized, open-label trial, we assigned, in a 1:1:1 ratio, patients 16 to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, to transcatheter PFO closure plus long-term antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group) (randomization group 1). Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative noncontraindicated treatment or to antiplatelet therapy (randomization groups 2 and 3). The primary outcome was occurrence of stroke. The comparison of PFO closure plus antiplatelet therapy with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 2, and the comparison of oral anticoagulation with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 3.

RESULTS

A total of 663 patients underwent randomization and were followed for a mean (±SD) of 5.3±2.0 years. In the analysis of randomization groups 1 and 2, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet-only group (hazard ratio, 0.03; 95% confidence interval, 0 to 0.26; P<0.001). Procedural complications from PFO closure occurred in 14 patients (5.9%). The rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%, P=0.02). The number of serious adverse events did not differ significantly between the treatment groups (P=0.56). In the analysis of randomization groups 1 and 3, stroke occurred in 3 of 187 patients assigned to oral anticoagulants and in 7 of 174 patients assigned to antiplatelet therapy alone.

CONCLUSIONS

Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT00562289.)

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*A complete list of the Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on September 14, 2017, at NEJM.org.

N Engl J Med 2017;377:1011-21.
DOI: 10.1056/NEJMoa1705915
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Case–control studies have shown an association between patent foramen ovale (PFO) and cryptogenic stroke, particularly among patients younger than 55 years of age and among patients with an associated atrial septal aneurysm or a substantial right-to-left interatrial shunt.[1-6] The role of closure of PFO in preventing stroke recurrence in these patients remains uncertain.[7] Although it is plausible that closure of the defect could reduce the risk of recurrent stroke, several randomized trials have not shown the superiority of PFO closure over antithrombotic therapy.[8-10]

We performed the Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial to compare transcatheter closure of PFO plus long-term antiplatelet therapy with antiplatelet therapy alone and to compare oral anticoagulant therapy with antiplatelet therapy for the prevention of stroke recurrence in patients, 16 to 60 years of age, who had had a recent cryptogenic stroke attributed to PFO with an atrial septal aneurysm or large right-to-left shunt.[11]

Methods

Study Design

This was an investigator-initiated, multicenter, randomized, open-label, superiority trial with three randomization groups. The trial was conducted at 32 sites in France and at 2 sites in Germany from December 2007 through December 2016. The trial was approved by the Paris Ile de France IV ethics committee. All patients provided written informed consent. The Assistance Publique–Hôpitaux de Paris was responsible for the management and monitoring of the data. An independent data and safety monitoring board met periodically to assess safety and trial integrity. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

Patient Eligibility

Patients 16 to 60 years of age were eligible for the trial if they had had an ischemic stroke within the previous 6 months with no identifiable cause other than a PFO with an associated atrial septal aneurysm or large interatrial shunt. The investigations that were used to rule out alternative causes of strokes are shown in Table S1 in the Supplementary Appendix, available at NEJM.org. Long-term (≥30 days) electrocardiographic monitoring was not performed. Findings from transthoracic and transesophageal echocardiography were reviewed at a central location by two echocardiographers before patients were included in the trial. Atrial septal aneurysm was diagnosed on the basis of a septum primum excursion greater than 10 mm, as identified on transesophageal echocardiography.[3] Large shunt was defined by the appearance of more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium. Ischemic stroke was defined as acute focal neurologic symptoms with a recent cerebral infarct, as identified on brain imaging, regardless of the duration of the symptoms.

Randomization

Eligible patients were randomly assigned, in a 1:1:1 ratio, to undergo PFO closure followed by long-term antiplatelet therapy (PFO closure group), to receive antiplatelet therapy alone (antiplatelet-only group), or to receive oral anticoagulation (anticoagulation group) (randomization group 1); randomization was performed with the use of dedicated Web-based software. Patients who had a contraindication to oral anticoagulation were randomly assigned to PFO closure plus antiplatelet therapy (PFO closure group) or to antiplatelet therapy alone (antiplatelet-only group) (randomization group 2). Patients who had a contraindication to PFO closure were randomly assigned to anticoagulant therapy (anticoagulation group) or to antiplatelet therapy (antiplatelet-only group) (randomization group 3) (Fig. 1).[12,13] Randomization was stratified according to participating center, randomization group, and type of septal anomaly (atrial septal aneurysm vs. large shunt) and was performed with the use of permuted blocks with varying block sizes.

Trial Treatments

Treatments were administered in an open-label fashion and were started as soon as possible, but in all cases within 3 weeks after randomization. PFO closure was performed by experienced interventional cardiologists who used implantable medical devices approved by the Interventional Cardiology Committee (see the Supplementary Appendix). All the patients who underwent PFO closure received dual antiplatelet therapy (75 mg

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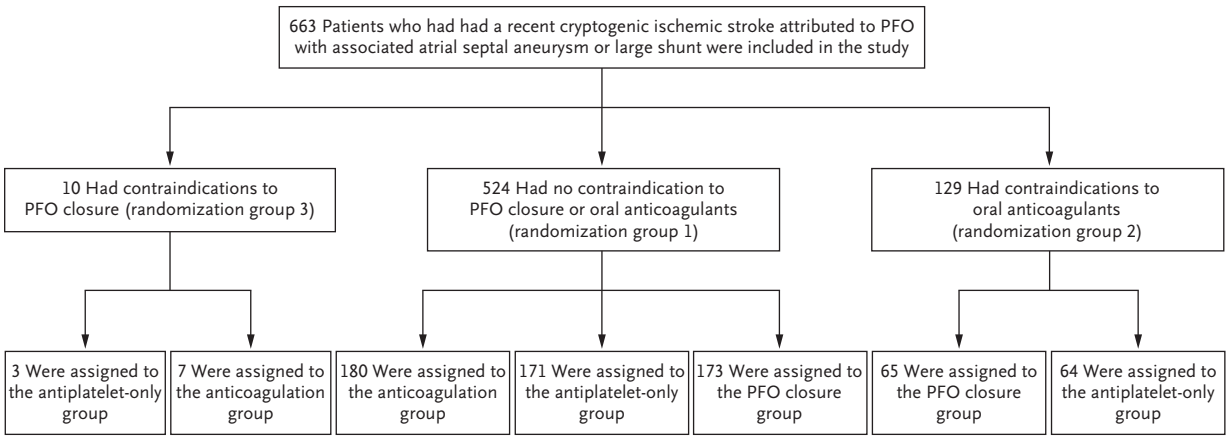


Figure 1. Randomization of Patients.

Of the 664 patients initially enrolled, 1 patient withdrew consent soon after randomization. According to French law, data concerning this patient cannot be used. Therefore, data from only 663 patients are presented. The patent foramen ovale (PFO) closure group comprised patients assigned to transcatheter PFO closure plus long-term antiplatelet therapy; the antiplatelet-only group, patients assigned to antiplatelet therapy alone; and the anticoagulation group, patients assigned to oral anticoagulation.

of aspirin plus 75 mg of clopidogrel per day) for 3 months, followed by single antiplatelet therapy throughout the remainder of the trial. Patients assigned to oral anticoagulants could be treated with vitamin K antagonists (with a target international normalized ratio [INR] of 2 to 3) or with direct oral anticoagulants. Patients assigned to antiplatelet therapy alone or to PFO closure plus antiplatelet therapy could receive aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole (except for the 3 months after PFO closure during which time dual-antiplatelet therapy was used).

ASSESSMENTS

Study neurologists, who were aware of the treatment assignments, evaluated all patients at 2 months, 6 months, and every 6 months thereafter until the end of the trial. At each visit, clinical outcomes, cardiac rhythm, adherence to trial treatment, blood pressure, smoking status, and INR values were recorded; cardiac rhythm was assessed by cardiac auscultation, which was followed by electrocardiography in the case of an abnormal auscultation result. The results of PFO closure were assessed with the use of contrast echocardiography 6 to 12 months after the procedure. Because the trial was prolonged beyond the planned duration of 5 years, patients who reached 5 years of follow-up were then followed by means of regular telephone interviews and were requested to continue their assigned treatment until the end of the study. At each telephone interview, the Questionnaire for Verifying Stroke-Free Status[14] was administered to identify potential cerebrovascular events.

OUTCOMES

The primary efficacy outcome was the occurrence of fatal or nonfatal stroke. Secondary efficacy outcomes were the composite of ischemic stroke, transient ischemic attack, or systemic embolism; disabling stroke; ischemic stroke; cerebral hemorrhage; transient ischemic attack; systemic embolism; all-cause mortality; death from vascular-related causes; success of device implantation; and success of PFO closure. Safety outcomes were major or fatal procedural or hemorrhagic complications. A clinical events committee, whose members were unaware of the treatment assignments, independently adjudicated outcome events and assessed their severity (definitions of outcomes are provided in the Supplementary Appendix).

STATISTICAL ANALYSES

We calculated the sample size so that the study would have 80% power to detect a 50% lower annual rate of the primary outcome with PFO closure plus antiplatelet therapy or with oral anticoagulation than with antiplatelet therapy alone during a 2-year inclusion period and 3-year

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follow-up period, at an overall type 1 error rate of 5%. We used two one-sided superiority hypotheses and Bonferroni adjustment, with an assumed correlation of 0.5 between the two test statistics. We estimated the total sample for this three-randomization-group trial by calculating a theoretical sample for a fictitious two-randomization group trial, at a type 1 error rate of 0.035, and then multiplying the result by 1.5.[15,16] An inflation factor of 1.05 was used to account for one planned interim analysis. Assuming an annual stroke risk of 3.5% with antiplatelet therapy alone, we projected that we would need to enroll 900 patients.

Because of a lower-than-expected rate of patient recruitment, the sponsor determined that the study budget would not be sufficient to reach the target of 900 patients. Therefore, the steering committee decided to stop enrollment on December 18, 2014, and to pursue follow-up of all patients until December 18, 2016. Because the rate of the primary end point was also lower than expected, the data and safety monitoring board did not perform a planned interim analysis.

The test for superiority of PFO closure plus antiplatelet therapy over antiplatelet therapy alone was performed with combined patient data from randomization groups 1 and 2, after verification of the absence of interaction between treatment effect and treatment group.[12,13] The comparison of oral anticoagulants with antiplatelet therapy was performed with combined patient data from randomization groups 1 and 3. The primary efficacy analysis was performed in the intention-to-treat cohort, which included all patients who were randomly assigned to a treatment. An additional analysis was performed in the per-protocol cohort, which included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation. Survival curves were estimated by means of the Kaplan–Meier method. Hazard ratios with 95% confidence intervals and corresponding P values were calculated with the use of a stratified Cox model with Firth's penalized likelihood method.[17,18] Data from the patients who did not reach the primary outcome or who were lost to follow-up were censored at the end of the follow-up period, at the time of death, or at the last known follow-up visit. Planned subgroup analyses were performed in subgroups defined according to age (above vs. below the median), sex, presence of an atrial septal aneurysm versus a large interatrial shunt, history of a cerebrovascular event (before the qualifying event) versus no previous cerebrovascular event, and Risk of Paradoxical Embolism (RoPE) score[19] (<7 vs. ≥7; scores range from 0 to 10, with higher scores representing a higher probability that a PFO is related to the cryptogenic stroke); these analyses were not corrected for multiple comparisons. All P values were two-sided.

RESULTS

PATIENTS

From December 2008 through December 2016, a total of 664 patients were enrolled. Treatment assignments for the patients in the three randomization groups are shown in Figure 1. One patient withdrew consent. Of the 663 remaining patients, 524 (randomization group 1) were randomly assigned to the PFO closure group (173 patients), the anticoagulant group (180 patients), or the antiplatelet-only group (171 patients). The 129 patients who had contraindications to oral anticoagulants (randomization group 2) were randomly assigned to the PFO closure group (65 patients) or the antiplatelet-only group (64 patients), and the 10 patients who had contraindications to PFO closure (randomization group 3) were randomly assigned to the anticoagulant group (7 patients) or the antiplatelet group (3 patients). Contraindications to oral anticoagulants or to PFO closure are shown in Table S2 in the Supplementary Appendix. The main contraindications to oral anticoagulation were work-related and athletic activities that posed a risk of bleeding.

CHARACTERISTICS OF PATIENTS IN THE PFO CLOSURE GROUP AND THE ANTIPLATELET-ONLY GROUP

In an analysis that included randomization groups 1 and 2, baseline characteristics did not differ significantly between the patients in the PFO closure group and those in the antiplatelet-only group, either when the randomization groups were analyzed separately (Table S3 in the Supplementary Appendix) or when they were analyzed together (Table 1). Because the treatment effect of PFO closure versus antiplatelet therapy did

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Randomization Groups 1 and 2		Randomization Groups 1 and 3	
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)
Age — yr	42.9±10.1	43.8±10.5	43.8±9.5	44.7±10.5
Male sex — no. (%)	137 (57.6)	142 (60.4)	104 (55.6)	102 (58.6)
Medical history				
Hypertension — no. (%)	27 (11.3)	24 (10.2)	15 (8.0)	19 (10.9)
Diabetes mellitus — no. (%)	3 (1.3)	9 (3.8)	2 (1.1)	7 (4.0)
Current smoker — no. (%)	68 (28.6)	69 (29.4)	54 (28.9)	50 (28.7)
Hypercholesterolemia — no. (%)	30 (12.6)	36 (15.3)	22 (11.8)	25 (14.4)
Body mass index ≥30 — no. (%)†	32 (13.4)	27 (11.5)	20 (10.7)	24 (13.8)
Oral contraceptive pills — no./total no. (%)	42/101 (41.6)	37/93 (39.8)	31/83 (37.3)	28/72 (38.9)
Migraine — no. (%)‡	67 (28.2)	78 (33.2)	50 (26.7)	49 (28.2)
Stroke — no. (%)	10 (4.2)	7 (3.0)	6 (3.2)	5 (2.9)
Myocardial infarction — no. (%)	0	0	1 (0.5)	0
Deep-vein thrombosis or pulmonary embolism — no. (%)	5 (2.1)	4 (1.7)	4 (2.1)	3 (1.7)
Qualifying event — no. (%)				
Carotid infarct	146 (61.3)§	139 (59.1)¶	104 (55.6)¶	107 (61.5)¶
Vertebrobasilar infarct	92 (38.7)	96 (40.9)	83 (44.4)	67 (38.5)
Modified Rankin scale — no. (%)‖				
0 or 1	197 (82.8)	189 (80.4)	151 (80.7)	140 (80.5)
2 or 3	41 (17.2)	46 (19.6)	36 (19.3)	34 (19.5)
RoPE score**	7.4±1.3	7.2±1.3	7.3±1.2	7.1±1.3
Septal anomaly — no. (%)				
PFO with large shunt without atrial septal aneurysm	157 (66.0)	161 (68.5)	113 (60.4)	124 (71.3)
PFO with large shunt and atrial septal aneurysm	59 (24.8)	62 (26.4)	60 (32.1)	42 (24.1)
PFO with mild-to-moderate shunt and atrial septal aneurysm	22 (9.2)	12 (5.1)	14 (7.5)	8 (4.6)

* Plus–minus values are means ±SD. Baseline characteristics did not differ significantly (P<0.05) between randomization groups. The patent foramen ovale (PFO) closure group comprised patients assigned to transcatheter PFO closure plus long-term antiplatelet therapy; the antiplatelet-only group, patients assigned to antiplatelet therapy alone; and the anticoagulation group, patients assigned to oral anticoagulation.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Migraine included migraine with or without aura, as defined according to the International Classification of Headache Disorders.

§ Two patients had both carotid and vertebrobasilar infarcts.

¶ One patient had both carotid and vertebrobasilar infarcts.

‖ The modified Rankin scale is a measure of disability. Scores range from 0 (no symptoms) to 6 (death). A score of 3 or higher indicates at least moderate disability, with the need for some help in daily affairs.

** Risk of Paradoxical Embolism (RoPE) is a score index used to indicate whether a PFO in cryptogenic stroke is stroke-related or incidental. Scores range from 0 to 10, with larger values representing a higher probability that a PFO is related to cryptogenic stroke.

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not differ between randomization groups 1 and 2 (P=0.99 for interaction), the outcome data from the patients assigned to PFO closure in each randomization group were combined, as were the outcome data from the patients assigned to antiplatelet therapy alone. Among the 238 patients in the combined PFO closure group, 2 declined the intervention, 1 had no PFO at the time of intervention, 1 had an atrial septal defect alone rather than a PFO, and 17 discontinued antiplatelet therapy. Among the 235 patients in the combined antiplatelet-only group, 2 were lost to follow-up and 10 discontinued antiplatelet treatment (of whom 3 underwent PFO closure) (Fig. S1 in the Supplementary Appendix).

Eleven different devices were used for PFO closure; the number of patients treated with each device and the anesthesia procedures used during the closure are shown in Table S4 in the Supplementary Appendix. In the antiplatelet-only group and the PFO closure group, 410 patients (86.7%) received aspirin, 51 (10.8%) received clopidogrel, 6 (1.3%) received aspirin with extended-release dipyridamole, and 6 (1.3%) received aspirin with clopidogrel. Antiplatelet treatments did not differ significantly between the PFO closure group and the antiplatelet-only group, with the exception that, as stipulated in the protocol, dual antiplatelet therapy was administered for 3 months after PFO closure.

The mean (±SD) duration of follow-up was 5.4±1.9 years in the PFO closure group and 5.2±2.1 years in the antiplatelet-only group (P=0.28). The treatment groups remained balanced with respect to blood pressure, percentage of smokers, and low-density lipoprotein cholesterol concentrations, as determined at follow-up visits over the course of the trial (Figs. S2 through S4 in the Supplementary Appendix).

OUTCOMES IN THE PFO CLOSURE GROUP VERSUS THE ANTIPLATELET-ONLY GROUP

In the intention-to-treat cohort, no patient in the PFO closure group had a stroke, whereas stroke occurred in 14 patients in the antiplatelet-only group (hazard ratio, 0.03; 95% confidence interval [CI], 0 to 0.26; P<0.001) (Fig. 2 and Table 2). The Kaplan–Meier 5-year cumulative estimate of the probability of stroke was 4.9% in the antiplatelet-only group. Among these patients, no explanation for recurrent stroke other than PFO was found on repeated investigations. Of the 14 recurrent strokes that occurred in the antiplatelet-only group, 9 occurred among the 74 patients (12.2%) who had both PFO and atrial septal aneurysm, and 5 occurred among the 161 patients (3.1%) who had large PFO without atrial septal aneurysm.

The secondary composite outcome of stroke, transient ischemic attack, or systemic embolism occurred in significantly fewer patients in the PFO closure group than in the antiplatelet-only group (3.4% vs. 8.9%; hazard ratio, 0.39; 95% CI, 0.16 to 0.82; P=0.01). The rates of transient ischemic attack, disabling stroke, major hemorrhagic complications, and serious adverse events did not differ significantly between the treatment groups, and there were no events of cerebral hemorrhage, systemic emboli, or death in either treatment group (Tables 2 and 3). Follow-up echocardiography was performed in 228 patients at a mean of 10.8 months after closure. Among these patients, 212 (93.0%) had no or minimal (<10 microbubbles) residual shunt.

A total of 440 patients were available for the per-protocol analysis. Baseline characteristics and mean duration of follow-up did not differ significantly between the PFO closure group and the antiplatelet-only group (Fig. S1 and Table S5 in the Supplementary Appendix). None of the 217 patients in the PFO closure group had a stroke, whereas stroke occurred in 14 of the 223 patients in the antiplatelet-only group (hazard ratio, 0.04; 95% CI, 0 to 0.27; P<0.001) (Table 2). There was no evidence of heterogeneity of treatment effect in the subgroup analyses (Fig. S5 in the Supplementary Appendix).

PROCEDURAL COMPLICATIONS AND SERIOUS ADVERSE EVENTS

Major procedural complications occurred in 14 patients (5.9%) in the PFO closure group. The rate of new-onset atrial fibrillation or flutter was higher in the PFO closure group than in the antiplatelet-only group: 11 patients in the PFO closure group (4.6%; 10 with atrial fibrillation and 1 with atrial flutter, with atrial fibrillation or flutter occurring within 1 month after the procedure in 10 of the 11 patients), as compared with 2 patients (0.9%) in the antiplatelet-only group (P=0.02) (Table 3). In the PFO closure group, atrial fibrillation did not recur during a median follow-up of 4.4 years (range, 1.4 to 5.0). Of the 11 patients with atrial fibrillation or flutter in

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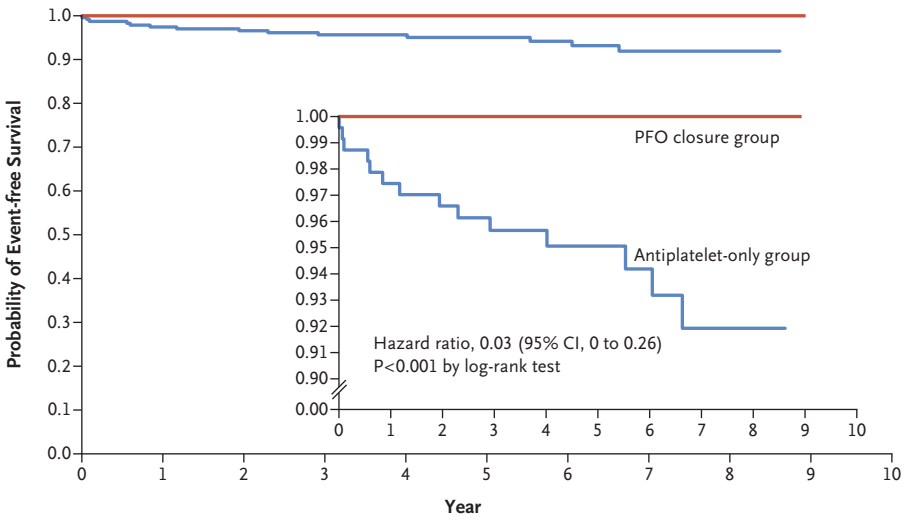


Figure 2. Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.

The analysis was performed in the intention-to-treat cohort, which included all patients who were randomly assigned to a treatment. The inset shows the same data on an enlarged y axis.

the group, 10 were treated with oral anticoagulants, which were discontinued in 7 patients after a median of 0.5 years (range, 0.2 to 2.1). Three patients were still receiving an anticoagulant at the last follow-up visit (Table S6 in the Supplementary Appendix). None of the procedural complications resulted in death or permanent disability. Serious adverse events occurred in 35.7% of the patients in the PFO closure group and in 33.2% of the patients in the antiplatelet-only group (P=0.56) (Table S7 in the Supplementary Appendix).

OUTCOMES IN THE ANTICOAGULATION GROUP VERSUS THE ANTIPLATELET-ONLY GROUP

Baseline characteristics did not differ significantly between the anticoagulation group and the antiplatelet-only group (including data from randomization groups 1 and 3, which were combined for the purposes of this analysis) (Table 1, and Table S8 in the Supplementary Appendix). Among the 187 patients in the anticoagulant group, 5 were lost to follow-up, 1 did not receive anticoagulation, and 38 discontinued anticoagulation (of whom 3 underwent PFO closure). Among the 174 patients in the antiplatelet-only group, 1 was lost to follow-up and 9 discontinued treatment (of whom 3 underwent PFO closure) (Fig. S6 in the Supplementary Appendix). The mean duration of follow-up was 5.4±2.0 years in the anticoagulant group and 5.3±2.0 years in the antiplatelet-only group. Among the patients in the anticoagulant group, 174 (93.0%) received vitamin K antagonists and 13 (7.0%) received direct oral anticoagulants (6 received dabigatran, 6 received rivaroxaban, and 1 received apixaban). Patients receiving vitamin K agonists had an INR in the range of 2 to 3 at 74.3% of visits.

In the intention-to-treat cohort, stroke occurred in 3 patients in the anticoagulation group and in 7 patients in the antiplatelet-only group (Table 2, and Fig. S7 in the Supplementary Appendix). The Kaplan–Meier 5-year cumulative estimate of the probability of stroke was 1.5% in the anticoagulant group and 3.8% in the antiplatelet-only group. Statistical significance was not analyzed because the study was not adequately powered to compare outcomes in these groups. The rates of secondary efficacy and safety outcomes are shown in Table 2 and Table 3.

A total of 307 patients were available for the per-protocol analysis (Fig. S6 and Table S5 in the Supplementary Appendix). Strokes occurred in 2 patients in the anticoagulant group and in

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Table 2. Efficacy Outcomes.*

Outcome	Randomization Groups 1 and 2				Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	Hazard Ratio (95% CI)†	P Value	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	Hazard Ratio (95% CI)‡
Primary efficacy outcome							
Stroke in the intention-to-treat population — no. of patients	0	14§	0.03 (0.00–0.26)	<0.001	3¶	7§	0.44 (0.11–1.48)
Stroke in the per-protocol population — no./total no. of patients	0/217	14/223§	0.04 (0.00–0.27)	<0.001	2/143¶	7/164§	0.37 (0.07–1.38)
Secondary efficacy outcomes‖							
Disabling stroke**	0	1	0.33 (0.00–6.18)	0.63	1	1	0.96 (0.08–11.85)
Cerebral hemorrhage	0	0	NA	NA	0	0	NA
Ischemic stroke, transient ischemic attack, or systemic embolism	8	21	0.39 (0.16–0.82)	0.01	8	12	0.64 (0.26–1.50)
Transient ischemic attack	8	8	0.97 (0.37–2.56)	0.96	5	6	0.80 (0.25–2.52)
Systemic embolism	0	0	NA	NA	0	0	NA
Death from any cause	0	0	NA	NA	1††	0	2.84 (0.15–414.86)
Success of device implantation — no./total no. (%)‡‡	234/235 (99.6)	NA	NA	NA	NA	NA	NA
Success of PFO closure — no./total no. (%)§§	202/228 (88.6)	NA	NA	NA	NA	NA	NA

* NA denotes not applicable. The intention-to-treat cohort included all patients who were randomly assigned to a treatment. The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation.
† The hazard ratio was calculated for the PFO closure group as compared with the antiplatelet-only group.
‡ The hazard ratio was calculated for the anticoagulant group as compared with the antiplatelet-only group. Statistical significance was not analyzed because the study was not adequately powered to compare outcomes in these groups.
§ No patient had an alternative explanation for recurrent stroke.
¶ One patient had an alternative cause of stroke (aneurysmal subarachnoid hemorrhage complicated by vasospasm and ischemic strokes).
‖ Secondary efficacy outcomes were analyzed in the intention-to-treat cohort.
** Disabling stroke was defined as a modified Rankin scale score of 3 or higher.
†† The one death was due to pancreatic cancer.
‡‡ Success of device implantation was defined as deployment of the device in the appropriate place and removal of the placement system.
§§ Success of PFO closure was defined as successful implantation with no complication before the patient's discharge and no or minimal residual shunt.

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Table 3. Procedural Complications and Serious Adverse Events.*

Complication or Event	Randomization Groups 1 and 2			Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	P Value	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	P Value
	no. of patients (%)			*no. of patients (%)*		
Major or fatal device-related or procedure-related complication†	14 (5.9)	NA	NA	NA	NA	NA
Major or fatal bleeding complication	2 (0.8)	5 (2.1)	0.28	10 (5.3)	4 (2.3)	0.18
Atrial fibrillation or flutter‡	11 (4.6)§	2 (0.9)	0.02	0	2 (1.1)	0.23
Death	0	0	NA	1 (0.5)¶	0	0.65
At least one serious adverse event	85 (35.7)	78 (33.2)	0.56	62 (33.2)	59 (33.9)	0.88

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.
† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).
‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.
§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.
¶ The one death was due to pancreatic cancer.

7 patients in antiplatelet-only group. Outcomes of subgroup analyses are shown in Figure S8 in the Supplementary Appendix.

DISCUSSION

In this trial of PFO closure in a selected group of patients who had had a recent cryptogenic ischemic stroke attributed to PFO with an associated atrial septal aneurysm or large right-to-left interatrial shunt, the rate of recurrent stroke was significantly lower with closure of the PFO plus long-term antiplatelet therapy than with antiplatelet therapy alone. The 5-year risk of stroke, according to the Kaplan–Meier probability estimate, was 4.9 percentage points lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone, which would result in one stroke avoided at 5 years for every 20 treated patients (95% CI, 17 to 25).[20] Among patients in the antiplatelet-only group, most strokes occurred in patients with both PFO and atrial septal aneurysm, a finding that is consistent with the results from our previous observational study.[4]

Three previous randomized trials have not shown the superiority of PFO closure over medical therapy alone in the prevention of stroke recurrence in patients with PFO.[8-10] There were signals in two of these trials that suggested a potential benefit with PFO closure — although the results were nonsignificant — with hazard ratios in favor of PFO closure of 0.20 (95% CI, 0.02 to 1.72)[9] and 0.49 (95% CI, 0.22 to 1.11).[10] Furthermore, in a pooled analysis of individual participant data from the three trials, rates of recurrent stroke were significantly lower with PFO closure than with medical therapy alone.[21]

The rate of effective PFO closure (defined as no or minimal residual shunt at follow-up echocardiography) in our trial (93.0%) was similar to that in previous trials, as was the rate of procedural complications (5.9%).[8-10] The rate of new-onset atrial fibrillation was significantly higher in the PFO closure group than in antiplatelet-only group in our trial, with most cases detected within 1 month after the procedure — a finding that suggests that the procedure itself induces atrial fibrillation. The risk of stroke from atrial fibrillation induced by PFO closure has not been determined. In our trial, atrial fibrillation did not recur during a median follow-up of 4.4 years.

The comparison of oral anticoagulants with antiplatelet agents in the current trial was underpowered, and the wide confidence interval for the hazard ratio prevents any conclusions. A previous systematic review suggested that anticoagulant therapy may be superior to antiplatelet therapy for the prevention of stroke recurrence in patients with PFO.[22]

The restricted patient characteristics in our trial may explain the difference in results from

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previous trials. First, we included only patients who had PFO with features that have been associated with cryptogenic stroke. Second, we used a standardized evaluation to define a previous cryptogenic stroke, which resulted in a low likelihood of alternative causes of recurrent stroke besides PFO.[23,24] Third, patients enrolled in the current trial had a lower burden of vascular risk factors than did the patients in previous trials; thus, the strokes were less likely to have been caused by the usual vascular factors.[19] Finally, we used a reference treatment group that included patients who received antiplatelet therapy alone; in contrast, the reference treatment group used in previous trials included patients who received either antiplatelet drugs or oral anticoagulants (or sometimes both) according to physician preference.

The limitations of this trial were a lower-than-expected rate of patient recruitment and the absence of prolonged electrocardiographic monitoring to detect occult atrial fibrillation[25]; the latter was not included in the evaluation of cryptogenic stroke at the time our trial protocol was devised.[26,27] However, the yield of prolonged electrocardiographic monitoring in young patients with cryptogenic stroke has not been determined, and the potential lack of detection of atrial fibrillation does not explain why the rate of stroke recurrence was lower in the PFO closure group.

In conclusion, among patients 16 to 60 years of age who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke was lower with PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone. The effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined.

Supported by a grant (P060406) the French Ministry of Health.

Dr. Mas reports receiving advisory board fees and lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo; Dr. Guillon, receiving advisory board fees from Boehringer Ingelheim and Pfizer and lecture fees from Bristol-Myers Squibb and Covidien; Dr. Massardier, receiving travel support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer and advisory board fees from Bristol-Myers Squibb; Dr. Arquizan, receiving fees for serving on a scientific committee from Bayer, Boehringer Ingelheim, and Covidien; Dr. Béjot, receiving grant support and fees for serving on a scientific board from AstraZeneca, lecture fees from Bristol-Myers Squibb, Pfizer, MSD, and Bayer, and fees for serving on a scientific board from Covidien, Daiichi Sankyo, and Boehringer Ingelheim; Dr. Canaple, receiving grant support and travel support from Boehringer Ingelheim and travel support from Bayer; Dr. Garnier, receiving lecture fees from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb and advisory board fees from Daiichi Sankyo; Dr. Ferrier, receiving consulting fees and lecture fees from Boehringer Ingelheim, advisory board fees from Bayer and Daiichi Sankyo, and lecture fees from Pfizer; Dr. Timsit, receiving lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo and grant support from Boehringer Ingelheim, Bayer, and Astra Zeneca; Dr. Zuber, receiving advisory board fees from Bayer and Boehringer Ingelheim and lecture fees from Euthérapie, Sanofi, and Bristol-Myers Squibb; Dr. Pinel, receiving fees for serving on a scientific board from Bristol-Myers Squibb–Pfizer and lectures fees from Boehringer Ingelheim and Bristol-Myers Squibb–Pfizer; Dr. Guérin, receiving grant support and lecture fees from Abbott, Boston Scientific, Biotronic, and General Electric; Dr. Meneveau, receiving consulting fees and lecture fees from Abbott Vascular, Bayer Healthcare, Bristol-Myers Squibb–Pfizer, and Boehringer Ingelheim; Dr. Thambo, receiving consulting fees and lecture fees from Boston Scientific; and Dr. Michel, receiving grant support and lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo, lecture fees from Bayer and Pfizer, and consulting fees from Medtronic, Amgen, and AstraZeneca. No other potential conflict of interest relevant to this article was reported.

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

APPENDIX

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