

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

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ABSTRACT

BACKGROUND

The options for secondary prevention of cryptogenic embolism in patients with patent foramen ovale are administration of antithrombotic medications or percutaneous closure of the patent foramen ovale. We investigated whether closure is superior to medical therapy.

METHODS

We performed a multicenter, superiority trial in 29 centers in Europe, Canada, Brazil, and Australia in which the assessors of end points were unaware of the study-group assignments. Patients with a patent foramen ovale and ischemic stroke, transient ischemic attack (TIA), or a peripheral thromboembolic event were randomly assigned to undergo closure of the patent foramen ovale with the Amplatzer PFO Occluder or to receive medical therapy. The primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. Analysis was performed on data for the intention-to-treat population.

RESULTS

The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical-therapy group. The primary end point occurred in 7 of the 204 patients (3.4%) in the closure group and in 11 of the 210 patients (5.2%) in the medical-therapy group (hazard ratio for closure vs. medical therapy, 0.63; 95% confidence interval [CI], 0.24 to 1.62; $P=0.34$). Nonfatal stroke occurred in 1 patient (0.5%) in the closure group and 5 patients (2.4%) in the medical-therapy group (hazard ratio, 0.20; 95% CI, 0.02 to 1.72; $P=0.14$), and TIA occurred in 5 patients (2.5%) and 7 patients (3.3%), respectively (hazard ratio, 0.71; 95% CI, 0.23 to 2.24; $P=0.56$).

CONCLUSIONS

Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT00166257.)

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PARADOXICAL EMBOLISM BY MEANS OF A patent foramen ovale has been blamed as a cause of stroke and other systemic ischemic events since the 19th century.¹ The actual passage of a venous clot through a patent foramen ovale has been documented in a few cases and resulted in systemic embolic events such as ischemic stroke, transient ischemic attack (TIA),²⁻⁶ or myocardial infarction.⁷ Catheter-based closure of patent foramen ovale was introduced in 1992.⁸

Observational long-term data suggest that closure of patent foramen ovale in patients with a history of ischemic stroke may reduce the risk of recurrent stroke as compared with medical therapy alone.^{9,10} However, meta-analyses¹¹⁻¹⁶ suggest that adverse effects of catheter-based closure of patent foramen ovale may result in a clinical course inferior to that after medical treatment. A science advisory from the American Heart Association and the American Stroke Association recommended restricting the closure of patent foramen ovale to randomized trials.¹⁷ We initiated the Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (PC Trial) 14 years ago to determine whether the closure of patent foramen ovale is superior to medical therapy in preventing recurrence of embolic events.¹⁸

METHODS

STUDY DESIGN AND OVERSIGHT

The PC Trial was conducted at 29 sites in Europe, Canada, Brazil, and Australia. The trial design has been described previously.¹⁸ The academic members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study without involvement of the funder, St. Jude Medical. An independent data and safety monitoring board (see the Supplementary Appendix) met periodically for oversight of the trial. No formal stopping rules were specified. The funder was not involved in the conduct of the trial, the writing of the manuscript, or the decision to submit the manuscript for publication, but it did provide organizational support for the adjudication of clinical events and the meetings of the data and safety monitoring board.

The members of the steering committee, the

trial statistician, and the senior author had full access to all the data in the study, wrote the manuscript, and had final responsibility for the decision to submit the manuscript for publication. These same authors vouch for the accuracy of the data and analyses and for the fidelity of the study to the protocol, available at NEJM.org. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee at each site. All patients provided written informed consent.

STUDY PATIENTS AND RANDOMIZATION

Patients less than 60 years of age with a patent foramen ovale documented on transesophageal echocardiography and no other identifiable cause of stroke or peripheral thromboembolism were eligible for the study if they presented with clinically and neuroradiologically verified ischemic stroke, a TIA with a neuroradiologically verified cerebral ischemic lesion, or a clinically and radiologically verified extracranial peripheral thromboembolic event.

Patients underwent central randomization by means of a Web-based system either to undergo percutaneous, catheter-based closure of the patent foramen ovale (closure group) with the use of the Amplatzer PFO Occluder (St. Jude Medical) or to receive medical therapy (medical-therapy group). See the Supplementary Appendix for details regarding eligibility criteria, echocardiographic characterization of patent foramen ovale, and randomization. Patients were followed up in the hospital and in office visits at 6 months and annually for up to 5 years (see the Supplementary Appendix).

STUDY PROCEDURES AND ANTITHROMBOTIC TREATMENTS

Patients in the closure group were generally admitted on the day of the procedure and discharged the same day or the following day. The closure procedure was typically performed with the use of local anesthesia, and device implantation was guided by means of fluoroscopy with or without transesophageal or intracardiac echocardiography. Prophylactic antibiotic therapy was recommended during the periprocedural period, and prophylaxis against endocarditis was recommended for 2 to 6 months after closure of the patent foramen ovale.

Recommended antithrombotic treatment in the closure group included acetylsalicylic acid at

a dose of 100 to 325 mg per day for at least 5 to 6 months, as well as ticlopidine at a dose of 250 to 500 mg per day or clopidogrel at a dose of 75 to 150 mg per day for 1 to 6 months. For patients with intolerance to acetylsalicylic acid, ticlopidine or clopidogrel alone was recommended.

In the medical-therapy group, antithrombotic treatment was left to the discretion of the treating physician and could have included antiplatelet therapy or oral anticoagulation, provided that patients received at least one antithrombotic drug.

STUDY END POINTS

The prespecified primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. Secondary end points were the individual components of the primary end point as well as cardiovascular death, new arrhythmias (particularly new-onset atrial fibrillation), myocardial infarction, hospitalization related to the patent foramen ovale or its treatment, device problems, and bleeding (see the Supplementary Appendix for outcome definitions).¹⁸ A clinical-events committee whose members were unaware of study-group assignments independently adjudicated all potential events.

STATISTICAL ANALYSIS

We calculated that a sample size of 205 patients per group would yield a power of 80% to detect a reduction in the rate of the primary composite end point from 3% to 1% per year¹⁹⁻²¹ over a mean follow-up period of 4.5 years and at an alpha level of 0.0492 (allowing for one interim analysis). No interim analysis was actually performed; therefore, we used the conventional alpha level of 0.05.

Cox proportional-hazard models were used to calculate hazard ratios, 95% confidence intervals, and corresponding P values. The primary analysis was of data from the intention-to-treat population. In a per-protocol analysis, we restricted the analysis to data from patients in the closure group in whom implantation of a device was attempted and patients in the medical-therapy group who received treatment as assigned at the time of randomization; if patients in the medical-therapy group crossed over to the closure group, the data were censored at the time of crossover. (See the Supplementary Appendix for details regarding the statistical methods.)

RESULTS

STUDY PATIENTS

Between February 24, 2000, and February 19, 2009, a total of 414 patients were enrolled, of whom 204 were randomly assigned to the closure group and 210 to the medical-therapy group (Fig. S1 in the Supplementary Appendix). Baseline characteristics were similar in the two groups (Table 1). The mean ages in the closure group and the medical-therapy group were 44.3 years and 44.6 years, respectively, and the mean body-mass indexes (the weight in kilograms divided by the square of the height in meters) were 26.6 and 26.3, respectively.

Data on transesophageal echocardiography were available for 185 patients in the closure group and 184 patients in the medical-therapy group. The results showed a large right-to-left shunt in 43 patients (23.2%) and 37 patients (20.1%), respectively. The patients in our study were younger ($P=0.006$), had a lower rate of diabetes ($P<0.001$), and were less likely to be men ($P=0.08$), as compared with 39 cohorts of patients in a meta-analysis who underwent closure of patent foramen ovale in routine clinical settings¹⁴ (Fig. S2 in the Supplementary Appendix).

STUDY TREATMENTS AND FOLLOW-UP

Among the 204 patients in the closure group, device implantation was attempted in 196 and was completed in 191 (Fig. S1 in the Supplementary Appendix). In 2 patients who underwent device implantation there was access-site bleeding, and in another patient there was transient periprocedural atrial fibrillation of less than 24 hours' duration. All three events were classified as minor procedural complications. Therefore, implantation was deemed to be successful in 188 of the 196 patients (95.9%) in whom it was attempted.

At 6 months, 148 patients in the closure group underwent transesophageal echocardiography. Of these patients, the device was correctly positioned in 145 (133 with no shunt, 9 with minimal shunt, 1 with moderate shunt, and 2 with severe shunt). Effective closure was defined as closure with no or minimal shunting and therefore was achieved in 142 of the 148 patients (95.9%).

Among the 210 patients in the medical-therapy group, 200 received the intervention as assigned,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	PFO Closure (N=204)	Medical Therapy (N=210)
Age — yr	44.3±10.2	44.6±10.1
Male sex — no. (%)	92 (45.1)	114 (54.3)
Body-mass index†	26.6±5.6	26.3±4.8
Family history of cerebrovascular event — no. (%)	53 (26.0)	40 (19.0)
Current smoker — no. (%)	52 (25.5)	47 (22.4)
Arterial hypertension — no. (%)	49 (24.0)	58 (27.6)
Diabetes mellitus — no. (%)	5 (2.5)	6 (2.9)
Hypercholesterolemia — no. (%)	50 (24.5)	62 (29.5)
Valvular heart disease — no. (%)	8 (3.9)	5 (2.4)
Peripheral vascular disease — no. (%)	3 (1.5)	2 (1.0)
Coronary artery disease — no. (%)	4 (2.0)	4 (1.9)
History of myocardial infarction — no. (%)	3 (1.5)	1 (0.5)
Migraine — no. (%)	47 (23.0)	38 (18.1)
Cerebrovascular index event — no. (%)		
Peripheral embolism	6 (2.9)	5 (2.4)
Transient ischemic attack	33 (16.2)	42 (20.0)
Stroke	165 (80.9)	163 (77.6)
>1 Previous cerebrovascular event — no. (%)	76 (37.3)	79 (37.6)
Time from index event to randomization — mo		
Median	4.3	4.5
Interquartile range	1.1–8.2	1.3–8.9
Atrial septal aneurysm — no. (%)	47 (23.0)	51 (24.3)
Interatrial right-to-left shunt — no./total no. (%)‡		
Small	55/185 (29.7)	72/184 (39.1)
Medium	87/185 (47.0)	75/184 (40.8)
Large	43/185 (23.2)	37/184 (20.1)

* Plus-minus values are means ±SD. There were no significant differences ($P<0.05$) between the two groups for any of the baseline characteristics. PFO denotes patent foramen ovale.

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

‡ Baseline transesophageal echocardiography was performed for 185 patients in the closure group and 184 patients in the medical-therapy group, providing information on grading of right-to-left shunts.

4 had no documented antiplatelet or anticoagulant treatment at discharge, and 6 crossed over and underwent closure of patent foramen ovale during the first month after randomization. Subsequently, 22 more patients in the medical-therapy group crossed over to the closure group. The median time to closure of patent foramen ovale in the 28 patients who crossed over from the medical-therapy group was 8.8 months (inter-

quartile range, 1.2 to 26.4) (Fig. S3 in the Supplementary Appendix). Reasons for crossover included patient preference (in 19 patients), stroke (in 4 patients), TIA (in 2 patients), and physician preference (in 3 patients).

Table S1 in the Supplementary Appendix shows the frequency of the use of antithrombotic medication in the two study groups. From 12 months onward, antithrombotic treatment was significantly less frequent in the closure group than in the medical-therapy group ($P<0.001$ for each year). Use of oral anticoagulation was significantly less common in the closure group at all time points, including at discharge and at 6 months ($P<0.001$ for all comparisons).

The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical-therapy group, with 845.1 and 835.0 patient-years of accumulated follow-up time, respectively. Seven patients in the closure group and 11 in the medical-therapy group withdrew from the study; 24 and 31 others, respectively, were lost to follow-up (Fig. S1 in the Supplementary Appendix). Patients with incomplete follow-up were less frequently obese ($P=0.02$) and had a lower rate of hypercholesterolemia ($P=0.001$) than those with complete follow-up (Table S2 in the Supplementary Appendix).

EFFICACY OUTCOMES

Potential primary end points occurred in 9 patients in the closure group and 18 patients in the medical-therapy group. After independent adjudication, the primary end point was confirmed to have occurred in 7 patients (3.4%) in the closure group and 11 patients (5.2%) in the medical-therapy group (hazard ratio for closure vs. medical therapy, 0.63; 95% confidence interval [CI], 0.24 to 1.62; $P=0.34$) (Table 2). Figure 1 presents the corresponding Kaplan–Meier curves for the primary composite end point. Results of the per-protocol analysis of the primary composite end point were similar to the intention-to-treat analysis, with a hazard ratio of 0.70 (95% CI, 0.27 to 1.85; $P=0.48$).

In an analysis of the individual components of the primary end point, stroke occurred in one patient (0.5%) in the closure group and five patients (2.4%) in the medical-therapy group (hazard ratio, 0.20; 95% CI, 0.02 to 1.72; $P=0.14$), with all strokes being confirmed on neuroimag-

Table 2. Clinical Outcomes.*

Outcome	PFO Closure (N=204)	Medical Therapy (N=210)	Hazard Ratio or Relative Risk (95% CI)†	P Value
<i>no. of patients (%)</i>				
Primary composite outcome of death, stroke, TIA, or peripheral embolism	7 (3.4)	11 (5.2)	0.63 (0.24–1.62)	0.34
Death‡	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Cardiovascular	0	0	NA	
Noncardiovascular	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Thromboembolic event				
Stroke§	1 (0.5)	5 (2.4)	0.20 (0.02–1.72)	0.14
TIA	5 (2.5)	7 (3.3)	0.71 (0.23–2.24)	0.56
Peripheral embolism	0	0	NA	
Secondary composite outcome of stroke, TIA, or peripheral embolism	5 (2.5)	11 (5.2)	0.45 (0.16–1.29)	0.14

* NA denotes not applicable, PFO patent foramen ovale, and TIA transient ischemic attack.
 † Hazard ratios were calculated by means of the Cox proportional-hazards model. For the comparison of deaths (for which one group had no events), the relative risk was calculated instead of the hazard ratio with the use of continuity correction, and the corresponding P value was obtained by means of a two-sided Fisher's exact test.
 ‡ One patient died of respiratory failure because of chronic obstructive pulmonary disease; the other died from a glioma.
 § All listed strokes were major strokes.

ing studies (Table 2, and Fig. S4, S5, and S6 in the Supplementary Appendix). TIAs occurred in five patients (2.5%) and seven patients (3.3%), respectively (hazard ratio, 0.71; 95% CI, 0.23 to 2.24; P=0.56). There were no peripheral embolic events.

In an exploratory analysis based on a contemporary stroke definition,²² as used in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial,²³ one patient in the closure group and seven patients in the medical-therapy group had a stroke (hazard ratio, 0.14; 95% CI, 0.02 to 1.17; P=0.07). Two patients in the closure group (1.0%) versus no patients in the medical-therapy group died (hazard ratio, 5.20; 95% CI, 0.25 to 107.61; P=0.24). One patient died of respiratory failure caused by chronic obstructive pulmonary disease, and the other from a glioma.

Figure 2 presents results from subgroup analyses. There were statistical trends toward a subgroup interaction for age and the presence or absence of an atrial septal aneurysm, but there were no formally significant differences between subgroups (P=0.10 and P=0.09 for interaction, respectively).

ADVERSE EVENTS

A total of 113 adverse events were reported in 71 patients (34.8%) in the closure group and 120 events in 62 patients (29.5%) in the medical-therapy group (Table 3). Of these, 60 events in 43 patients (21.1%) in the closure group and

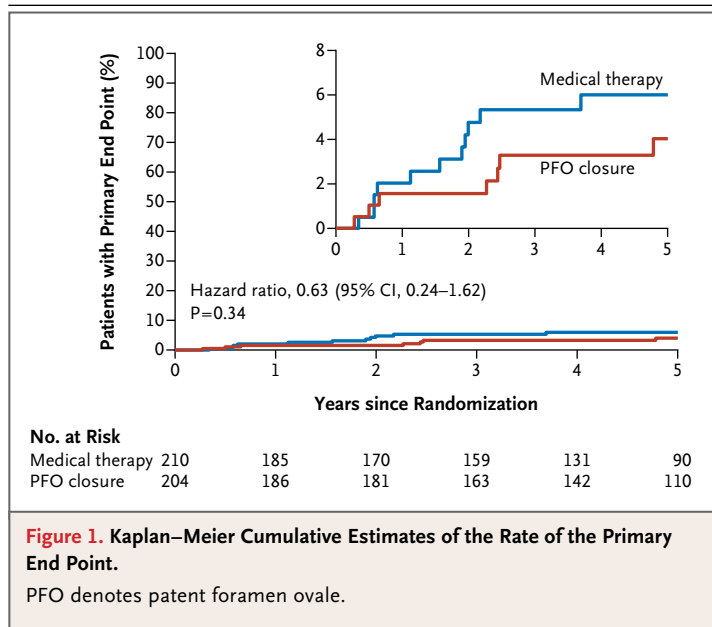


Figure 1. Kaplan–Meier Cumulative Estimates of the Rate of the Primary End Point.

PFO denotes patent foramen ovale.

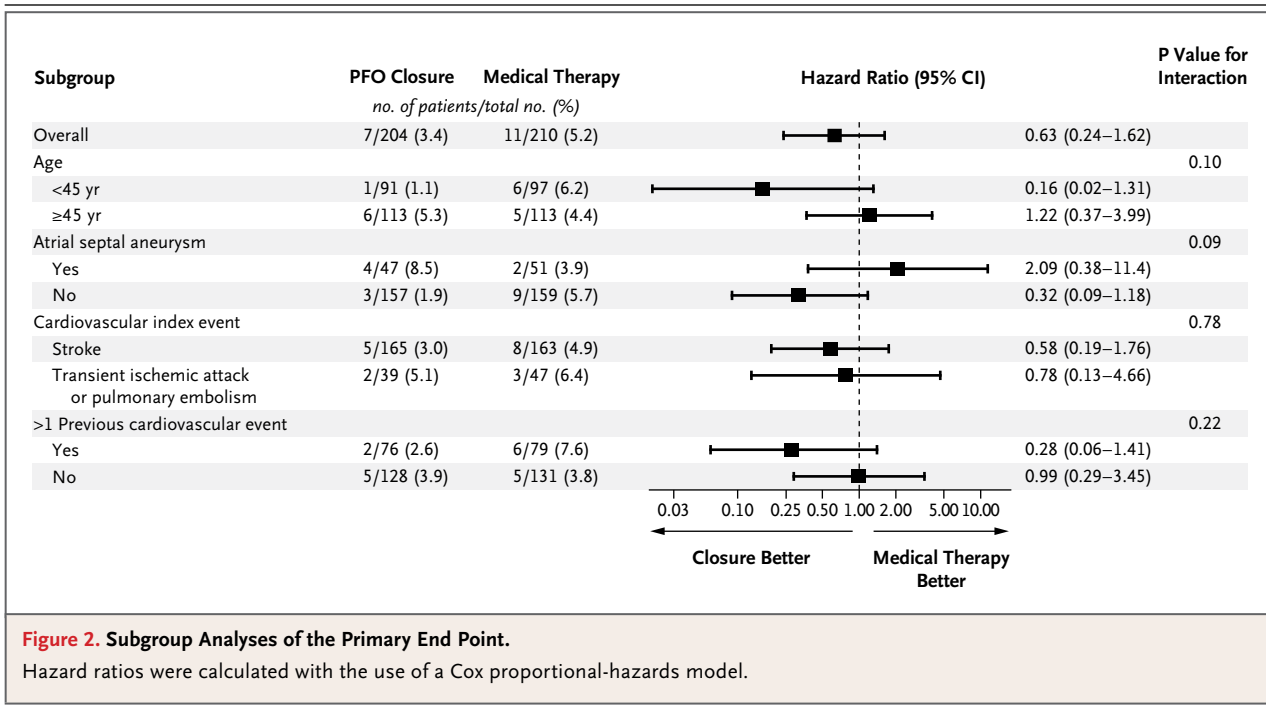


Figure 2. Subgroup Analyses of the Primary End Point.
Hazard ratios were calculated with the use of a Cox proportional-hazards model.

56 events in 37 patients (17.6%) in the medical-therapy group were adjudicated as serious.

New-onset atrial fibrillation was observed in six patients (2.9%) in the closure group and in two patients (1.0%) in the medical-therapy group (hazard ratio, 3.15; 95% CI, 0.64 to 15.6; P=0.16); none of these patients subsequently had a potential or confirmed primary-end-point event. Of the six affected patients in the closure group, two had transient atrial fibrillation, two had pharmacologic and one had electrical conversion to sinus rhythm, and one had sustained atrial fibrillation. Of the two affected patients in the medical-therapy group, one had pharmacologic conversion to sinus rhythm, and one had sustained atrial fibrillation.

There was no evidence of device-associated thrombi in any patient. Myocardial infarction occurred in 2 patients (1.0%) in the closure group and 1 patient (0.5%) in the medical-therapy group (hazard ratio, 2.04; 95% CI, 0.19 to 22.5; P=0.62); hospital admission related to patent foramen ovale occurred in 13 patients (6.4%) and 13 patients (6.2%), respectively (hazard ratio, 1.02; 95% CI, 0.48 to 2.21; P=0.95). Bleeding occurred in 8 patients (3.9%) undergoing closure and 12 patients (5.7%) receiving medical therapy (hazard ratio, 0.66; 95% CI, 0.27 to 1.62; P=0.40).

DISCUSSION

In this trial, closure of patent foramen ovale with the Amplatzer PFO Occluder for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of embolic events or death, as compared with medical therapy alone. There were fewer strokes in the closure group, but overall, few patients had a stroke and the difference was not significant. Our trial was designed to detect a reduction of 66% in the risk of embolic events or death, from 3% per year in the medical-therapy group to 1% per year in the closure group. However, at a mean follow-up of 4 years, we found an event rate of 5.2% in the medical-therapy group, which was less than half of the anticipated 12%. The power of our trial to detect the planned reduction of 66% in relative risk was therefore less than 40%. Thus, there is a risk of a type II error in our trial — that is, a clinically relevant benefit of the closure of patent foramen ovale might exist but we were unable to detect it.

When we designed our trial in 1999, only a few relevant studies had been performed.¹⁴ We based our assumptions on observational studies using data from a population-based stroke registry, which reported a rate of recurrent crypto-

genic embolism–related events of 3.8% per year among patients receiving medical treatment¹⁹ but 0% among patients who had undergone surgical closure of patent foramen ovale.^{20,21} The patients in our study appeared to have been at lower risk for cardiovascular events than the cohorts of patients who underwent closure of patent foramen ovale in routine clinical settings¹⁴ (Fig. S2 in the Supplementary Appendix), a factor that may have contributed to the considerably lower-than-expected event rate in our study.

Our trial has several limitations. First, our primary composite end point may be considered problematic. Overall death accounts for all potential benefits and harms of the experimental intervention but is not specific to the studied condition. TIA is a less clear-cut end point than stroke. Including TIA as a component resulted in an increased event rate but also may have resulted in a dilution of effects, as suggested by the difference in the estimated hazard ratios for stroke (0.20) and TIA (0.71). Second, we had difficulty recruiting patients, which led to an unusually long recruitment period and a selected patient population, which may in turn limit the generalizability of our findings.²⁴ Third, patient retention was lower than expected, which might have resulted in attrition bias that could distort the results in either direction.²⁴ Fourth, the clinical-events committee discounted potential primary-end-point events more often in the medical-therapy group than in the closure group. Even though the numbers of discounted events were small, this difference could constitute indirect evidence of selective reporting of potential events, owing to the open nature of the trial: mild or transient events in patients in the closure group may have been less likely to be reported than events in the medical-therapy group if investigators or patients were confident that successful closure of patent foramen ovale reduces the risk of another event.

Two other trials have compared closure of patent foramen ovale with medical therapy for secondary prevention of cryptogenic embolism. The CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) study, the results of which were published in March 2012,²⁵ had a similar primary composite end point to the one in our study: stroke or

Table 3. Adverse Events.*

Adverse Event	PFO Closure (N=204)	Medical Therapy (N=210)	P Value
	no. of patients (%)		
Procedural complication†	3 (1.5)	0	0.12
PFO-related hospital admission‡	13 (6.4)	13 (6.2)	0.95
Myocardial infarction‡	2 (1.0)	1 (0.5)	0.62
Atrial fibrillation§	6 (2.9)	2 (1.0)	0.17
Serious	2 (1.0)	2 (1.0)	1.00
Minor	4 (2.0)	0	0.058
Bleeding	8 (3.9)	12 (5.7)	0.40
Serious	1 (0.5)	3 (1.4)	0.62
Minor	7 (3.4)	9 (4.3)	0.65
Any adverse event	71 (34.8)	62 (29.5)	0.25
Serious	43 (21.1)	37 (17.6)	0.37
Minor	40 (19.6)	42 (20.0)	0.92
Other adverse event, occurring in ≥3 patients			
Headache	3 (1.5)	1 (0.5)	0.37
Migraine	5 (2.5)	5 (2.4)	1.00
Syncope	2 (1.0)	1 (0.5)	0.62
Dizziness	1 (0.5)	4 (1.9)	0.37
Paresthesia	0	3 (1.4)	0.25
Seizure	1 (0.5)	3 (1.4)	0.62
Dyspnea	0	4 (1.9)	0.12
Chest pain	3 (1.5)	4 (1.9)	1.00
Anxiety	1 (0.5)	4 (1.9)	0.37
Depression	1 (0.5)	2 (1.0)	1.00
Diverticulitis	1 (0.5)	2 (1.0)	1.00
Inguinal hernia	1 (0.5)	2 (1.0)	1.00
Bariatric surgery	4 (2.0)	1 (0.5)	0.21
Viral infection	1 (0.5)	2 (1.0)	1.00
Allergic drug reaction	1 (0.5)	2 (1.0)	1.00
Traumatic injury	6 (2.9)	3 (1.4)	0.33
Vaginal childbirth¶	2 (1.0)	3 (1.4)	1.00

* Not listed are primary composite end point events (see Table 2) and PFO closures in the medical-therapy group (see Fig. S3 in the Supplementary Appendix). P values were obtained from a chi-square test (or Fisher's exact test if the expected number of events was less than 5).

† Procedural complications included two episodes of minor bleeding at the access site and one periprocedural episode of atrial fibrillation that resolved within 6 hours; all were classified as minor.

‡ All admissions and myocardial infarctions were classified as serious adverse events.

§ One atrial fibrillation was periprocedural and resolved within 6 hours. In the PFO-closure group, one patient had atrial ectopy, one had sick sinus syndrome, and one had atrioventricular block. In the medical-therapy group, one patient had atrial ectopy.

¶ Vaginal childbirth was subsumed under adverse events for the purpose of analysis.

TIA within 2 years, death from any cause within 30 days, and death from neurologic causes from 31 days to 2 years. The estimated hazard ratio for the primary composite end point in the closure group versus the medical-therapy group was 0.78 (95% CI, 0.45 to 1.35). In the RESPECT trial, the primary end point was recurrent ischemic stroke; the hazard ratio for closure versus medical therapy was 0.49 (95% CI, 0.22 to 1.11).²³ Thus, all three trials show a trend in favor of the closure group. However, the baseline risks, devices used, and end-point definitions differed among the trials, making direct comparisons of event rates and treatment effects difficult.

In conclusion, our trial compared the closure of patent foramen ovale and the administration of medical therapy in patients with a patent foramen ovale and a history of cryptogenic embolism. We did not find a significant reduction in the risk of recurrent embolic events or death in the closure group, as compared with the medical-therapy group.

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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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