ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

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ABSTRACT

BACKGROUND

The prevalence of patent foramen ovale among patients with cryptogenic stroke is higher than that in the general population. Closure with a percutaneous device is often recommended in such patients, but it is not known whether this intervention reduces the risk of recurrent stroke.

METHODS

We conducted a multicenter, randomized, open-label trial of closure with a percutaneous device, as compared with medical therapy alone, in patients between 18 and 60 years of age who presented with a cryptogenic stroke or transient ischemic attack (TIA) and had a patent foramen ovale. The primary end point was a composite of stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years.

RESULTS

A total of 909 patients were enrolled in the trial. The cumulative incidence (Kaplan–Meier estimate) of the primary end point was 5.5% in the closure group (447 patients) as compared with 6.8% in the medical-therapy group (462 patients) (adjusted hazard ratio, 0.78; 95% confidence interval, 0.45 to 1.35; P=0.37). The respective rates were 2.9% and 3.1% for stroke (P=0.79) and 3.1% and 4.1% for TIA (P=0.44). No deaths occurred by 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period. A cause other than paradoxical embolism was usually apparent in patients with recurrent neurologic events.

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

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As many as 40% of acute ischemic strokes have no identifiable cause and are classified as cryptogenic.[1-3] Some cryptogenic strokes or transient ischemic attacks (TIAs) may be the result of an embolus from the venous system traversing from the right to left atrium and into the systemic circulation through a patent foramen ovale — a phenomenon known as paradoxical embolism. Numerous studies have shown an association between patent foramen ovale and cryptogenic stroke.[4-14] The prevalence of patent foramen ovale at autopsy ranges from 20 to 26% in the general population, and it may be as high as 56% in patients younger than 55 years of age who have a cryptogenic stroke.[15-18] However, a population-based study of a cohort with a mean age of 69 years showed that the presence of a patent foramen ovale did not increase the risk of a cryptogenic stroke or TIA, as compared with the risk among age-matched control subjects.[19] Although some studies have correlated the size of a patent foramen ovale or the presence of an atrial septal aneurysm with an increased risk of initial or recurrent stroke, other studies have failed to show an increased risk.[5-7,10,12]

The way to implement secondary prevention for patients who present with a cryptogenic stroke or TIA and have a patent foramen ovale is not clear. In the United States, closure of a patent foramen ovale with the use of a percutaneous transcatheter device is currently considered an investigational procedure by the Food and Drug Administration (FDA). Nonetheless, many such patients are treated off-label with devices that are approved for the closure of secundum atrial septal defects.[20,21] There are also no definitive data on the usefulness of medical therapy or surgical procedures for the secondary prevention of stroke in this patient population.[22] We evaluated the potential benefit of a percutaneous device as compared with medical therapy for closure of a patent foramen ovale in patients with cryptogenic stroke or TIA.

Methods

Study Design and Oversight

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) was a prospective, multicenter, randomized, open-label, two-group superiority trial. The design of the trial has been reported previously.[23] The trial was sponsored by NMT Medical. The protocol was designed by the executive committee in consultation with the FDA and was approved by the institutional review board at each participating site. All participating institutions signed a confidentiality agreement with the sponsor. Data were collected and analyzed by the Harvard Clinical Research Institute, and study end points were adjudicated by an independent clinical events committee. The sponsor had no role in the design of the trial, in the collection or analysis of the data, in the writing of the manuscript, or in the decision to submit the manuscript for publication. The manuscript was written by the executive committee, which vouches for the accuracy and completeness of the data and the analyses and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

Patients

Patients were eligible for participation in the trial if they were between 18 and 60 years of age, had had an ischemic stroke or TIA within the previous 6 months, and had evidence of a patent foramen ovale, as documented by transesophageal echocardiography with a bubble study (i.e., with the injection of agitated saline) showing right-to-left shunting at the atrial level during a Valsalva maneuver. Exclusion criteria were any identified potential cause of ischemic stroke or TIA other than the patent foramen ovale, such as clinically significant carotid-artery stenosis, complex aortic-arch atheroma, clinically significant left ventricular dysfunction or left ventricular aneurysm, or atrial fibrillation. Detailed inclusion and exclusion criteria are provided in Table 1 in the Supplementary Appendix, available at NEJM.org. All trial participants provided written informed consent.

Study Procedures and End Points

Eligible patients were randomly assigned in a 1:1 ratio to either closure with the percutaneous device plus antiplatelet therapy (closure group) or medical therapy alone (medical-therapy group). Randomization was performed with the use of an interactive voice-response system and was stratified by study site and by the presence or absence of an atrial septal aneurysm, as visualized on transesophageal echocardiography.

Patients assigned to closure with the device un-

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derwent percutaneous closure of the patent foramen ovale with the STARFlex device (NMT Medical), and the procedure was performed as soon as possible after randomization, preferably within 1 week. Transesophageal echocardiography or intracardiac echocardiography was used during the procedure to guide placement of the device. After the procedure, all patients were given a standard antiplatelet regimen, including clopidogrel, 75 mg daily for 6 months, and aspirin, 81 or 325 mg daily for 2 years. Patients assigned to medical therapy were treated with warfarin (with a target international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site. Crossovers between the two treatment groups were not permitted.

Assessments of clinical end points and adverse events were planned at 1 month, 6 months, 12 months, and 24 months. A transesophageal echocardiogram was obtained at the 6-month visit for patients in the closure group.

The primary end point was a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, and death from neurologic causes between 31 days and 2 years. Secondary end points included major bleeding, death from any cause, stroke, TIA, and transient neurologic events of uncertain cause. (Definitions of the major end points are provided in Table 2 in the Supplementary Appendix.)

STATISTICAL ANALYSIS

The sample-size calculation and adjustments to that calculation during the course of the trial are described in the Supplementary Appendix. The primary analysis was performed in the intention-to-treat population, defined as all patients randomly assigned to a treatment group. Kaplan–Meier estimates of the proportion of patients who met the primary end point through 2 years of follow-up were calculated for each of the two treatments. Cox proportional-hazards regression was used to compare the two treatments with respect to the primary end point, with adjustment for age at baseline; presence or absence of a history of atrial septal aneurysm, TIA, or stroke; and status with respect to hypertension and hypercholesterolemia. The adjusted hazard ratio for the primary end point (in the closure group as compared with the medical-therapy group) and its two-sided 95% confidence interval were also calculated. For the Kaplan–Meier and Cox regression analyses, data for patients who did not reach the primary end point were censored at the end of the 2-year follow-up period or at the last known follow-up visit, whichever was earlier. Patients who were randomly assigned to one of the two groups but were not treated were included in follow-up, with the exception of eight patients in the closure group and three patients in the medical-therapy group who withdrew consent or were lost to follow-up after randomization (Fig. 1 in the Supplementary Appendix). A two-sided test at the 0.05 level of significance was used to determine whether the results differed significantly between the two treatment groups. Safety analyses were performed in the safety population, which was defined as all patients who received the randomly assigned treatment. Other prespecified secondary-analysis populations are defined in the Supplementary Appendix.

RESULTS

STUDY PARTICIPANTS

Between June 23, 2003, and October 24, 2008, a total of 909 patients were enrolled at 87 sites in the United States and Canada. Of these patients, 447 were randomly assigned to closure with the percutaneous device and 462 to medical therapy. (Information about enrollment, randomization, and follow-up can be found in Fig. 1 in the Supplementary Appendix.) The last patient was enrolled in October 2008, and the complete database was locked in October 2010. Table 1 shows the baseline characteristics of the patients enrolled in the trial. There were no significant differences between the two groups with respect to medical history, prior events, or risk factors for stroke.

PROCEDURAL RESULTS AND DEVICE PERFORMANCE

A total of 405 patients in the closure group underwent attempted implantation of the STARFlex device, and the procedure was successful in 362 (89.4%). Procedural success was defined as successful implantation of one or more STARFlex devices at the closure site during the index procedure, with no procedural complications (see the Supplementary Appendix).

At 6 months, a total of 366 patients in the closure group underwent transesophageal echocardiography, and effective closure was documented in 315 (86.1%). Effective closure was defined as procedural success with a grade 0 or 1 residual

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Closure (N=447)	Medical Therapy (N=462)	P Value
Age — yr			
Mean†	46.3±9.6	45.7±9.1	0.39
Range	18–60	18–60	
Male sex — no. of patients (%)	233 (52.1)	238 (51.5)	0.89
Race or ethnic group — no. of patients (%)‡			0.53
Asian	7 (1.6)	8 (1.7)	
Black	19 (4.2)	26 (5.6)	
White	398 (89.0)	414 (89.6)	
Hispanic or Latino	30 (6.7)	22 (4.8)	
Cigarette smoking during the previous year — no. of patients/total no. (%)	96/447 (21.5)	104/460 (22.6)	0.69
Blood pressure — mm Hg			
Mean§	91.7±10.6	92.3±10.7	0.37
Range	59–127	63–137	
Medical history — no. of patients (%)			
Hypertension	151 (33.8)	131 (28.4)	0.08
Hypercholesterolemia	212 (47.4)	189 (40.9)	0.05
Family history of cardiovascular disease	247 (55.3)	257 (55.6)	0.95
Congestive heart disease	2 (0.4)	0	0.24
Ischemic heart disease	6 (1.3)	4 (0.9)	0.54
Myocardial infarction	7 (1.6)	5 (1.1)	0.57
Valvular dysfunction	49 (11.0)	45 (9.7)	0.59
Arrhythmia	26 (5.8)	19 (4.1)	0.28
Catheterization	23 (5.1)	17 (3.7)	0.33
PTCA	6 (1.3)	2 (0.4)	0.17
Peripheral vascular disease	5 (1.1)	7 (1.5)	0.77
Stokes–Adams syndrome	4 (0.9)	3 (0.6)	0.72
Pulmonary embolus	0	4 (0.9)	0.12
Pericarditis	2 (0.4)	3 (0.6)	1.00
Cardiomyopathy	1 (0.2)	0	0.49
Index neurologic event for study entry — no. of patients/total no. (%)			0.71
Cryptogenic stroke	324/446 (72.6)	329/461 (71.4)	
TIA	122/446 (27.4)	132/461 (28.6)	
Result on TEE — no. of patients (%)			
Moderate or substantial shunt	250 (55.9)	231 (50.0)	0.07
Atrial septal aneurysm ≥10 mm	168 (37.6)	165 (35.7)	0.56

* Plus–minus values are means ±SD. PTCA denotes percutaneous transluminal coronary angioplasty, TEE transesophageal echocardiography, and TIA transient ischemic attack.
† Data on age were available for 447 patients in the closure group and 461 in the medical-therapy group.
‡ Race or ethnic group was self-reported.
§ Data on blood pressure were available for 431 patients in the closure group and 445 in the medical-therapy group. Mean values were calculated with the use of the equation [(2×diastolic)+systolic]/3.

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Table 2. Kaplan–Meier Event Rates for Primary End Point at 2 Years.*

End Point	Closure (N=447)	Medical Therapy (N=462)	Hazard Ratio (95% CI)†‡	P Value†
Intention-to-treat population				
Composite end point — no. (%)	23 (5.5)	29 (6.8)	0.78 (0.45–1.35)	0.37
Stroke — no. (%)	12 (2.9)	13 (3.1)	0.90 (0.41–1.98)	0.79
TIA — no. (%)	13 (3.1)	17 (4.1)	0.75 (0.36–1.55)	0.44
Modified intention-to-treat population				
Composite end point — no./total no. (%)	22/400 (5.6)	29/451 (6.9)	0.78 (0.44–1.35)	0.37
Stroke — no./total no. (%)	12/400 (3.1)	13/451 (3.1)	0.94 (0.43–2.07)	0.88
TIA — no./total no. (%)	12/400 (3.0)	17/451 (4.2)	0.72 (0.34–1.51)	0.38
Per-protocol population				
Composite end point — no./total no. (%)	22/378 (5.8)	29/375 (7.7)	0.74 (0.42–1.29)	0.28
Stroke — no./total no. (%)	12/378 (3.2)	13/375 (3.5)	0.91 (0.41–1.99)	0.80
TIA — no./total no. (%)	12/378 (3.2)	17/375 (4.6)	0.68 (0.33–1.43)	0.31

* Percentages in parentheses are Kaplan–Meier estimates of the event rates. Totals for the composite-end-point categories may be higher than the sum of the individual events in that category, since some patients may have had both types of events (i.e., stroke and transient ischemic attack [TIA]).
† Values were adjusted with the use of Cox proportional-hazards regression for age, presence or absence of atrial septal aneurysm, presence or absence of a history of TIA or cerebrovascular accident, and status with respect to smoking, hypertension, and hypercholesterolemia.
‡ The hazard ratio was calculated for the closure group as compared with the medical-therapy group.

shunt (see the Supplementary Appendix). Thrombus in the left atrium was present on the transesophageal echocardiogram within 6 months in 4 of the 366 patients (1.1%), 2 of whom had a stroke (at 4 and 52 days after the closure procedure). At 2 years, effective closure was maintained in 320 of 369 patients (86.7%).

PRIMARY OUTCOME

The Kaplan–Meier estimate of the cumulative incidence of the primary end point in the intention-to-treat population after 2 years of follow-up was 5.5% in the closure group and 6.8% in the medical-therapy group (adjusted hazard ratio, 0.78; 95% confidence interval [CI], 0.45 to 1.35; P=0.37) (Table 2 and Fig. 1). The Kaplan–Meier estimates of 2-year rates of stroke were 2.9% in the closure group and 3.1% in the medical-therapy group (adjusted hazard ratio, 0.90; 95% CI, 0.41 to 1.98), with respective rates of 3.1% and 4.1% for TIA (adjusted hazard ratio, 0.75; 95% CI, 0.36 to 1.55). No deaths had occurred at 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period. Primary-end-point results for the modified intention-to-treat and per-protocol populations were similar to those for the intention-to-treat population (Table 2). There was no evidence of heterogeneity of treatment effect in subgroups, including those defined by the presence or absence of atrial septal aneurysm and by shunt size (Fig. 2).

ADVERSE EVENTS

Of the patients who were randomly assigned to treatment, 402 underwent attempted implantation of the STARFlex closure device and 458 received medical therapy; all these patients were included in the safety analysis. There were no significant differences in the rates of serious adverse events between the two groups, although the types of serious adverse events did differ (Table 3). Protocol-specified major vascular procedural complications (as defined in the Supplementary Appendix) occurred only in the closure group, with a rate of 3.2% (13 patients). Atrial fibrillation was significantly more frequent in the closure group than in the medical-therapy group (23 patients [5.7%] vs. 3 patients [0.7%], P<0.001). Atrial fibrillation occurred within 30 days after the implantation procedure in 14 of 23 patients (61%); it was transient in 17 patients and persistent in 6 patients.

RECURRENT STROKES AND TIAS

Three TIAs occurred in the closure group after randomization but before device insertion, and these were included in the intention-to-treat analysis.

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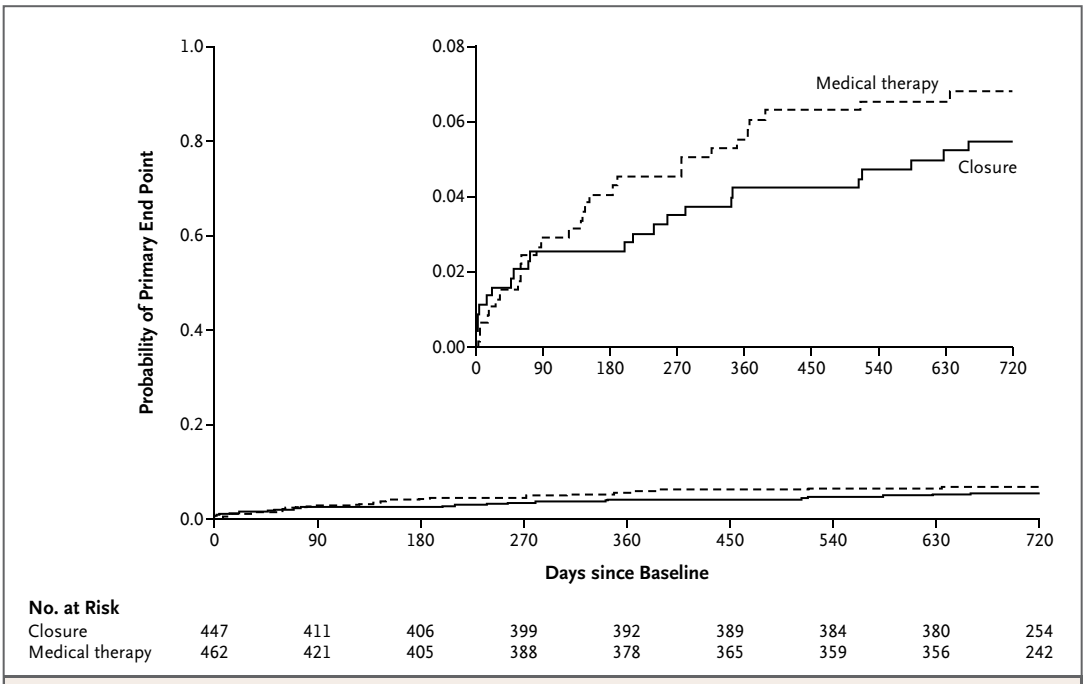

Figure 1. Kaplan–Meier Curve of Time to Primary End Point through 2 Years of Follow-up in the Closure and Medical-Therapy Groups.

Three of 12 strokes and 2 of 13 TIAs in this group occurred within 30 days after the procedure. In the medical-therapy group, 2 strokes and 4 TIAs occurred within 30 days after randomization.

Possible alternative explanations for recurrent TIA or stroke were apparent in 20 of 23 patients in the closure group and in 22 of 29 patients in the medical-therapy group; these included new-onset atrial fibrillation, a clot in the left atrium, subcortical lacunar infarction with risk factors, aortic-arch atheroma, complex migraine, vasculitis, and conversion disorder. Three of the 12 strokes in the closure group were ascribed to atrial fibrillation, and in 2 of these cases, the patients had device-associated thrombus on transesophageal echocardiography. One of 13 strokes in the medical-therapy group occurred in a patient who had atrial fibrillation, which was documented after the event and after implantation of an off-study device.

DISCUSSION

We compared treatment with a percutaneous closure device plus antiplatelet medical therapy with medical therapy alone for preventing recurrent stroke and TIA in patients who presented with cryptogenic stroke or TIA and who had a documented patent foramen ovale. At 2 years, there was no significant difference between the two treatment groups in the rate of recurrent stroke or TIA. Periprocedural major vascular complications occurred in 3.2% of patients in the closure group (13 of 402). Within 6 months, thrombus was found in the left atrium in 1.1% of patients in this group (4 of 366); 2 of the 4 patients with thrombus had a recurrent stroke.

The rate of effective closure of the patent foramen ovale was 86%, which is consistent with previously reported results for the STARFlex implant and other transcatheter closure devices.[24,25] Excluding periprocedural events, none of the patients in the closure group who had a recurrent stroke or TIA had residual leaking on the transesophageal echocardiogram at 6 months.

Our trial was designed to detect a two-thirds reduction in the risk of recurrent events in the closure group, which is an ambitious objective. Thus, it did not have the power to detect a smaller reduction in the event rate. The insignificant trend toward a higher rate of the primary outcome in the medical-therapy group was driven by the lower rate of TIAs in the closure group. TIA is a less precise end point than stroke. We included strictly defined and independently adjudicated TIAs as an end point, because these events may be caused by paradoxical embolism and because the

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Subgroup	Closure	Medical Therapy	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of patients/total no. (%)				
Overall modified intention-to-treat population	22/400 (5.6)	29/451 (6.9)	0.78 (0.44–1.35)	0.37	
Sex					0.16
Male	7/208 (3.4)	15/232 (6.8)	0.50 (0.20–1.22)	0.13	
Female	15/192 (7.9)	14/219 (7.0)	1.13 (0.55–2.34)	0.74	
Atrial septal aneurysm					0.95
No	15/249 (6.2)	20/291 (7.4)	0.81 (0.42–1.59)	0.55	
Yes	7/151 (4.6)	9/160 (6.0)	0.78 (0.30–2.13)	0.64	
Shunt size					0.78
None or trace	8/118 (6.9)	10/155 (6.8)	0.99 (0.39–2.52)	0.99	
Moderate	7/144 (5.0)	12/163 (7.9)	0.61 (0.24–1.55)	0.30	
Substantial	3/87 (3.5)	3/65 (4.9)	0.72 (0.15–3.57)	0.69	
Entry event					0.33
Stroke	15/300 (5.1)	15/324 (5.1)	1.01 (0.49–2.07)	0.98	
Transient ischemic attack	7/100 (7.1)	14/126 (11.6)	0.60 (0.24–1.49)	0.27	
Baseline medication					
None	0/13 (0)	2/38 (5.9)	—	—	0.65
Aspirin alone	15/286 (5.3)	16/252 (6.7)	0.79 (0.39–1.59)	0.50	
Warfarin alone	1/25 (4.2)	8/111 (7.9)	0.52 (0.06–4.12)	0.53	
Aspirin plus warfarin	6/72 (8.5)	2/40 (5.4)	1.59 (0.32–7.89)	0.57	

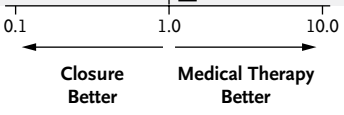

Figure 2. Results of Primary-End-Point Analysis at 2 Years, According to Subgroup, in the Modified Intention-to-Treat Population.
Percentages in parentheses are Kaplan–Meier estimates of the event rates.

required sample size would have been prohibitively large if stroke had been used as the only end point.[26,27] The 2-year rate of stroke (approximately 3%) was low and virtually identical in the closure and medical-therapy groups, suggesting that a much larger sample would be required if stroke were the only end point and that a follow-up interval longer than 2 years would be unlikely to show a significant difference in stroke outcomes.

Although we used strict inclusion and exclusion criteria, the evaluation of cryptogenic stroke in clinical practice has not been standardized. In this regard, the Patent Foramen Ovale in Cryptogenic Stroke Study (ClinicalTrials.gov number, NCT00697151)[10] showed that the 2-year risk of recurrent stroke was the same among patients with cryptogenic stroke whether or not they had a patent foramen ovale. This indicates that the causes of cryptogenic stroke are heterogeneous and speaks to the difficulty of precisely diagnosing paradoxical embolism.[3] Indeed, a key finding in our trial was that an alternative explanation for recurrent stroke or TIA, unrelated to paradoxical embolism, was usually apparent.

Of particular note was the increased rate of atrial fibrillation in the closure group. Atrial fibrillation has been reported in 5 to 20% of patients in whom a patent foramen ovale was closed with the use of various devices.[25,28,29] Occult atrial fibrillation is common in patients with cryptogenic stroke or TIA.[30,31] The relationship between atrial tachyarrhythmias and the presence of a patent foramen ovale — if any — is not clear, but the higher frequency of atrial fibrillation in the closure group in our trial suggests that the closure procedure itself may increase the risk of atrial fibrillation. Indeed, in the closure group, 61% of the observed cases of atrial fibrillation were periprocedural.

Our findings do not preclude a possible role for closure of a patent foramen ovale in highly selected patient populations. We did not address this question in the patients who had a neurologic event while receiving medical therapy. Various clinical, neuroimaging, and anatomical criteria have been suggested for identifying patients in whom stroke is more likely to be due to paradoxical embolism through a patent foramen ovale.[32-36] However, it may be difficult to prove that closure with a percutaneous device is superior to medical therapy even

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Table 3. Serious Adverse Events.*

Event	Closure (N=402)	Medical Therapy (N=458)	P Value
Major vascular procedural complication — no. (%)†	13 (3.2)	0	<0.001
Atrial fibrillation — no. (%)	23 (5.7)‡	3 (0.7)	<0.001
Major bleeding episode — no./total no. (%)§	10/378 (2.6)	4/374 (1.1)	0.11
Death other than end point — no. (%)	2 (0.5)¶	4 (0.9)‖	0.51
Nervous system disorder — no. (%)**	6 (1.5)	16 (3.5)	0.15
Convulsion	1	3	
Hypesthesia	2	2	
Migraine	1	3	
Headache	0	2	
Syncope	0	2	
Amyotrophic lateral sclerosis	0	1	
Brain abscess	0	1	
Facial palsy	1	0	
Loss of consciousness	0	1	
Paresthesia	0	1	
Parkinson's disease	1	0	
Any serious adverse event — no. (%)	68 (16.9)	76 (16.6)	0.90

* The results shown include all treated patients.
† Major vascular events included hematoma larger than 5 cm in diameter at the access site (in 4 patients), procedure-related transfusion (3), retroperitoneal hemorrhage (3), perforation of the left atrium (1), vascular surgical repair (1), and peripheral-nerve injury (1).
‡ Of these 23 cases of atrial fibrillation, 14 were periprocedural.
§ Major bleeding status was not ascertained for all treated patients.
¶ The two deaths in the closure group were caused by cardiac arrest on day 232 and by cardiac arrhythmia on day 242.
‖ The four deaths in the medical-therapy group were caused by septic shock on day 269, suicide on day 489, amyotrophic lateral sclerosis on day 557, and metastatic cancer on day 569.
** This category excludes primary-end-point events.

in such populations. We found no significant effect of the presence or absence of atrial septal aneurysm or the degree of shunting on the primary end point. Selected subgroups, such as patients under 45 years of age with no risk factors and only cortical infarcts on magnetic resonance imaging at baseline, will probably have even lower recurrent-event rates, requiring even larger samples or longer follow-up. It is also possible that adverse events and outcomes vary according to the specific device, an issue that was not addressed in our trial.

Although the patients in our trial are representative of many patients who undergo closure with off-label devices, those who may be at highest risk for paradoxical embolism (e.g., patients with active deep-vein thrombosis or clinically significant hypercoagulability) were excluded from the trial because such patients require long-term warfarin therapy. It is likely that enrollment in CLOSURE I was hampered by the preference of some patients or physicians for closure with a percutaneous device, leading them to decline participation in the trial. The sponsor, NMT Medical, did not allow the use of its commercially available CardioSEAL device for this purpose during the course of the trial. Moreover, we do not know how many potential study participants underwent closure with the use of a device from another company or how those patients differed, if at all, from the patients who participated in our study.

In conclusion, among patients who presented with cryptogenic stroke or TIA and a patent foramen ovale, we found no significant difference between closure with a percutaneous device plus antiplatelet therapy and medical therapy alone with respect to the prevention of recurrent stroke or TIA.

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