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PERIPHERAL VASCULAR

Predictors of Recurrent Events in Patients With Cryptogenic Stroke and Patent Foramen Ovale Within 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) Trial

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ABSTRACT

OBJECTIVES This study sought to identify predictors of recurrent ischemic neurologic events within 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) trial.

BACKGROUND The CLOSURE I trial found that transcatheter patent foramen ovale (PFO) closure using the STARFlex device was not superior to medical therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and PFO.

METHODS The CLOSURE I trial is a multicenter, randomized trial of transcatheter PFO closure compared with medical therapy in patients who presented with cryptogenic stroke or TIA and had a PFO. We identified clinical predictors of recurrent ischemic stroke or TIA during 2 years of follow-up using Cox proportional hazards regression within the pooled intention-to-treat cohort.

RESULTS In 909 patients, the incidence of recurrent events was 5.7% with 25 patients suffering a recurrent stroke and 30 a TIA. Patients who had a recurrent event had higher body mass index (30.2 ± 6.2 vs. 28.3 ± 5.8%; $p = 0.03$) and more frequently had diabetes (19.2% vs. 7.1%; $p = 0.0016$), hypertension (46.2% vs. 30.1%; $p = 0.015$), and ischemic heart disease (3.8% vs. 0.9%; $p = 0.05$). Diabetes (hazard ratio [HR]: 3.39; 95% confidence interval [CI]: 1.69 to 6.84; $p = 0.0007$), index TIA (HR vs. stroke: 2.13; 95% CI: 1.20 to 3.80; $p = 0.01$), and the detection of atrial fibrillation after study enrollment (HR: 4.85; 95% CI: 2.05 to 11.47; $p = 0.0003$) independently predicted recurrent ischemic neurologic events. Recurrent neurologic events were more frequent in subjects with RoPE (Risk of Paradoxical Embolism) score ≤5 than those with >5 (14.5% vs. 4.2%; $p < 0.0001$).

CONCLUSIONS These findings suggest an alternative etiology to paradoxical embolism was frequently responsible for recurrent events within the CLOSURE I trial. (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO) [CLOSURE I]; NCT00201461) (J Am Coll Cardiol Intv 2014;7:913–20) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation or flutter
CI = confidence interval
HR = hazard ratio
PFO = patent foramen ovale
TIA = transient ischemic attack

As many as 40% of acute ischemic strokes have no identifiable cause and are classified as cryptogenic (1–3). Some cryptogenic strokes may be the result of an embolus from the venous system traversing a patent foramen ovale (PFO) into the left-sided circulation, a phenomenon known as a paradoxical embolism, but other mechanisms are likely responsible for neurologic events in some patients. There have been many studies demonstrating an association between PFO and cryptogenic stroke (4–15), but this relationship has not been consistent (16).

Among the difficulties in studying PFO closure for the treatment of cryptogenic stroke is the fact that the

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presence of PFO does not ensure that a stroke, even in the absence of an identifiable cause, is actually the result of a paradoxical embolism. Previous investigators have coined the term "PFO propensity" as the probability of finding a PFO in a patient with a cryptogenic stroke on the basis of age and other risk factors (17). Central to this idea is the understanding that stroke is more prevalent with advancing age, as are traditional stroke risk factors (18). Significant controversy remains about the optimal approach to secondary stroke prevention in patients with PFO and a cryptogenic stroke (19,20). Several observational studies have suggested a potential benefit to PFO closure in patients with PFO and previous stroke (21–30), but the results of the first randomized clinical trials comparing PFO closure in patients with cryptogenic stroke have failed to show a definitive benefit from the procedure (31–33).

The goal of this analysis is to identify risk factors for the development of recurrent neurologic events in patients with previous cryptogenic stroke or transient ischemic attack (TIA) and PFO within 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) trial.

METHODS

STUDY DESIGN. Details of the study design and overall results have been reported previously (31). Briefly, the CLOSURE I study was a prospective, multicenter, randomized, open-label, 2-group superiority trial, comparing transcatheter PFO closure to medical therapy alone in patients between 18 and 60 years of age who presented with cryptogenic stroke or TIA and had a PFO. The trial was sponsored by NMT Medical, and the study protocol was designed by the executive committee in consultation with the U.S. Food and Drug Administration. Data were collected and analyzed by the Harvard Clinical Research Institute.

PATIENT POPULATION. Patients were eligible to participate in the trial if they were between 18 and 60 years of age; presented with a definite, clinically confirmed TIA or ischemic stroke within the previous 6 months; and had evidence of a PFO by transesophageal echocardiography with bubble study showing right-to-left shunting during Valsalva maneuver. Definite clinically confirmed TIA was defined as a sudden, focal neurologic event lasting at least 10 min without evidence of acute ischemic brain injury on diffusion-weighted magnetic resonance imaging, with symptoms consisting of hemiplegia/paresis, monoplegia/paresis, quadriplegia/paresis, language disturbance other than isolated slurred speech, blindness in one or both eyes, or significant difficulty walking. Patients were excluded from the study if a

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potential cause of the neurological event, other than the PFO, was identified at the time of screening. Such factors included clinically significant carotid artery disease, complex aortic arch atheroma, left ventricular dysfunction or aneurysm, or atrial fibrillation. All trial participants provided written informed consent.

STUDY PROCEDURES AND ENDPOINTS. Eligible patients were randomly assigned in a 1:1 ratio to either percutaneous PFO closure with medical therapy or medical therapy alone. Patients assigned to closure with the device underwent percutaneous closure of the PFO using the STARFlex device (NMT Medical, Boston, Massachusetts). 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.

Clinical endpoint assessment was performed at 6, 12, and 24 months following initial randomization by a board-certified neurologist. The primary outcome for this analysis is recurrent neurologic event (TIA or stroke) in the 2-year follow-up period following randomization. A TIA was defined as previously described. A neurologic event with positive cardiac magnetic resonance imaging was considered a stroke, regardless of duration of clinical symptoms. An independent clinical events committee adjudicated the study endpoints. Echocardiographic data were analyzed by the Echo Core Lab of the University of Pennsylvania Cardiac Care at Radnor.

RISK OF PARADOXICAL EMBOLISM SCORE. The RoPE (Risk of Paradoxical Embolism) study is a retrospective study of 12 component databases of patients with cryptogenic stroke (n = 3,674) aimed at developing predictive models to identify those patients most likely to benefit from preventative treatments for PFO-related stroke recurrence (34). The compiled data were used to derive the RoPE score, which aims to predict the likelihood of PFO in patients with cryptogenic stroke with the premise that doing so identifies those patients in whom PFO likely mediated a cryptogenic stroke (35). The RoPE score is a 10-point index that includes a subtracted point for each of 5 nonage factors (diabetes, hypertension, smoking, previous TIA or stroke, and presence of a cortical stroke on neuroimaging) and for each full decade over age 20 years (up to 5 points). The prevalence of PFO and PFO-attributable risk increases with increasing score. For example, those with 0 to 3 points have a PFO prevalence of 23% compared with 73% prevalence in those with 9 or 10 points. Based on Bayes theorem and assuming a PFO prevalence in the general population of ~25%, the PFO-attributable risk increases from near 0 in those with lowest scores to ~88% in those with the highest score. Application of the score in 1,324 patients with follow-up data demonstrated that stroke recurrence rates decrease as the RoPE score increases, suggesting that patients with index events most likely to be PFO-attributable are the least likely to experience recurrent ischemic events (35).

In the present analysis, we applied the RoPE score to the CLOSURE I trial study population to assess the estimated distribution of PFO-mediated index events. We subsequently stratified recurrent neurologic events by RoPE score to evaluate the relationship of recurrent events to the likelihood that the index event was PFO-related.

STATISTICAL ANALYSIS. Analyses were performed in the intention-to-treat population, defined as all patients randomly assigned to a treatment group (this included both the closure group and the medical therapy group). For the purposes of this analysis, the population was pooled and considered independent of treatment assignment within the trial. Poolability of these data is supported by the comparable patient demographics and major adverse event rates across treatment arms. Descriptive statistics are shown for demographics, comorbidities, and clinical characteristics. Data are expressed as mean ± standard deviation (SD) or proportions as appropriate. Univariable analyses of continuous variables were performed using a 2-sided unpaired Student *t*-test and categorical variables were compared using the chi-square test. Clinical predictors of recurrent ischemic stroke or TIA were identified using univariable and multivariable Cox proportional hazards regression modeling. Candidate predictors included age, sex, body mass index, diabetes mellitus, hypertension, ischemic heart disease, cigarette smoking, type of index neurologic event (TIA vs. stroke), and detection of atrial fibrillation or flutter (AF) after enrollment. Stepwise selection was used to generate final multivariable models with $p < 0.20$ used for entry and 0.05 for retention. A 2-sided Cochran-Armitage trend test was used to test for trend. A p value of < 0.05 was used to define statistical significance.

RESULTS

PATIENT CHARACTERISTICS. A total of 909 patients were included in this analysis, 447 of which underwent PFO closure. There were 857 patients without a subsequent neurological event. The 52 patients with a

TABLE 1 Baseline Patient Characteristics

	No Recurrent Neurologic Event n = 857	Recurrent Neurologic Event n = 52	p Value
Age, yrs	45.9 ± 9.4	47.1 ± 9.2	0.36
Male	449 (52)	22 (42)	0.16
Race			0.09
American Indian/Alaskan	7 (1)	0 (0)	
Asian	15 (2)	0 (0)	
Black	39 (5)	6 (12)	
Pacific Islander	4 (0)	1 (2)	
White	767 (90)	45 (87)	
Other	25 (3)	0 (0)	
Cigarette smoking	184 (22)	16 (31)	0.12
Mean blood pressure	91.9 ± 10.6	93.1 ± 11.6	0.45
BMI	28.3 ± 5.8	30.2 ± 6.2	0.030
Diabetes mellitus	61 (7)	10 (19)	0.0016
Hypertension	258 (30)	24 (46)	0.015
Hypercholesterolemia	377 (44)	24 (46)	0.76
Family history of CVD	478 (56)	26 (50)	0.42
Ischemic heart disease	8 (1)	2 (4)	0.05
Valvular dysfunction	87 (10)	7 (13)	0.45
Arrhythmia	43 (5)	2 (4)	0.71
Peripheral vascular disease	10 (1)	2 (4)	0.10
Pulmonary embolus	3 (0)	1 (2)	0.10
Migraine	273 (32)	22 (42)	0.12
Index event for study entry			0.018
Cryptogenic stroke	623 (73)	30 (58)	
TIA	232 (27)	22 (42)	

Values are mean ± SD or n (%).
BMI = body mass index; CVD = cardiovascular disease; TIA = transient ischemic attack.

recurrent neurological event suffered 25 cryptogenic strokes and 30 TIA. Baseline characteristics, comorbidities, and neuroimaging results of the groups are detailed in Table 1. Patients with subsequent neurological events had higher body mass index (30.2 ± 6.2 vs. 28.3 ± 5.8, p = 0.03) and more prevalent diabetes (19.2% vs. 7.1%; p = 0.0016), hypertension (46.2% vs. 30.1%, p = 0.015), and ischemic heart disease (3.8% vs. 0.9%, p = 0.05). With increasing decades of life, an increasing proportion of patients suffered recurrent neurologic events, although this pattern did not reach statistical significance (p = 0.37, p trend = 0.23) (Fig. 1). AF was diagnosed after randomization more frequently in those who suffered a recurrent neurologic event than in those who did not (13.5% vs. 2.6%; p < 0.0001).

PREDICTORS OF RECURRENT NEUROLOGICAL EVENTS. Univariable Cox proportional hazards regression identified baseline body mass index (hazard ratio [HR]: 1.05, 95% confidence interval [CI]: 1.00 to 1.09; p = 0.03), history of diabetes (HR: 2.88, 95% CI: 1.45 to 5.74; p = 0.0027), hypertension (HR: 1.92, 95% CI: 1.11 to 3.31; p = 0.02), ischemic heart disease (HR: 4.38, 95% CI: 1.07 to 18.01; p = 0.04), and index TIA (vs. stroke; HR: 1.98, 95% CI: 1.14 to 3.43; p = 0.02) as predictors of recurrent neurologic events (Table 2). In addition, the detection of AF during follow-up portended a markedly increased risk (HR: 4.94, 95% CI: 2.23 to 10.96; p < 0.0001). On multivariable analyses,

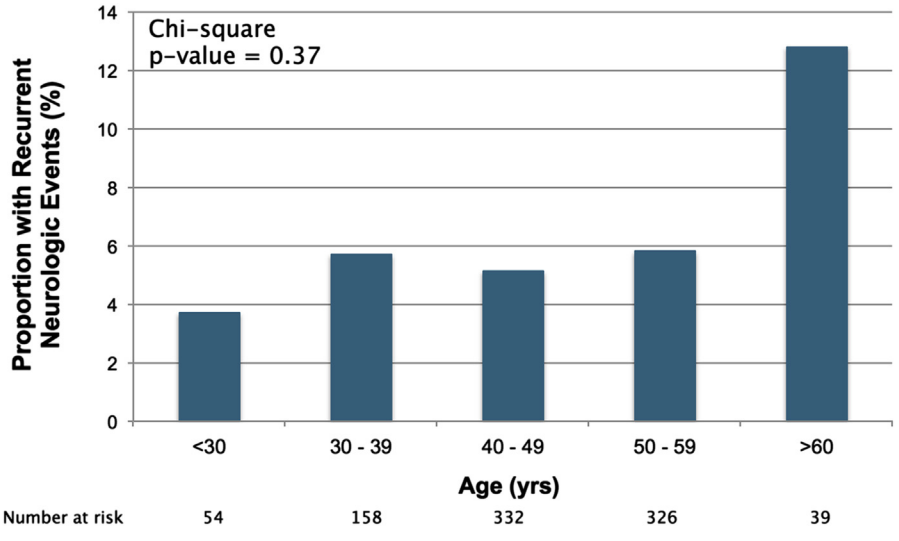

FIGURE 1 Distribution of Recurrent Ischemic Neurologic Events by Decade of Age

Distribution of recurrent ischemic neurologic events by decade of age.

history of diabetes (HR: 3.39, 95% CI: 1.69 to 6.84; p = 0.0007), index TIA (HR: 2.13, 95% CI: 1.20 to 3.80; p = 0.01), and the detection of AF (HR: 4.85, 95% CI: 2.05 to 11.47; p = 0.0003) independently predicted recurrent ischemic neurologic events.

Separate models were built to identify predictors of recurrent TIA and of recurrent stroke (Table 3). A history of diabetes (HR: 5.54, 95% CI: 2.27 to 13.57; p = 0.0002) and detection of AF (HR: 7.29, 95% CI: 2.46 to 21.61; p = 0.0003) independently predicted recurrent ischemic strokes; whereas only index TIA (HR: 4.71, 95% CI: 2.16 to 10.30; p = 0.0001) was associated with recurrent TIA.

ASSOCIATION OF THE ROPE SCORE WITH RECURRENT NEUROLOGICAL EVENTS. The distribution of RoPE scores within the CLOSURE I study is depicted in Figure 2. A RoPE score of >5 was noted in 778 (85.6%) patients. The RoPE score was associated with rates of recurrent neurologic events such that 14.5% (19 of 131) of subjects with a RoPE score ≤5 suffered a recurrent event compared with 4.2% (33 of 778) of those with a RoPE >5 (p < 0.0001) (Fig. 2).

TABLE 2 Predictors of Recurrent Ischemic Neurologic Events

	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
Device closure	0.81 (0.47–1.40)	0.45		
Age/yrs	1.01 (0.98–1.04)	0.40		
Male	1.49 (0.86–2.69)	0.15		
BMI/kg/m^2	1.05 (1.00–1.09)	0.033		
Diabetes mellitus	2.88 (1.45–5.74)	0.0027	3.39 (1.69–6.84)	0.0007
Hypertension	1.92 (1.11–3.31)	0.019		
Ischemic heart disease	4.38 (1.07–18.01)	0.04		
Cigarette smoking	1.68 (0.94–3.04)	0.08		
Index TIA (vs. stroke)	1.98 (1.14–3.43)	0.015	2.13 (1.20–3.80)	0.010
Detection of AF	4.94 (2.23–10.96)	<0.0001	4.85 (2.05–11.47)	0.0003

AF = atrial fibrillation or flutter; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

DISCUSSION

The present analysis identified an association between several cardiovascular risk factors and recurrent neurologic events within the CLOSURE I trial. Specifically, increased body mass index, diabetes, hypertension, and ischemic heart disease predict recurrent events, but among these, only diabetes was an independent predictor of recurrent neurologic events. Patients whose qualifying event was a TIA (vs. ischemic stroke) and those in whom AF was diagnosed after study enrollment were also at increased risk of experiencing recurrent neurologic events. Subgroup analyses further identified diabetes and AF to be independent predictors of recurrent stroke; whereas, an index TIA portended an increased risk of recurrent TIA. Together, these data suggest that a substantial proportion of recurrent events within the CLOSURE I trial were not due to paradoxical embolization.

Paradoxical embolization via a PFO may be implicated as a cause of stroke in the absence of alternative identifiable cause. To what degree stroke can be attributed to PFO in this setting is a matter of debate. Within the CLOSURE I, clinically significant carotid artery stenosis, complex aortic arch atheroma, or other sources of cardioembolic phenomenon served as exclusion criteria. Whereas causality cannot be definitively determined, the association of cardiovascular risk factors such as diabetes with recurrent events within this analysis implies that subclinical atherosclerosis and noncardioembolic causes of neurologic events may have been present in many patients presumed to have had PFO-mediated events.

The RoPE score reflects the probability that a discovered PFO is likely to be stroke-related and not incidental (high scores). We found a broad distribution of RoPE scores within trial participants; however, only 14% of patients had RoPE scores ≤5, indicating that the inclusion criteria for the CLOSURE I trial were largely effective in identifying patients with PFO-mediated index events. However, in these 14% of patients with low scores, the likelihood of PFO-mediated stroke is low, ranging from 0 to 34% (35). Moreover, over one-third of recurrent neurologic events occurred within this subset of patients, lending additional support to the notion that a substantial proportion (37%) of recurrent events within

TABLE 3 Predictors of Recurrent Ischemic Strokes and TIA

	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
Stroke				
BMI/kg/m^2	1.06 (1.00–1.12)	0.057		
Diabetes mellitus	4.76 (1.99–11.39)	0.0005	5.54 (2.27–13.57)	0.0002
Hypertension	1.74 (0.79–3.84)	0.17		
Ischemic heart disease	9.09 (2.14–38.54)	0.0028		
Index TIA (vs. stroke)	0.65 (0.24–1.73)	0.39		
Detection of AF	7.79 (2.93–20.77)	<0.0001	7.29 (2.46–21.61)	0.0003
TIA				
BMI/kg/m^2	1.04 (0.98–1.10)	0.19		
Diabetes mellitus	1.83 (0.64–5.24)	0.26		
Hypertension	1.95 (0.95–4.00)	0.07		
Ischemic heart disease	3.78 (0.51–27.73)	0.19		
Index TIA (vs. stroke)	4.66 (2.22–9.80)	<0.0001	4.71 (2.16–10.30)	0.0001
Development of AF	2.08 (0.50–8.72)	0.32		

Abbreviations as in Tables 1 and 2.

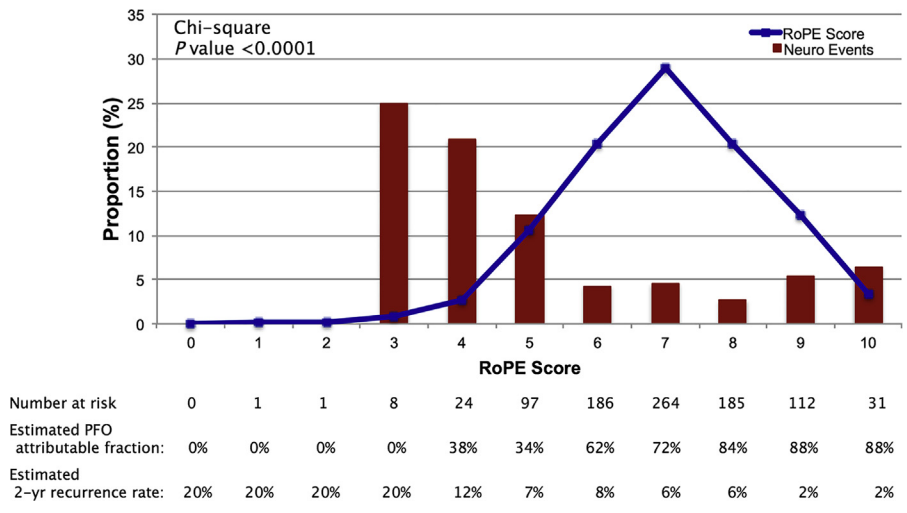

FIGURE 2 RoPE Score Within the CLOSURE I trial

The prevalence of each RoPE (Risk of Paradoxical Embolism) score (0 through 10) within trial participants is depicted **(blue line)**, superimposed on the proportion of patients within each score category suffering a recurrent neurologic event **(red bars)**. The risk of recurrent events increases with decreasing RoPE score ($p < 0.0001$). Estimations for the PFO-attributable fraction, defined as the estimated proportion of cryptogenic strokes that are PFO-related, and the estimated 2-year recurrence rate of ischemic neurologic events based on corresponding RoPE score are listed for reference (35). 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.

CLOSURE I were unlikely PFO-related. Should percutaneous closure become available, patient selection might be improved by more stringently considering the burden of conventional vascular risk factors that to a large degree drive the RoPE score. Additional trials may be required to demonstrate treatment efficacy in this more focused population (e.g., excluding patients with lower RoPE scores).

We found that the diagnosis of AF was the strongest predictor of recurrent neurologic events, further supporting concerns that recurrent events within CLOSURE I were not PFO-mediated. Occult AF is common in patients with cryptogenic neurologic events (36,37). However, the distribution of occult paroxysmal AF should equally distribute across treatment arms with randomization; whereas, the rate of AF was more than 8× greater in the device closure arm than in the medical therapy arm within the CLOSURE I trial (38). Such imbalance suggests that the closure procedure or the NMT STARFlex device induce AF, as has been suggested previously (39). This device- and trial-specific finding may also help to explain the high event rates in CLOSURE I compared with rates of other PFO randomized controlled trials (31).

The causal mechanisms responsible for ischemic stroke and for TIA are largely shared. It was consequently surprising that an index TIA (vs. stroke) would portend an increased risk of recurrent events. Further analysis revealed that index TIA was associated with recurrent TIA, not recurrent stroke. Transient ischemic attack is a nonspecific diagnosis that is often assigned to a myriad of transient neurologic symptoms (38,40,41). Moreover, disorders mimicking TIA, such as epileptic seizure and migraine, are known to recur. The CLOSURE I trial employed a rigorous definition of TIA with adjudication of neurologic events after enrollment. Nonetheless, our findings suggest that the relative lack of specificity of TIA affected patient enrollment as well as adjudication of recurrent neurologic events within CLOSURE I. The inclusion of imaging negative TIA within inclusion criteria and endpoint definitions in CLOSURE I may further explain the high rate of recurrence when compared with rates of recurrence in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial, in which TIA was not considered, and the PC-Trial (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism), which included clinical TIA only in the presence of a "neuroradiologically verified cerebral ischemic lesion" (32,33). The apparent lack of specificity of the TIA diagnosis in the absence of

positive neuroimaging has significant implications not only for future PFO trials, but also for studies of other cardioembolic phenomena and perhaps all trials in which cerebrovascular events serve as an endpoint. Rigorous measures are necessary to ensure that TIA mimics are not used to justify trial entry and are not adjudicated as neurologic events.

Together our findings emphasize the need for clearer definitions and more stringent evaluation of patients with suspected paradoxical embolism, not only within clinical trials, but also in routine clinical care. In addition, they highlight the need to implement comprehensive secondary prevention strategies when managing patients with suspected paradoxical embolism. Whereas the presence of cardiovascular risk factors suggests an atherosclerosis-mediated neurologic event, true causation often cannot be determined, and such patients may certainly experience paradoxical embolism. The RoPE score adds to our armamentarium for identifying PFO-mediated stroke; similar efforts are needed to distinguish TIA from TIA mimics. The emergence of diffusion-weighted magnetic resonance neuroimaging has partially filled this need (42), but additional criteria are needed to help identify TIA due to paradoxical embolism.

STUDY LIMITATIONS. First, the number of recurrent neurologic events within the CLOSURE I trial, and hence statistical power to identify independent predictors of recurrent events was limited. Second, the prevalence of diabetes and incidence of AF may each be underestimated as their occurrence was not systematically collected within the CLOSURE I trial. The magnitude of association between these factors and recurrent events may consequently be overestimated. Third, data from the device closure and medical therapy arms of the CLOSURE I trial were pooled for this analysis, eliminating the possibility of identifying PFO-related predictors of recurrent neurologic events. Similarly, device-related factors, such as residual shunt or device-related thrombus, were not evaluated, although none of the recurrent neurologic events occurred in patients with residual shunt. Fourth, we used the RoPE score to gauge the PFO-attributable risk within the CLOSURE I trial cohort. Whereas the RoPE score effectively generates strata of cryptogenic stroke, patients with greatly different PFO prevalences and therefore different PFO-attributable risks, as with most risk prediction models, it is not comprehensive of all potentially relevant factors and cannot be used in exclusion of clinical judgment. Finally, it is important to note that the identified risk factors for recurrent neurologic events represent statistical associations and that inference of causal mechanisms should be done with caution, if at all. Despite these limitations, our analysis provides valuable insights into the results of the CLOSURE I trial and for the clinical management of patients with suspected paradoxical embolism.

CONCLUSIONS

Within the CLOSURE I trial, several atherosclerotic risk factors, including increased body mass index, diabetes, hypertension, and history of ischemic heart disease predicted recurrent ischemic neurologic events. However, a diagnosis of AF after trial enrollment portended the greatest risk of recurrent events. An increased risk of recurrent TIA, but not stroke, was present in those patients whose qualifying event was a TIA. Together, these data support an alternative etiology to paradoxical embolization for many of the observed recurrent ischemic neurologic events within the CLOSURE I trial and emphasize the challenges inherent in managing patients with PFO and cryptogenic stroke.

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