Off-Label Closure During CLOSURE Study

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ABSTRACT: Background. The role of percutaneous closure of patent foramen ovale (PFO) in patients with cryptogenic stroke or transient ischemic attack remains controversial. Registry data have suggested considerable benefit of closure over medical therapy, but the prospective, randomized CLOSURE I trial found no benefit for device closure. **Methods.** We compared patients enrolled into CLOSURE I at a single large institution to off-label closures performed during the study recruitment period and prospectively enrolled into an institutional registry of PFO closure. We also compared CLOSURE I patients at our institution to the reported characteristics of the entire study to ensure generalizability. **Results.** Between 11/3/2003 and 4/16/2007, there were 100 off-label closures and 33 patients randomized into CLOSURE I. Compared with off-label closure, patients in CLOSURE I were younger (41.6 ± 10.1 years vs 50.0 ± 14.0 years; *P*<.001) and had fewer cardiovascular risks including hypertension (12% vs 36%; *P*=.009), hyperlipidemia (24% vs 53%; *P*=.008), and coronary disease (3% vs 44%; *P*<.001). Degree of right-to-left shunting was considerably higher in off-label closures (28%, 14%, and 58% vs 45%, 30%, and 25% for mild, moderate, and severe, respectively; *P*=.026). **Conclusion.** Off-label closures outnumbered patient recruitment into CLOSURE 3:1 at our institution during study recruitment. Certain demographic differences were expected (age over 60 was an exclusion for CLOSURE I), but vascular risks were considerably greater in the off-label group and may be important mechanistically. Large shunts were considerably more common in off-label patients, suggesting that higher-risk patients may have been preferentially closed off-label. These results suggest that the results of CLOSURE I may not apply to all patients with initial cryptogenic stroke.

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Patent foramen ovale (PFO) is the most common defect of the atrial septum, present in approximately 25% of the population.[1] The majority of patients with PFO are asymptomatic, though several previous studies have suggested an association with cryptogenic stroke and transient ischemic attack, with PFO approximately three times more common in patients with cryptogenic stroke compared to age-matched and sex-matched controls.[2]

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Though causation has never been clearly established, a handful of cases have reported thrombi that resembled vein casts found trapped within a PFO,[3-7] suggesting a mechanism of paradoxic embolization with transit across the PFO. Deep venous thrombosis is present in only a small minority of these patients.[8,9] The precise pathologic mechanism linking PFO to cryptogenic stroke remains uncertain. Co-morbid conditions, including large and small artery disease, cardioembolism, and thrombophilic disorders have been associated with recurrent stroke after percutaneous PFO closure,[10] though hypercoagulable states are rarely indentified.[11]

A PFO likely functions only as the pathway for a venous thrombus to enter the arterial circulation, and the most appropriate therapeutic strategy remains uncertain. Percutaneous device closure was pioneered nearly 3 decades ago[12] and has become the standard of care for most secundum atrial septal defects.[13] Hospital coding data suggest a great rise in PFO closure over the past decade,[14] despite a lack of rigorously designed studies to confirm the benefit of this strategy. Alternatively, pharmacologic therapy to prevent thrombus formation — anticoagulation or antiplatelet therapy — can be utilized. Previous meta-analyses of published data have suggested a considerable benefit of device closure compared to medical therapy,[14,15] although publication bias is likely to have been a considerable limitation of these analyses. A recent propensity-matched cohort has also suggested a considerable benefit to those undergoing percutaneous closure, further fueling the controversy over the most appropriate management strategy in these patients.[16]

The CLOSURE study was a prospective, multicenter, randomized open-label, two-arm superiority trial that was designed to compare device closure to medical therapy.[17] It evaluated patients aged 60 years or younger with initial cryptogenic stroke or magnetic resonance imaging (MRI)-documented transient ischemic attack (TIA) in the context of a PFO and absent hypercoaguable state or deep venous thrombus. No difference in the primary endpoint, the 2-year incidence of stroke or TIA, and mortality (all-cause for the first 30 days and neurological-related from 31 days to 2 years) was seen.[17] Why these findings should differ so much from previous studies largely remains unexplained.

Patient enrollment into CLOSURE lagged considerably behind expectations and the goal recruitment was reduced during execution. Off-label closure was also undoubtedly common during this time. Some of the latter was related to

Table 1. Demographic characteristics.

Variable	CLOSURE Group (n = 33)	Off-Label Group (n = 100)	P-Value
Age (years)	41.6 ± 10.1	50 ± 14.0	<.001
Female sex	36%	49%	.232
Race			.915
Caucasian	94%	94%	
African American	3%	2%	
Other	3%	4%	
Hypertension	12%	36%	.009
Diabetes	6%	10.0%	.729
Hyperlipidemia	24%	53%	.008
Coronary artery disease	3%	44%	<.001
Hemoglobin (g/dL)	14.5 ± 1.3	13.7 ± 1.7	.018
Hematocrit (%)	42.5 ± 3.1	41.1 ± 4.4	.047

Data given as mean ± standard deviation or percentage.

Table 2. Transesophageal echocardiographic measurements.

Variable	CLOSURE Group (n = 33)	Off-Label Group (n = 100)	P-Value
Degree of shunt			.026
Mild	45%	28%	
Moderate	30%	14%	
Severe	25%	58%	
PFO size (mm)	1.4 (IQR, 1.0-2.3)	1.9 (IQR, 1.1-3.0)	.233
Tunnel length (mm)	11.8 ± 6.1	11.3 ± 6.1	.746
Atrial septal aneurysm	21%	40%	.091
Presence of Eustachian valve	15%	6.3%	.189
Presence of Chiari network	5.3%	2.1%	.424

Data given as mean ± standard deviation or percentage. IQR = interquartile range.

study exclusion criteria, but physician and patient-related bias may have also contributed greatly. As such, the results of CLOSURE may not apply to the average cryptogenic patient in whom device closure is being considered. We sought to more carefully examine the differences between study patients and off-label closures in a large institution that actively participated in the CLOSURE trial.

Methods

The Cleveland Clinic participated in the CLOSURE trial, with active patient enrollment between 11/3/2003 and 4/16/2007. All patients undergoing device closure of atrial septal defect or PFO at our institution are prospective entered into a comprehensive database. We searched this database to identify all patients who underwent PFO closure for initial documented stroke or TIA during CLOSURE enrollment dates. The electronic medical records of these patients were reviewed to collect additional comprehensive data. Demographic and clinical variables examined included age, sex, race, body mass index, hypertension, the presence of diabetes mellitus, hyperlipidemia, personal history of coronary artery disease, and bloodwork including hemoglobin, hematocrit, platelet count, creatinine, and blood urea nitrogen. Echocardiographic studies were also fully reviewed for chamber sizes, ventricular function, and the presence of valvular disease. All transesophageal echocardiograms (CLOSURE patients and off-label closures) were reviewed by two blinded readers for details of PFO morphology, including degree of right-to-left shunt, PFO size, tunnel length, and the presence of concomitant atrial septal aneurysm, Eustachian valve and prominent Chiari network. TEE measurements were made as follows: (1) The presence of at least 3 microbubbles in the left atrium within 3 cycles after complete opacification of the right atrium, with or without Valsalva, was diagnostic of right-to-left shunt. The degree of shunting was considered mild if 3 to 9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared, and severe if at least 30 microbubbles appeared. (2) Tunnel length was defined as the maximum overlap between the septum primum and septum secundum, measured in multiple views. (3) The size of the PFO was defined as the maximum separation between the septum primum and septum secundum in multiple views. (4) The presence of atrial septal aneurysm was diagnosed when the atrial septum extended at least 10 mm into the left or right atrium or if the sum of the excursion into the left and right atria was at least 10 mm. Mobility of the septum was measured in multiple views. (5) The presence of a Eustachian valve was defined as an echo-dense, ridge-like structure at the junction of the inferior vena cava and the right atrium. (6) The presence of Chiari's network was defined as a network of coarse fibers in the right atrium connected to the Eustachian valve or coronary sinus with attachments to the upper wall of the right atrium or interatrial septum.[18,19] The study was approved by our institutional review board.

Comparison of dichotomous variables was performed using the Pearson Chi-squared test or Fisher's exact test where appropriate. Comparisons of continuous variables between groups were performed using two-sided t-tests. For all tests, a *P*-value <.05 was considered statistically significant. Data were analyzed using JMP 9.0 software (SAS Institute, Inc).

Results

Significant differences were identified between patients enrolled in CLOSURE I and patients closed off-label during the same time frame (Table 1). Patients enrolled in CLOSURE I were younger (41.6 ± 10.1 years vs 50.0 ± 14.0 years; *P*=.0005) and had fewer cardiovascular risks,

Table 3. Transthoracic echocardiographic measurements.

Variable	CLOSURE Group (N=33)	Off-Label Group (N=100)	*P*-Value
Normal LV size	100%	98%	1.00
LV ejection fraction (%)	58.5 (55-60)	56 (55-60)	.919
Normal RV size	100%	100%	1.00
Normal RV function	100%	99%	1.00
Normal RA size	92%	92%	1.00
Tricuspid regurgitation			
Normal	21%	12%	
Mild	75%	87%	.150
Mild-to-moderate	4%	0%	
Moderate	0%	1%	

Data given as mean (interquartile range) or percentage.

including hypertension (6% vs 36%; *P*=.0007), hyperlipidemia (24% vs 52%; *P*=.008), and prevalence of coronary artery disease (3% vs. 44%; *P*<.0001). Transthoracic echocardiographic features are listed in Table 2. No significant differences were noted in chamber sizes, degree of tricuspid valve regurgitation, or right or left ventricular function on transthoracic echocardiography. Transesophageal echocardiographic measurements are listed in Table 3. A trend toward more atrial septal aneurysms on transesophageal echocardiography was seen in the off-label population (21% vs 40%; *P*=.09). Degree of right-to-left shunting was considerably greater in patients closed off-label (45%, 30%, and 25% vs 28%, 14%, and 58% for mild, moderate, and severe, respectively; *P*=.026). This degree of shunting (seen in our CLOSURE trial population) is similar to that reported for the entire study.[20]

Discussion

In a large institution actively participating in the CLOSURE I trial, off-label closures outnumbered patient enrollment 3:1 during the enrollment period. Undoubtedly, many other patients with cryptogenic stroke and patent foramen ovale were also seen and preferred to be treated medically, though proper identification of this latter cohort was not possible given our study design. There are other significant limitations to our study design including its single center nature and the small sample size, which limited meaningful comparison of several features including clinical outcomes. Enrollment of a patient into a randomized clinical trial requires the belief of equipoise on the part of the physician. Prior epidemiological studies suggesting improved outcomes with device closure of patent foramen ovale undoubtedly challenged this assertion. Patient access to such medical information via the internet is now incredibly common and patients come to clinical visits much more knowledgeable than in the past; active participation in decision-making has thus become the norm in the physician-patient relationship. This can greatly influence the clinical plan. In addition, certain patient and PFO characteristics may bias referring physicians toward/against closure, prior to the patient being referred to neurologists or cardiologists involved in the final decision-making process. On this background, we sought to examine in more detail the differences between patients enrolled in CLOSURE I and those closed off-label to gain greater insight into patient selection and attempt to determine the applicability of CLOSURE I study findings.

Significant differences were found between patients enrolled in CLOSURE I and patients who were closed off-label during the same time frame. Some of these differences were expected, such as age. CLOSURE I only investigated patients under 60 years of age; thus, the average age of the off-label closure group was older. A previous study has suggested that PFO may also play a considerable role in recurrence of cryptogenic stroke in the elderly patient population, and it remains unclear if exclusion of these patients was necessary or a wise decision.[21] Other differences may be important for prognosis and risks associated with PFO closure. Vascular risks, including hypertension, hyperlipidemia, and coronary artery disease, were more frequent in patients closed off-label. This could have contributed to the low number of events seen in CLOSURE I, as patients who were at highest risk may have not been enrolled in the trial. Vascular risk factors may also be important mechanistically, as paradoxical embolism presumably requires venous thrombosis as an initial step.

Certain morphologic characteristics of PFO may predict a higher risk of stroke recurrence, including size of the defect, maximal number of microbubbles that cross during saline microcavitation study, and the presence of atrial septal aneurysm,[22] suggesting the concept of a more "pathologic" PFO. Patients closed off-label were more likely to have a severe shunt, defined as >30 microbubbles present in the left atrium. Patients with a larger physiologic shunt are presumably higher risk, as this may increase the likelihood of an embolus passing through the PFO. Patients closed off-label also trended toward having more atrial septal aneurysms. This may suggest more pathologic PFOs in patients being closed off-label than in those enrolled into CLOSURE I.

CLOSURE I is the first major clinical trial directly comparing closure of a PFO to best medical therapy in patients with a cryptogenic stroke or TIA. It was a major undertaking for which the investigators and participants should be greatly commended. The conclusions from this trial have great potential to shape standard of care recommendations. Whether this trial should apply to all patients with initial cryptogenic stroke or TIA, however, deserves further attention to assure that the correct decisions about individual patient care are made. We found considerable differences between patients enrolled in CLOSURE and patients closed off-label. This may have biased the results, and the conclusions of CLOSURE I may therefore not be generalizable to all patients

with cryptogenic stroke. The discrepancies identified in our study may be helpful in modifying future study designs in this important patient population.

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