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Long-Term Follow-Up After Closure of Patent Foramen Ovale in Patients With Cryptogenic Embolism

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ABSTRACT

BACKGROUND Patent foramen ovale (PFO) closure is the gold standard for treating patients with cryptogenic stroke and PFO. However, scarce data exist on the long-term outcomes following PFO closure.

OBJECTIVES The purpose of this study was to determine the long-term (>10 years) clinical outcomes (death, ischemic, hemorrhagic events) following transcatheter PFO closure.

METHODS We included 201 consecutive patients (mean age: 47 ± 12 years, 51% women) who underwent PFO closure due to a cryptogenic embolism (stroke: 76%, transient ischemic attack [TIA]: 32%, systemic embolism: 1%). Echocardiographic examinations were performed at 1- to 6-month follow-up. Ischemic and bleeding events and antithrombotic medication were collected at a median follow-up of 12 years (range 10 to 17 years), and follow-up was complete in 96% of the patients.

RESULTS The PFO closure device was successfully implanted in all cases, and residual shunt was observed in 3.3% of patients at follow-up echocardiography. A total of 13 patients died at follow-up (all from noncardiovascular causes), and nondisabling stroke and TIA occurred in 2 and 6 patients, respectively (0.08 strokes per 100 patient-years; 0.26 TIAs per 100 patient-years). A history of thrombophilia (present in 15% of patients) tended to associate with a higher rate of ischemic events at follow-up ($p = 0.067$). Bleeding events occurred in 13 patients and were major (intracranial bleeding) in 4 patients (all of them under aspirin therapy at the time of the event). A total of 42 patients stopped the antithrombotic treatment at a median of 6 months (interquartile range 6 to 14 months) post-PFO closure, and none of them had any ischemic or bleeding episode after a mean of 10 ± 4 years following treatment cessation.

CONCLUSIONS PFO closure was associated with a low rate of ischemic events (stroke, 1%) at >10 years of follow-up. Major bleeding events occurred in 2% of the patients (all of them in patients on antiplatelet therapy). One-fifth of patients stopped the antithrombotic therapy during the follow-up period (the majority within the first-year post-PFO closure), and this was not associated with any increase in ischemic events at long-term follow-up.
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Transcatheter patent foramen ovale (PFO) closure has been recently established as the new gold-standard therapy for patients with cryptogenic stroke and PFO (1,2). Up to 4 randomized trials and subsequent meta-analyses have shown a significant reduction in recurrent ischemic stroke events over time in those patients who had PFO closure compared with those managed medically (mainly with aspirin treatment) (3-9). However, the mean follow-up in these studies was limited to about 4 years (range 2 to 6 years). Considering the (young) age of the patients undergoing PFO closure nowadays (mean age <50 years in all studies), we may anticipate a long life expectancy following PFO closure in this

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population. Limited data exist on long-term outcomes following PFO closure (10); it would therefore be important to obtain much longer-term follow-up data among PFO closure recipients to determine recurrent ischemic events as well as the occurrence of concomitant events such as atrial fibrillation or venous thrombosis at long-term follow-up. Also, long-term antiplatelet therapy is currently recommended in such patients (as for any patient diagnosed with ischemic stroke) (11,12), but the optimal duration of antithrombotic therapy following PFO closure has not yet been evaluated (13). Thus, the objective of this study was to determine the long-term (>10 years) clinical outcomes (ischemic, hemorrhagic events) in a cohort of consecutive patients who had PFO closure because of a cryptogenic ischemic stroke, transient ischemic attack, or peripheral embolism.

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METHODS

A total of 201 consecutive patients who had PFO closure between 2001 and 2008 at our institution because of cryptogenic stroke/TIA or peripheral embolism were included. Presumed diagnostic of paradoxical embolism was established by a neurologist after a screening including brain magnetic resonance imaging and/or brain computed tomography, 24-h Holter monitoring, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcarotid Doppler. Thrombophilia research was performed in 107 (53%) patients and included a complete hematologic assay with platelet count and assessment of coagulation protein abnormalities including presence of factor V Leiden, antithrombin III, proteins C and S, antiphospholipid, and anticardiolipin antibodies. The diagnosis of PFO was established on the basis of a right-to-left shunt during TEE examination with agitated saline contrast test with and without Valsalva maneuver. The shunt was classified as small, moderate, or large, with or without atrial septal aneurysm (14).

The procedures were performed under general anesthesia and TEE guidance. The type and size of the implanted device were left to the criteria of the physician performing the procedure. Post-procedure TTE was performed in all patients prior to hospital discharge, typically a few hours after the procedure to confirm device position, look for residual shunt, and exclude pericardial effusion. Medical therapy at discharge was (usually) aspirin (indefinitely), and clopidogrel was added in some cases (for 6 months) according to the preference of the physician performing the procedure. Anticoagulation was prescribed in the presence of other medical reasons requiring anticoagulation therapy (pulmonary embolism, deep venous thrombosis [DVT]). At 1 to 6 months post-procedure, patients had a clinical visit and an echocardiographic (TTE and/or TEE) examination. All procedural and 1- to 6-month follow-up data were prospectively entered into a dedicated database.

ABBREVIATIONS AND ACRONYMS

DVT = deep venous thrombosis

PFO = patent foramen ovale

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TTE = transthoracic echocardiography

FOLLOW-UP. Follow-up was ensured by the referring neurologist/cardiologist or the physician performing the PFO closure along with the family doctor responsible for the patient, but there was no pre-established timing for the clinical visits during the follow-up period after the 1-year follow-up. The medical records of all patients were reviewed, and data regarding all clinical events and current medications were collected. Also, a systematic clinical visit or phone call was conducted in every patient for whom no follow-up data were available at a minimum of 10 years post-procedure. Each patient was asked about recurrences of stroke, TIA, or peripheral embolism; new hospitalizations (and reason); bleeding; arrhythmias and cardiac events; migraine; and current medications. When an event was suspected on the basis of the questionnaire, the complete medical file of the center taking care of the patient was consulted. The patient's primary care physician and cardiologist/neurologist responsible for the patient were consulted if any further information was needed. If the medication prescribed following PFO closure was stopped, the reasons for and timing of medication cessation were recorded. Occasionally, information about current medication and medication changes over time was obtained by contacting the patient's pharmacy. The information from the pharmacy was matched with that obtained during the clinical visit or phone call.

All neurological events (stroke, TIA) were diagnosed by a neurologist and defined according to TOAST criteria (15). Bleeding events were defined and classified according to the BARC (Bleeding Academic Research Consortium) criteria (16).

STATISTICAL ANALYSIS. Categorical variables were reported as n (%) and continuous variables as mean ± SD or median (25th to 75th interquartile range), depending on variable distribution. Group comparisons were analyzed using the Student's *t*-test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables. Survival curves for time-to-event variables were performed with the use of Kaplan-Meier

TABLE 1 Baseline Characteristics of the Study Population (n = 201)

Age, yrs	47 ± 12
Female	102 (50.8)
Body mass index, kg/m^2	26.9 ± 5.7
Current smoking	22 (10.9)
Hypertension	48 (23.9)
Dyslipidemia	46 (22.9)
Diabetes mellitus	9 (4.5)
Migraine antecedents	46 (22.9)
Oral contraception	9 (4.5)
VTE	16 (8.0)
Pulmonary embolism	8 (4.0)
Deep venous thrombosis	10 (5.0)
Thrombophilia*	16 (14.9)
Closure indication	
Stroke	153 (76.1)
TIA	65 (32.3)
Peripheral embolism	3 (1.5)
Shunt size	
Small	74 (36.8)
Moderate	79 (39.3)
Large	37 (18.4)
Undefined	11 (5.5)
Atrial septal aneurysm	77 (38.3)
RoPE score	6.6 ± 2.1

Values are mean ± SD or n (%). *Data available in 107 patients.
RoPE = risk of paradoxical embolism; TIA = transient ischemic attack; VTE = venous thromboembolism.

estimates, and comparison between groups performed with the log-rank test. Results were considered significant at $p < 0.05$. All analyses were conducted using the statistical package SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The baseline characteristics of the study population are shown in Table 1. The mean age of the patients was 47 ± 12 years, with 51% women. Most patients (76%) had PFO closure because of cryptogenic stroke, followed by TIA (32%) and systemic embolism (2%). A total of 46 patients (22.9%) had a prior history of migraine attacks. The right-to-left shunt was moderate or severe in most cases (57.8%), and the presence of an atrial septal aneurysm was documented in 38% of patients.

The procedural characteristics and in-hospital outcomes following PFO closure are shown in Table 2. The PFO closure device was successfully implanted in all cases, and the majority of patients (78%) received an Amplatzer PFO closure device (Abbott, Chicago, Illinois). TTE examination (with bubble test) at hospital discharge showed no residual shunt in 93% of patients. There were no cases of periprocedural death, device embolization, thrombosis, major vascular complication, or cardiac tamponade during the study period. One patient experienced a transient AF and an esophageal hematoma secondary to the TEE probe with no late consequences and a full recovery without intervention. Another patient had an episode of deep vein thrombosis complicated with pulmonary embolism within the 24 h following the procedure.

FOLLOW-UP. A total of 183 patients (91% of the study population) had an echocardiographic examination (with bubble test) at 1- to 6-month follow-up. There were no cases of late device embolization, dislocation or thrombosis, or late pericardial effusion. A residual shunt was demonstrated in 6 patients (3.3%), and it was mild in all cases but 1 (moderate), which required a second closure procedure after a recurrent TIA. Mild shunts were considered as procedural success.

The median follow-up for the entire study population was 12 years (range 10 to 17 years), and follow-up was complete in all patients but 8 (4% lost to follow-up). The main clinical outcomes at follow-up are presented in Table 3, and the Kaplan-Meier curves for the main clinical events up to 15 years post-PFO closure are shown in Figure 1. A total of 13 patients (6.5%) died during the follow-up period, all of them from noncardiovascular causes (cancer = 6; intracerebral hemorrhage = 1; chronic pulmonary embolism = 1; dementia = 1; car accident = 1; suicide = 1; and unknown = 2). A total of 7 patients (3.5%) had at least 1 ischemic (TIA or stroke) neurological event (0.3 per 100 person-years, 95% confidence interval [CI]: 0.08 to 0.53); 2 patients (1.0%) had an ischemic stroke (0.08 per 100 person-years, 95% CI: 0.03 to 0.21), and 6 patients (2.9%) had a TIA (0.26 per 100 person-years, 95% CI: 0.03 to 0.41). All patients were on antiplatelet treatment (aspirin or clopidogrel) at the time of the event. Regarding the 2 stroke events, both were considered nondisabling strokes: 1 was related to atherothrombotic disease (5 years after the PFO closure), and 1 due to a vertebral artery dissection (2.5 years after the PFO closure). The main clinical characteristics of the patients according to the occurrence of an ischemic neurological event (stroke or TIA) are shown in Table 4. There were no differences between groups except a trend toward a higher prevalence of a history of thrombophilia ($p = 0.067$) among patients who presented with an ischemic event during the follow-up period. Coagulation testing and thrombophilia details are shown in Table 5.

A total of 13 patients experienced a bleeding complication during the follow-up period, and all of

them were on antiplatelet therapy at the time of the event (aspirin alone in 10 patients; aspirin + clopidogrel in 3 patients). A total of 4 bleeding episodes were considered major bleeding events (BARC ≥3; fatal in 1 patient). The origin of the bleeding episode was as follows: subcutaneous hematoma (n = 5), gastrointestinal (n = 1), gynecologic (n = 1), severe epistaxis (n = 2), and intracranial (n = 4). A total of 5 episodes of atrial fibrillation occurred after PFO closure: 1 episode 5 days after the procedure, and 4 episodes several years after the procedure (2, 7, 10, and 11 years post-PFO closure). A total of 6 patients had a venous thrombosis during the follow-up period (6 DVT, 2 pulmonary embolism). Five of 6 patients who had a venous thrombo-embolism were treated with aspirin at the time of the episode, and 1 was on warfarin therapy.

EXPLORATORY ANALYSIS: ANTITHROMBOTIC TREATMENT CESSATION AT FOLLOW-UP. At the time of the last follow-up, 42 patients (20.9%) had been free of any antithrombotic therapy for a mean of 10 ± 4 years. In these patients, antithrombotic treatment cessation occurred at a median of 6 months (interquartile range: 6 to 14 months) following PFO closure. Four patients stopped the antiplatelet therapy because of bleeding events, and the rest because of a personal decision (with or without physician agreement). The clinical characteristics of these patients compared with those who pursued the antithrombotic treatment are shown in Table 6. Patients who stopped the antithrombotic treatment at follow-up were younger and had a lower body mass index, a higher RoPE (risk of paradoxical embolism) score, and less frequently a history of hypertension. The clinical outcomes of patients with and without antithrombotic treatment at follow-up are summarized in Table 7. There were no differences between groups in death or ischemic events. No ischemic or bleeding events occurred among those patients with no antithrombotic treatment at follow-up.

DISCUSSION

In patients with cryptogenic stroke/TIA undergoing transcatheter PFO closure, there was a low rate of ischemic events (stroke: 1%) at long-term follow-up (>10 years) (Central Illustration). A history of thrombophilia tended to be associated with a higher risk of ischemic neurological events at follow-up. Also, a rate of 2% of major bleeding events (1 of them fatal) was observed during the follow-up period, and all occurred in patients on antiplatelet therapy. Finally, about one-fifth of the patients stopped the antithrombotic therapy at a median time of 6 months post-PFO closure, and this was not associated with any increase in ischemic events at long-term follow-up.

TABLE 2 Procedural Characteristics and In-Hospital Outcomes (n = 201)

Successful device implantation	201 (100)
Device type	
Amplatzer PFO	156 (77.6)
Amplatzer ASD	27 (13.4)
Amplatzer cribriform	1 (0.5)
Premere	17 (8.5)
Device size, mm	25 ± 5
<25	23 (11.7)
25	147 (75.0)
>25	26 (13.3)
In-hospital complications	
Device embolization	0 (0.0)
Device thrombosis	0 (0.0)
AF	1 (0.5)
Tamponade	0 (0.0)
Esophageal hematoma	1 (0.5)
Deep venous thrombosis	1 (0.5)
Pulmonary embolism	1 (0.5)
Major vascular complication	0 (0.0)
Residual shunt at discharge	14 (7.0)
Mild	13 (6.5)
Moderate	1 (0.5)
Antithrombotic treatment at hospital discharge	
Aspirin	182 (90.6)
Clopidogrel	37 (18.4)
Aspirin + clopidogrel	29 (14.4)
Anticoagulation	16 (7.9)
Anticoagulation + aspirin	5 (2.5)

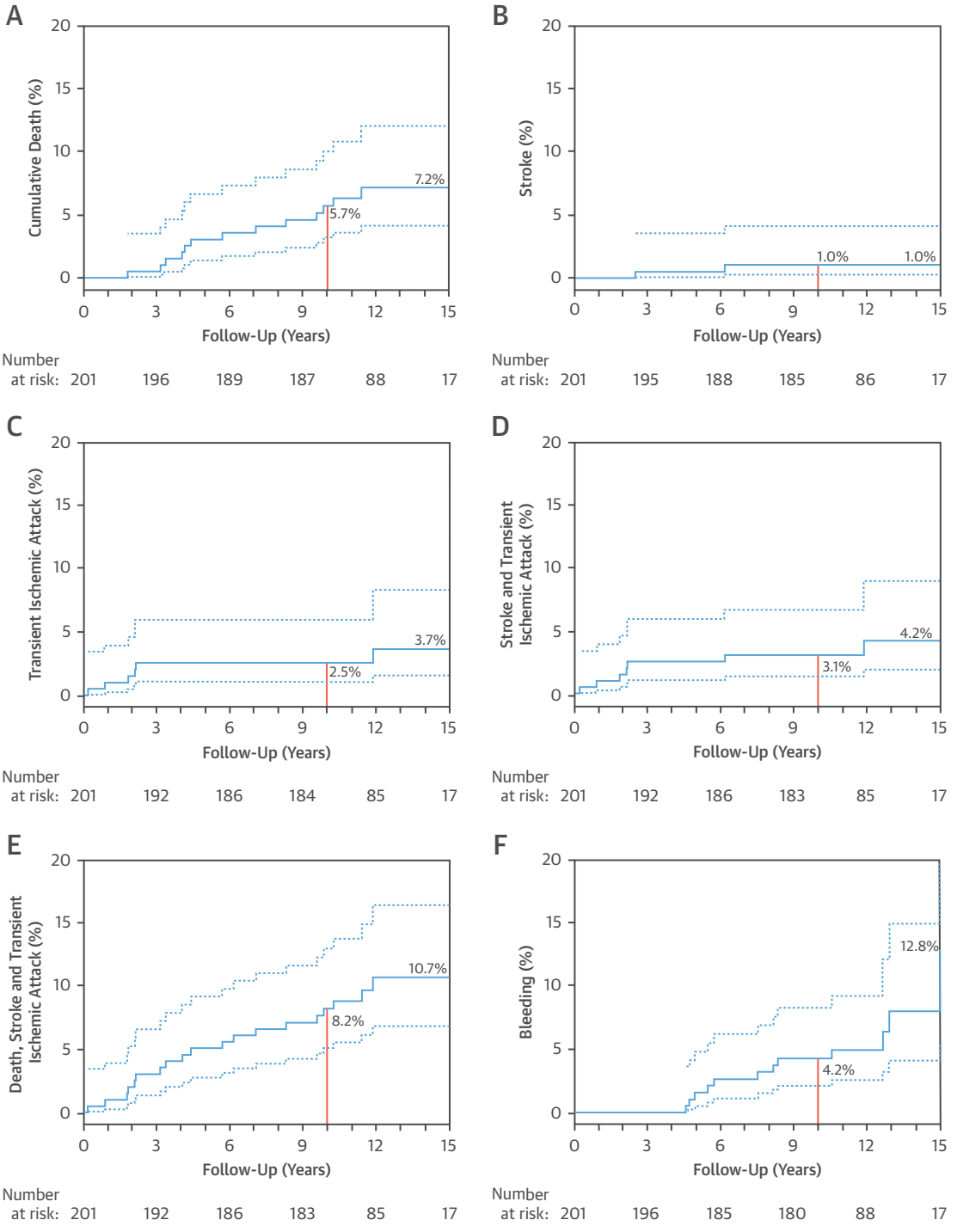
Values are n (%) or mean ± SD.
AF = atrial fibrillation; ASD = atrial septal defect; PFO = patent foramen ovale.

TABLE 3 Clinical Outcomes After PFO Closure (n = 201)

Follow-up, yrs	12 (10-17)
Death	13 (6.5)
Stroke	2 (1.0)
TIA	6 (2.9)
Composite of stroke or TIA	7 (3.5)
Composite of death, stroke, or TIA	19 (9.5)
Peripheral embolism	0 (0.0)
Deep vein thrombosis	6 (2.9)
Atrial fibrillation	5 (2.5)
Myocardial infarction	4 (2.0)
Bleeding	13 (6.5)
Major bleeding	4 (2.0)
Migraine	5 (2.6)

Values are median (range) or n (%).
PFO = patent foramen ovale; TIA = transient ischemic attack.

FIGURE 1 Kaplan-Meier Estimates for Clinical Events at 15-Year Follow-Up



Kaplan-Meier plots showing cumulative death **(A)**; stroke **(B)**; transient ischemic attack (TIA) **(C)**; stroke or TIA **(D)**; death, stroke, or TIA **(E)**; and bleeding **(F)** over a 15-year follow-up.

The clinical characteristics of our study population were similar to those reported in prior studies, with a mean age below 50 years, and a relatively low prevalence of classical cardiovascular risk factors (3-6). This was also reflected by a high RoPE score, similar to that reported in the CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) trial (4). According to prior studies, the PFO closure procedure was safe, with only 3 major periprocedural events (transient atrial fibrillation, pulmonary embolism, and esophageal hematoma). Interestingly, the use of intracardiac echocardiography or fluoroscopic guidance only could avoid the potential complications related to general anesthesia or TEE probe in these patients (17,18). The main results of our study extend the positive findings of the recent randomized PFO closure trials to the long-term (>10 years) follow-up of these patients. The low stroke rate (0.08 per 100 patient-years) observed in our study was similar to that reported in the CLOSE and DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) trials (0%), although slightly lower than that reported in the REDUCE (Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke) (0.39 per 100 patient-years) and RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) (0.58 per 100 patient-years) trials. These findings support the fact that the initial benefits observed with PFO closure with respect to medical treatment are maintained at long-term follow-up. The mean RoPE score in our study population was 6.6, and an ischemic cerebrovascular event rate of 3.4%/year would have been expected in our study population with medical therapy only (19) (Online Figure 1). Also, previous studies have shown that medical treatment alone in cryptogenic stroke patients with PFO was associated with recurrent stroke rates of 1.2 to 1.71 per 100 patient-years, a much higher incidence compared with that observed in our study (5,10). Of note, the 2 strokes in our study occurred several years after the procedure and were not cryptogenic or related to the device (carotid dissection, atherothrombosis), further reinforcing the high efficacy of transcatheter PFO closure for preventing paradoxical embolization in these patients. Importantly, there were no late or very late events related to the device, which also adds valuable data to the safety profile of PFO closure devices >10 years after their initial implantation. These data are in accordance with a prior report from Rigatelli et al. (20), with a mean follow-up over 10 years but including patients with <5 years of follow-up, and with the study from Wahl et al. (10) with a mean follow-up of 9 years and a stroke rate of 0.6 per 100 patient-years post-PFO closure. In that study, 106 patients with PFO closure and 106 with medical therapy only were compared using a propensity score-matched analysis, showing a lower rate of thromboembolic events in the closure group, mainly driven by a lower rate of TIAs (10).

A history of thrombophilia was diagnosed in 15% of the patients in our study, similar to prior studies in the field of PFO closure (21-23). Interestingly, this was the only factor associated with a tendency toward an increased rate of ischemic events at follow-up. Karttunen et al. (24) already showed an increased risk of cerebrovascular events in patients with thrombophilia and PFO, and Ford et al. (22) suggested

TABLE 4 Clinical Characteristics, According to the Occurrence of Ischemic Stroke/TIA at Follow-Up

	No Recurrent Stroke/TIA (n = 194)	Recurrent Stroke/TIA (n = 7)	p Value
Age, yrs	47 ± 12	42 ± 14	0.205
Female	98 (50.5)	4 (57.1)	0.282
Body mass index, kg/m^2	26.8 ± 5.4	28.8 ± 11.6	0.659
Current smoking	22 (11.3)	0 (0.0)	0.999
Hypertension	45 (23.2)	3 (42.9)	0.361
Dyslipidemia	43 (22.2)	3 (42.9)	0.198
Diabetes mellitus	8 (4.1)	1 (14.3)	0.278
Migraine antecedents	43 (22.2)	3 (42.9)	0.198
Oral contraception	9 (4.6)	0 (0.0)	0.999
Pulmonary embolism	8 (4.1)	0 (0.0)	0.999
Deep vein thrombosis	10 (5.2)	0 (0.0)	0.999
Thrombophilia*	13 (13.0)	3 (42.9)	0.067
Closure indication			
Stroke	139 (71.7)	4 (57.1)	0.414
TIA	61 (31.4)	4 (57.1)	0.216
Peripheral embolism	3 (1.6)	0 (0.0)	0.899
Shunt at 1 to 6 months	5/176 (2.8)	1/7 (14.3)	0.215
Atrial septal aneurysm	75 (41.4)	2 (28.6)	0.702
RoPE	6.6 ± 1.5	6.4 ± 2.6	0.852

Values are mean ± SD, n (%), or n/N (%). *Data available for 107 patients.
Abbreviations as in Table 1.

TABLE 5 Thrombophilia and Antiphospholipid Testing (n = 107)

Normal coagulation screen	91 (85.0)
Factor V Leiden	6 (5.6)
Factor II mutation	3 (2.8)
Anticardiolipin antibodies	4 (3.7)
Lupus anticoagulant	3 (2.8)
Anti-b2 glycoprotein-I antibodies	1 (0.9)

Values are n (%). One patient had both anticardiolipin antibodies and lupus anticoagulant.

TABLE 6 Clinical Characteristics, According to Antithrombotic Treatment Cessation at Follow-Up

	No Antithrombotic Treatment at FU (n = 42)	Antithrombotic Treatment at FU (n = 159)	p Value
Clinical characteristics			
Age, yrs	43 ± 10	48 ± 12	0.003
Female	25 (59.5)	77 (48.4)	0.227
Body mass index, kg/m^2	24.2 ± 3.2	27.6 ± 5.9	<0.001
Current smoking	5 (11.9)	17 (10.7)	0.177
Hypertension	3 (7.1)	45 (28.3)	0.004
Dyslipidemia	5 (11.9)	41 (25.8)	0.064
Diabetes mellitus	0 (0.0)	9 (5.7)	0.209
Migraine antecedents	9 (21.4)	37 (23.3)	0.161
Oral contraception	1 (2.4)	8 (5.0)	0.689
COPD	0 (0.0)	5 (3.1)	0.586
Pulmonary embolism	0 (0.0)	8 (5.0)	0.209
Deep vein thrombosis	3 (7.5)	7 (4.4)	0.439
Thrombophilia*	3 (12.5)	13 (15.7)	0.203
Closure indication			
Stroke	27 (64.3)	116 (72.9)	0.338
TIA	15 (35.7)	50 (31.5)	0.584
Peripheral embolism	1 (2.4)	2 (1.3)	0.507
Atrial septal aneurysm	17 (42.5)	60 (40.5)	0.857
RoPE	7.1 ± 1.3	6.5 ± 1.5	0.021
Shunt at 1 to 6 months	0 (0.0)	6 (3.8)	0.343

Values are mean ± SD or n (%). *Data available for 107 patients.
COPD = chronic obstructive pulmonary disorder; FU = follow-up; other abbreviations as in Table 1.

that this increased risk may persist after PFO closure. Our findings also point in this direction, although the data should be interpreted with caution due to the low number of events and the lack of systematic evaluation of coagulation disorders in our patients. However, these findings should stimulate further research and support a systematic evaluation of coagulation disorders in patients with cryptogenic stroke.

TABLE 7 Clinical Outcomes Following PFO Closure, According to the Continuation of Antithrombotic Treatment at Follow-Up

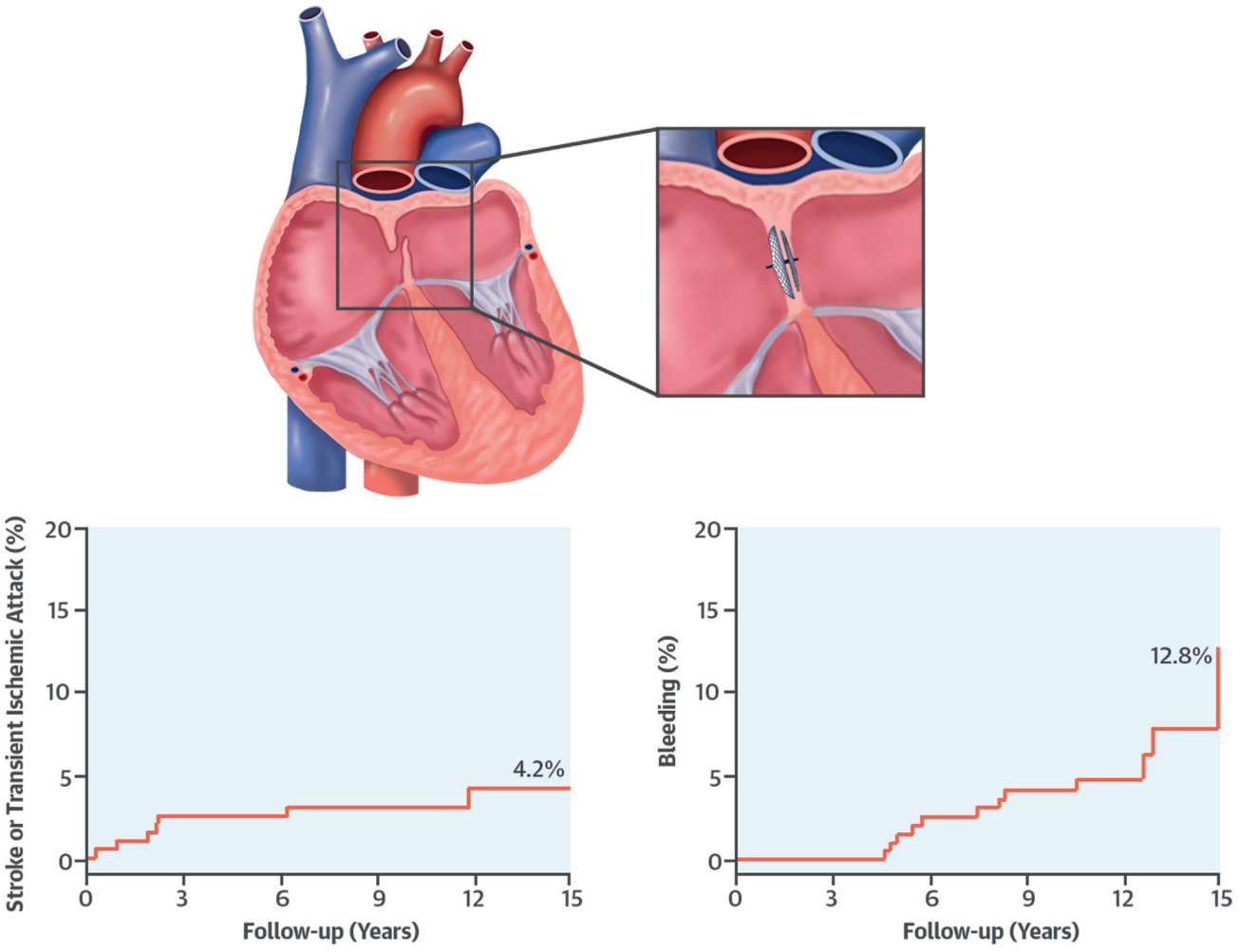
	No Antithrombotic Treatment at FU (n = 42)	Antithrombotic Treatment at FU (n = 159)	p Value
Follow-up, yrs	12 (11–13)	12 (11–13)	0.903
Death	2 (4.8)	11 (6.9)	0.263
Stroke	0 (0.0)	2 (1.3)	0.625
TIA	0 (0.0)	6 (3.8)	0.347
Composite of stroke and TIA	0 (0.0)	7 (4.4)	0.349
Composite of death, stroke, and TIA	2 (4.8)	17 (10.7)	0.375
Deep vein thrombosis	0 (0.0)	6 (3.8)	0.347
Atrial fibrillation	0 (0.0)	5 (3.2)	0.586
Myocardial infarction	0 (0.0)	4 (2.5)	0.581
Bleeding	0 (0.0)*	9 (5.7)	0.209
Migraine	2 (5.0)	3 (1.9)	0.280

Values are median (25th to 75th percentile) or n (%). *During the time without antiplatelet therapy (4 patients quit antithrombotic therapy due to bleeding events).
FU = follow-up; TIA = transient ischemic attack.

In the current study, antithrombotic therapy consisted of aspirin in the majority of patients. Only 8% of the patients were under anticoagulation at the time of PFO closure. As anticoagulation could be an alternative treatment in these patients, PFO closure was decided to allow anticoagulation therapy cessation and reduce bleeding risk at long-term follow-up. Anticoagulation therapy was ceased in most patients, and no bleeding events occurred in those patients remaining under anticoagulation therapy. CLOSE is the only trial comparing anticoagulation to antiplatelet treatment in the medical therapy-only group (4). Although there were more than twice as many major or fatal bleeding events in the anticoagulation group (5.3% vs. 2.3%), differences between groups remained nonsignificant, likely due to an underpowered sample size. Apart from systemic thromboembolic events, the risk of DVT or pulmonary embolism should also be considered in PFO closure recipients. Importantly, DVT/pulmonary embolism occurred in 3% of the patients in our study, and most of them had a history of prior venous thrombosis at the time of PFO closure. Similar rates of DVT/pulmonary embolism have been reported in the RESPECT trial (5). In such patients, the risks and benefits of long-term anticoagulation should probably be evaluated on a case-by-case basis.

Although long-term antithrombotic therapy is usually recommended following PFO closure, we found that up to one-fifth of the patients quit all antithrombotic treatment at a median of 6 months following the procedure. Interestingly, this was not associated with any negative effect on ischemic events. In fact, no patient experienced stroke or TIA after a cumulative mean time of 10 years without any antiplatelet or anticoagulant therapy. All ischemic neurological recurrences occurred in patients treated with aspirin or clopidogrel. The present study is the first to look at stroke/TIA recurrence in the light of ongoing antithrombotic therapy. In the RESPECT trial, 6% of the patients received no medication during the follow-up period, but no data were provided with respect to this subgroup (5). In the PC trial, 43% and 51% of the patients included in the closure group had no antithrombotic treatment at 1 and 5 years, respectively, and there was only 1 recurrence of stroke at 2-year follow-up (25). To date, there are no clear guidelines regarding medical treatment after PFO closure except for the fact that antiplatelet therapy is recommended as secondary stroke prevention (26). In fact, this is an important issue, considering that PFO closure is performed in young

CENTRAL ILLUSTRATION **Long-Term Outcomes Following Patent Foramen Ovale Closure**



Wintzer-Wehekind, J. et al. J Am Coll Cardiol. 2019;73(3):278–87.

(Top) A schema of the patent foramen ovale (PFO) closure procedure. **(Bottom)** Kaplan-Meier plots with the cumulative stroke and transient ischemic attack, and bleeding over a 15-year follow-up.

patients, exposing them to potentially serious bleeding events due to the long-term duration of antithrombotic therapy. The rate of major bleeding events in our study population was low (0.2 events per 100 patient-years), much lower than the risk estimated according to a mean HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly) score of 1.0 at the time of PFO closure (1.1 events per 100 patient-years) (27) (Online Figure 1). However, multiple studies have shown an increased risk of bleeding events with the chronic use of aspirin. In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, and in the Dutch Transient Ischemic Attack trial comparing 2 doses (30 vs. 283 mg a day) of aspirin, patients treated with low-dose aspirin (≤325 mg) had an incidence of gastrointestinal hemorrhage of 2.7% and 1.7% after a mean follow-up of 1.9 and 2.6 years, respectively (28,29). Furthermore, 3% of the Dutch TIA trial population had major bleeding complications (29). This was also confirmed in studies using aspirin in primary prevention for patients with type II diabetes (30). A systematic review of observational studies confirmed an increase in gastrointestinal and intracranial

bleeding with the use of aspirin (31). In our study, bleeding occurred in 13 patients including 4 intracranial hemorrhage events (1 fatal), all of them in patients on aspirin therapy (no bleeding events occurred in patients who stopped the antiplatelet therapy post-PFO closure). This study was not powered to assess the potential clinical benefit of short- versus long-term antiplatelet therapy post-PFO closure, and patients stopping antiplatelet therapy at follow-up were younger and healthier, which may have introduced a bias in the final results. However, these results point out, for the first time, the importance of the bleeding burden among these patients, and suggest that stopping antiplatelet therapy several months after PFO closure (similar to what is usually done following atrial septal defect closure) may be a safe alternative. Future randomized trials should determine the optimal duration of antiplatelet treatment post-PFO closure.

Although the evaluation of migraine was not the main purpose of this study, and as already suggested in observational studies (32) but not confirmed in randomized trials (33–35), we noticed that 89% of patients experiencing migraines reported an improvement in migraine attacks following PFO closure that was maintained at long-term follow-up. Also, as described by post hoc analyses from the PREMIUM (Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine) and PRIMA (Percutaneous Closure of PFO in Migraine with Aura) randomized trials, we noticed that close to one-half of patients with a history of migraine had migraine with aura, and the majority of them declared some benefit of PFO closure with respect to migraine attacks. However, these data should be interpreted with caution as no details about the specific number and severity of migraine attacks were available in this study.

STUDY LIMITATIONS. Limitations include those inherent to retrospective studies. Although the number of patients lost to follow-up was low (particularly considering the long-term follow-up), the possibility of missing some adverse events cannot be completely ruled out. However, this would be highly unlikely with regard to major events and those requiring rehospitalization. Also, medical records from our institution and the referral centers were reviewed to obtain data on patient hospitalizations over time. Finally, the referral cardiologist/neurologist, family doctors, and pharmacists were also contacted in case of doubts regarding events and/or medication. The echocardiography data were site-reported and were not analyzed in a central echocardiographic laboratory.

CONCLUSIONS

The results of this study showing the low stroke rate >10 years post-PFO closure support the long-term efficacy and safety of this treatment for patients with PFO and cryptogenic embolism (stroke, TIA, systemic embolism). Also, the study suggests that bleeding may exceed ischemic events at long-term follow-up in such patients and points out the possibility of short-term (<12 months) antiplatelet treatment as a safe option to be evaluated in future studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PFO closure is associated with durable efficacy against recurrent ischemic events for over a decade.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the adequacy of short-term (6 to 12 months) antiplatelet therapy following transcatheter PFO closure, compared with more extended antithrombotic therapy.

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KEY WORDS bleeding, patent foramen ovale, stroke, TIA

APPENDIX For a supplemental figure, please see the online version of this paper.