Impact of Discontinuation of Antithrombotic Therapy Following Closure of Patent Foramen Ovale in Patients With Cryptogenic Embolism

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No data exist on the optimal duration of antithrombotic therapy (AT) following patent foramen ovale (PFO) closure. We sought to assess the safety of AT discontinuation following PFO closure in patients with a cryptogenic ischemic event. A total of 453 consecutive patients (mean age: 48 ± 13 years, men: 51%) who underwent PFO closure due to a cryptogenic ischemic event were included. All patients were on AT following PFO closure (antiplatelet therapy: 92.7%, anticoagulation: 7.3%). Ischemic and bleeding events, and AT were assessed at a median follow-up of 8 (IQR: 4 to 11) years, and follow-up was complete in 96% of patients. Stroke and transient ischemic attack occurred in 4 (0.9%) and 12 (2.6%) patients, respectively, and 27 (6.0%) patients had bleeding events (major in 6 [1.3%] patients, including 4 episodes of intracranial hemorrhage). All major bleeding events occurred under aspirin therapy. A total of 82 patients (18%) stopped the AT at a median of 7 (IQR: 5 to 34) months post-PFO closure (due to a bleeding event or gastrointestinal symptoms: 13 patients, no specific reason: 69 patients), and none of them had any ischemic event after a median time of 7 (IQR 3 to 10) years without any AT. A propensity score matched analysis including 46 patients who discontinued the AT within 1-year post-PFO closure and 120 patients with an ongoing AT showed the lack of differences in ischemic events between groups (0 vs 0.2 stroke/transient ischemic attack per 100 patient-years in the no-AT and AT groups, respectively). In conclusion, in young patients who underwent PFO closure, bleeding events occurred in ∼6% of patients after a median follow-up of 8 years. AT was discontinued in about one fifth of patients (most of them within the year following PFO closure), and this was not associated with any increase in ischemic events at long-term follow-up. These results suggest that, in patients without other co-morbidities increasing the risk of stroke, temporary AT following PFO closure may be a reasonable strategy. **(Am J Cardiol 2019;123:1538−1545)**

Transcatheter patent foramen ovale (PFO) closure has been associated with a significant reduction of ischemic events in young patients with cryptogenic stroke,[1−4] and this therapy is currently considered the new gold standard for secondary prevention in such patients.[5,6] Following PFO closure, long-term antiplatelet therapy (usually lifelong aspirin) is recommended.[6,7] However, no evidence-based data supports this strategy, and multiple studies have shown an increased risk of major bleeding events in patients receiving long-term antiplatelet therapy.[8−10] In fact, major bleeding events seem to be at least as frequent as ischemic events within the years following PFO closure.[11] Whereas antithrombotic therapy (AT) within the few months following PFO closure appears to be necessary for preventing potential ischemic events related to device thrombosis, lifelong aspirin may not be needed in young patients with an effective closure (no significant residual shunt) of the PFO and without co-morbidities that could increase the risk of stroke. However, no data exist on the cessation of antiplatelet therapy post-PFO closure. Thus, the objective of our study was to assess the incidence and long-term clinical impact of antiplatelet therapy discontinuation following PFO closure.

Methods

A total of 453 consecutive patients who had PFO closure between 2001 and 2017 at our institution because of cryptogenic stroke/transient ischemic attack (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-hour Holter monitoring, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcarotid Doppler. Based on referral doctor criteria thrombophilia research was performed 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

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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 (ASA).[12]

The type and size of the implanted device were left to the criteria of the physician performing the procedure. Post-procedural TTE was performed in all patients before 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). At 1- to 6-month postprocedure, 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.

Follow-up was ensured by the referral 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. 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. 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. All neurological events (stroke, TIA) were diagnosed by a neurologist and defined according to TOAST criteria.[13] All bleeding events were recorder and classified according to the BARC criteria.[14]

Categorical variables were reported as n (%) and continuous variables as mean ± SD or median (25th to 75th interquartile range [IQR]) depending on variable distribution. Group comparisons were analyzed using the Student *t* test, or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables. A one-to-many propensity score matching analysis was performed to adjust intergroup (AT vs AT at 1-year follow-up) differences in baseline characteristics. Variables used in the propensity matched algorithm were those that showed a p value <0.1 at baseline and procedural characteristics. Selected variables were age, body mass index, gender, hypertension, dyslipidemia, diabetes, pulmonary embolism, previous stroke, previous TIA, RoPE score, and follow-up duration, using a logistic regression analysis. Survival curves for time-to-event variables were performed with the use of Kaplan-Meier estimates, and comparison between groups performed with the log-rank test. Results were considered significant at <0.05 level. All analyses were conducted using the statistical package SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

The main baseline, procedural characteristics, and in-hospital outcomes of the study population are shown in Table 1. The median follow-up for the entire study population was 8 (IQR: 4 to 11), and follow-up was complete in all patients but 20 (4%, lost to follow-up). The main clinical outcomes and the Kaplan-Meier curves for the main clinical events up to 15-year follow-up are presented in Supplemental Table 1 and Figure 1. A total of 15 patients (3.3%) experienced at least 1 cerebral ischemic event at follow-up. All these patients were under AT at the time of the event. Four patients (0.9%) had a stroke, one due to a vertebral artery dissection, one atherothrombotic, one cardio-embolic related

Table 1
Baseline, procedural characteristics and in-hospital outcomes of the study population

Variable	(n = 453)
Age (years)	48 ± 13
Women	219 (48%)
Current smoker	52 (12%)
Hypertension	98 (22%)
Dyslipidemia	87 (19%)
Diabetes mellitus	18 (4%)
Oral contraception	18 (4%)
Pulmonary embolism/deep venous thrombosis	43 (10%)
Closure indication	
Stroke	335 (74%)
Transient ischemic attack	138 (31%)
Peripheral embolism	12 (2.6%)
Shunt size	
Small	88 (19%)
Moderate/large	347 (77%)
Atrial septal aneurysm*	153 (34%)
Risk of paradoxical embolism score	6.7 ± 1.6
Successful device implantation	453 (100%)
Device type †	
Amplatzer Patent Foramen Ovale occluder	380 (84%)
Others	74 (16%)
In-hospital complications	
Atrial fibrillation	1 (0.2%)
Tamponade	0 (0%)
Esophageal hematoma	1 (0.2%)
Device embolization/thrombosis	0 (0%)
Deep venous thrombosis and pulmonary embolism	1 (0.2%)
Major vascular complication	1 (0.2%)
Residual shunt at discharge	53 (12%)
Antithrombotic treatment at hospital discharge	
One antiplatelet	380 (84%)
Dual antiplatelet	40 (9%)
Anticoagulation	33 (7%)

Values are reported as n (%) or mean ± standard deviation.

Dyslipidemia was defined as low-density cholesterol levels >3.50 mmol/l or treatment with lipid-lowering medication.

* Data available for 433 patients.

† One patient needed two devices (Amplatzer cribiform and PFO).

(in a patient with a prosthetic aortic valve), and one of unknown cause. Two patients of 4 had a disabling stroke (modified Rankin scale of 2 or more). **Twelve** patients (2.6%) experienced at least 1 TIA episode. Eight patients (1.8%) had a venous thrombosis during the follow-up period (8 DVT, 3 pulmonary embolisms; all but 1 on aspirin therapy at the time of the episode), and 6 patients (1.3%) had a myocardial infarction (all of them on aspirin at the time of the episode). A total of 17 deaths (3.7%) occurred, 3 were of unknown cause and 14 were noncardiovascular related. Also, device-related complications were extremely rare at long-term follow-up. One device thrombosis in an Ebstein disease patient was diagnosed after a recurrent TIA. A total of 4 patients had atrial fibrillation episodes within the first 3 months post-PFO closure, but only 2 had persistent atrial fibrillations at last follow-up. Other episodes of atrial fibrillation occurred in 8 patients several years after the closure and were not considered as procedural or device related.

A total of 27 patients (6.0%) experienced a bleeding event during the follow-up period, and all but 3 were on antiplatelet therapy at the time of the event (aspirin alone: 19 patients; aspirin + clopidogrel: 2 patients, clopidogrel alone: 2 patients, and rivaroxaban: 1 patient). A total of 6 bleeding episodes (all in patients under aspirin alone therapy) were considered as major bleeding events according to BARC. The origin of the bleeding episode was as follows: subcutaneous hematoma (n = 8), gastrointestinal (n = 6), gynecologic (n = 3), severe epistaxis (n = 4), hemoptysis (1), and intracranial (n = 5).

At the time of the last follow-up, a total of 82 patients (18%) had been free from any AT for a median of 7 (IQR 3 to 10) years (AT had been discontinued at a median of 7 [IQR: 5 to 34] months post-PFO closure). Thirteen patients (16%) stopped the AT due to bleeding complications (6 patients) or gastrointestinal discomfort (7 patients), and no specific reason was recorded in 69 patients (84%). The main clinical characteristics of the patients, classified according to AT discontinuation, are presented in Table 2. Patients without any AT were more often female, had a lower burden of cardiovascular risk factors and a higher RoPE score. The Kaplan-Meier curves for the main clinical events up to 15 years following AT discontinuation are shown in Figure 1. No patient had any ischemic event (stroke, TIA, and systemic embolism) following AT cessation. A total of 3 bleeding episodes (all of them minor) occurred following AT cessation.

To adjust for baseline differences between groups, a propensity score matched analysis was performed to compare the clinical outcomes of patients with and without AT discontinuation within the year following PFO closure. A total of 50 patients stopped the AT within the year following PFO closure, and of these, 46 could be matched to 120 patients with ongoing AT. There were no differences in baseline and procedural characteristics between the 2 groups (Table 3). A landmark analysis starting at 1-year follow-up and extending up to 9 (6 to 12) years showed the lack of differences in clinical outcomes between groups (Table 4). There were no stroke/TIA events in those patients who stopped the AT, compared with 7 TIA events in those who pursued AT. The number of bleeding events was also numerically (but not significantly) lower in those patients who stopped the AT (4.3% vs 8.3%, p = 0.332), and the only major bleeding occurred in a patient under AT (aspirin). The 2 bleeding episodes in the AT cessation group were minor (2 minor metrorrhagias managed conservatively with no intervention). The Kaplan-Meier curves for the clinical outcomes of the propensity-matched population are shown in Figure 2.

Table 2
Clinical characteristics, according to antithrombotic treatment cessation at follow-up

Variable	Antithrombotic treatment at last follow-up: No (n = 82)	Antithrombotic treatment at last follow-up: Yes (n = 371)	p value
Age (years)	42 ± 12	49 ± 12	<0.001
Women	50 (61%)	169 (46%)	0.014
Body mass index (kg/m^2)	25.7 ± 5.7	27.6 ± 5.6	0.008
Current smoker	6 (7%)	46 (12%)	0.251
Hypertension	5 (6%)	93 (25%)	<0.001
Dyslipidemia	7 (9%)	80 (22%)	0.005
Diabetes mellitus	0 (0%)	18 (5%)	0.054
Migraine antecedents	14 (17%)	68 (18%)	0.875
Oral contraception	4 (5%)	15 (4%)	0.760
Chronic obstructive pulmonary disease	0 (0%)	6 (2%)	0.597
Pulmonary embolism	0 (0%)	15 (4%)	0.085
Deep vein thrombosis	6 (7%)	28 (8%)	0.943
Closure indication			
Stroke	49 (60%)	286 (77%)	0.002
Transient ischemic attack	33 (40%)	105 (28%)	0.046
Peripheral embolism	2 (2%)	10 (3%)	0.896
Shunt postprocedure	7 (9%)	46 (12%)	0.447
Atrial septal aneurysm	28 (34%)	125 (34%)	0.982
Risk of paradoxical embolism score	7.3 ± 1.4	6.6 ± 1.7	<0.001
Follow-up (years)	10 (7-12)	8 (4-11)	0.004
Antithrombotic treatment at last follow-up			
Aspirin alone	–	286 (77%)	–
Clopidogrel alone	–	41 (11%)	–
Dual antiplatelet therapy	–	5 (1.3%)	–
Oral anticoagulation alone	–	36 (10%)	–
Oral anticoagulation and aspririn	–	3 (0.8%)	–

Values are reported as n (%), mean ± standard deviation or median (25th to 75th)

Discussion

The very low rate of ischemic events at long-term follow-up (median of 8 years) observed in our study (0.1 stroke events per 100 patient-years, 0.32 stroke/TIA events per 100 patient-years) is comparable to the data reported in recent PFO closure randomized trials and meta-analyses.[11,15–17] The clinical characteristics of our study population were similar to those reported in previous studies, with a mean age below 50 years, and a relatively low prevalence of classical cardiovascular risk factors.[1–4] This was also reflected by a high RoPE score, similar to that reported in the CLOSE trial.[4] In comparison, based on a 6 to 7 average RoPE score, an estimated 2-year stroke/TIA recurrence rate from 6% to 8 % (vs the 3.3% observed in our study) would have been expected under medical therapy alone.[18]

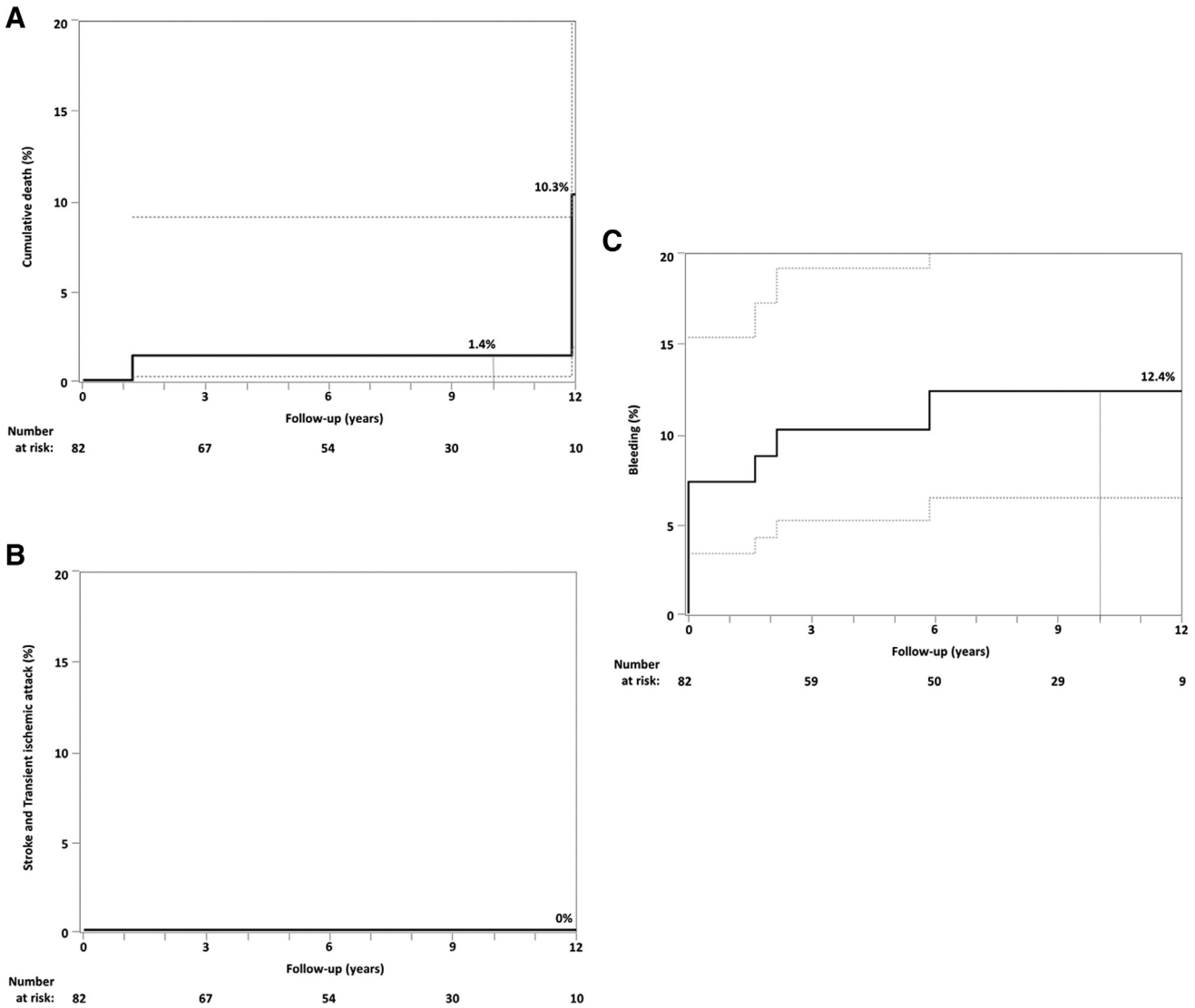

Figure 1. Kaplan-Meier estimates for clinical events up to 12-year follow-up after antithrombotic therapy cessation. Kaplan-Meier plots showing cumulative death (A), stroke and transient ischemic attack (B), and bleeding (C) over a 15-year follow-up with their 95% confidant interval's.

The recommendations regarding the type and duration of AT following PFO closure have evolved empirically. Dual antiplatelet therapy during the first 1 to 6 months followed by single antiplatelet therapy for at least 5 years was recommended in the recently published European guidelines.[6] In contrast, the latest American Academy of Neurology guidelines recommended lifelong AT post-PFO closure.[7] However, in 4 randomized trials comparing PFO closure versus medical treatment in patients with cryptogenic stroke, late bleeding events were at least as frequent as ischemic events in PFO closure patients.[1–4] In a meta-analysis including 6 randomized trials, major bleeding occurred in 1.8% and 1.7% of the patients randomized to PFO closure and medical treatment, respectively.[11] In the CLOSE trial, there was no stroke during follow-up in the closure group, but up to 24 bleeding events were described under antiplatelet therapy (in addition to 21 events under oral anticoagulation).[4] In our study, bleeding episodes occurred in 27 (6.0%) patients, including 6 major bleeding (1.3%) (BARC 3 or more) events, 4 of which consisting of an intracranial hemorrhage (1 fatal). This was numerically higher than the rate of ischemic events (3.3%, stroke: 0.9%) during the follow-up period. Overall, data on bleeding events post-PFO closure highlight the potential deleterious effects of long-term AT in these patients.

To date, no specific studies have focused on the clinical outcomes of patients not receiving long-term AT post-PFO closure. Nevertheless, close to half of the patients in the PFO closure group had no AT at 1-year follow-up in the PC trial, and this did not appear to be associated with an increased risk of ischemic events, with only 1 recurrent stroke after a mean follow-up of 2 years.[19] Moreover, no significant differences regarding new silent ischemic lesions on cerebral MRI (8.8% and 18.4% in the closure and medical treatment groups, respectively) were observed in the DEFENSE-PFO trial despite an 8% of antiplatelet treatment discontinuation in the closure group.[3] The present work specifically evaluated the outcomes in patients who

Table 3
Clinical characteristics of the propensity-matched population, according to antithrombotic treatment at 1-year follow-up

Variable	Antithrombotic treatment at 1-year follow-up		p value
	No (n = 46)	Yes (n = 120)	
Age (years)	42 ± 11	44 ± 12	0.447
Women	28 (61%)	66 (55%)	0.111
Body mass index (kg/m^2)	25.2 ± 3.6	24.9 ± 3.9	0.721
Current smoking	4 (9%)	16 (13%)	0.595
Hypertension	2 (4%)	1 (1%)	0.186
Dyslipidemia	3 (7%)	11 (9%)	0.759
Diabetes mellitus	0 (0%)	0 (0%)	–
Migraine antecedents	7 (15%)	31 (26%)	0.215
Oral contraception	1 (2%)	7 (6%)	0.446
Chronic obstructive pulmonary disease	0 (0%)	1 (1%)	1.00
Pulmonary embolism	0 (0%)	0 (0%)	–
Deep vein thrombosis	4 (9%)	8 (7%)	0.739
Closure indication			
Stroke	28 (61%)	86 (72%)	0.194
Transient ischemic attack	18 (39%)	36 (30%)	0.272
Peripheral embolism	0 (0%)	0 (%)	–
Shunt postprocedure	3 (7%)	17 (14%)	0.285
Atrial septal aneurysm	18 (39%)	37 (31%)	0.469
Risk of paradoxical embolism score	7.2 ± 1.4	7.3 ± 1.5	0.673
Follow-up (year)	10 (7-12)	10 (6-12)	0.379

Values are reported as n (%), mean ± standard deviation or median (25th to 75th).

discontinued the AT following PFO closure. We found that nearly one fifth of the patients discontinued all AT several months (median of 7 months) after the procedure. Treatment cessation was mainly related to patients' own decisions, and a medical reason was found in only 16% of patients. A similar nonadherence rate has already been reported in previous studies assessing the adherence to aspirin treatment in primary or secondary prevention.[20–22] Importantly, none of the patients who quitted the AT post-PFO closure experienced an ischemic event after a mean follow-up of 7 years without any antiplatelet or anticoagulant therapy. This is an important issue considering that PFO closure is performed in young patients, exposing them to potentially serious bleeding adverse events due to lifelong AT. The use of aspirin for primary prevention has been shown to increase by ~2-fold the risk of gastrointestinal bleeding in nondiabetic patients with low-to-moderate cardiovascular risk, without any benefit with respect to cardiovascular events.[23] Another recent study including diabetic patients without cardiovascular disease, showed an increase of 29% in major bleeding events and no clear benefit associated with the use of aspirin therapy.[24] Finally, similar results were reported regarding the use of long-term aspirin in other randomized studies and in a recent systematic review of observational studies, showing an increase in major bleeding complications including intracranial hemorrhage.[10,25,26]

The results of our study suggest that the discontinuation of antiplatelet therapy several months after PFO closure (similar to what is usually done following atrial septal defect closure) in young patients with a low prevalence of cardiovascular risk factors and a high RoPE score, may be a safe alternative. After an initial period of device endothelialization, the index causal factor (PFO) is fixed, and aspirin could probably be discontinued in most cases. Future randomized trials should determine the optimal duration of antiplatelet treatment post-PFO closure.

Limitations include those inherent to retrospective studies. Although the number of patients lost to follow-up was very 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, referral cardiologist/neurologist, family doctors, and pharmacists were also contacted in case of doubts regarding events and/or

Table 4
Clinical outcomes after closure of patent foramen ovale, according to antithrombotic therapy discontinuation at 1-year follow-up (propensity-matched population)

	Antithrombotic treatment at 1-year follow-up			
	No (n = 46)	Yes (n = 120)	HR (95%CI)	p value
Follow-up (years)	10 (8-12)	9 (6-12)	–	0.379
Death	1 (2.2%)	3 (2.5%)	0.81 (0.08-7.82)	0.857
Stroke	0 (0%)	0 (0%)		–
Transient ischemic attack	0 (0%)	7 (5.8%)	–	–
Peripheral embolism	0 (0%)	0 (0%)	–	–
Composite of stroke and transient ischemic attack	0 (0%)	7 (5.8)	–	–
Composite of death, stroke and transient ischemic attack	1 (2.2%)	10 (8.3%)	0.24 (0.03-1.89)	0.176
Deep vein thrombosis	0 (0%)	0 (0%)	–	–
Atrial fibrillation	0 (0%)	0 (0%)	–	–
Myocardial infarction	0 (0%)	0 (0%)	–	–
Bleeding	2 (4.3%)	10 (8.3%)	0.47 (0.10-2.15)	0.332
Major bleeding	0 (0%)	1 (0.8%)	–	–
Composite of death, stroke, transient ischemic attack and bleeding	3 (6.5%)	19 (15.8%)	0.37 (0.11-1.25)	0.109
Remaining migraine	2 (4.3%)	3 (2.5%)	–	0.618

Values are reported as n (%), or median (twenty-fifth to seventy-fifth).

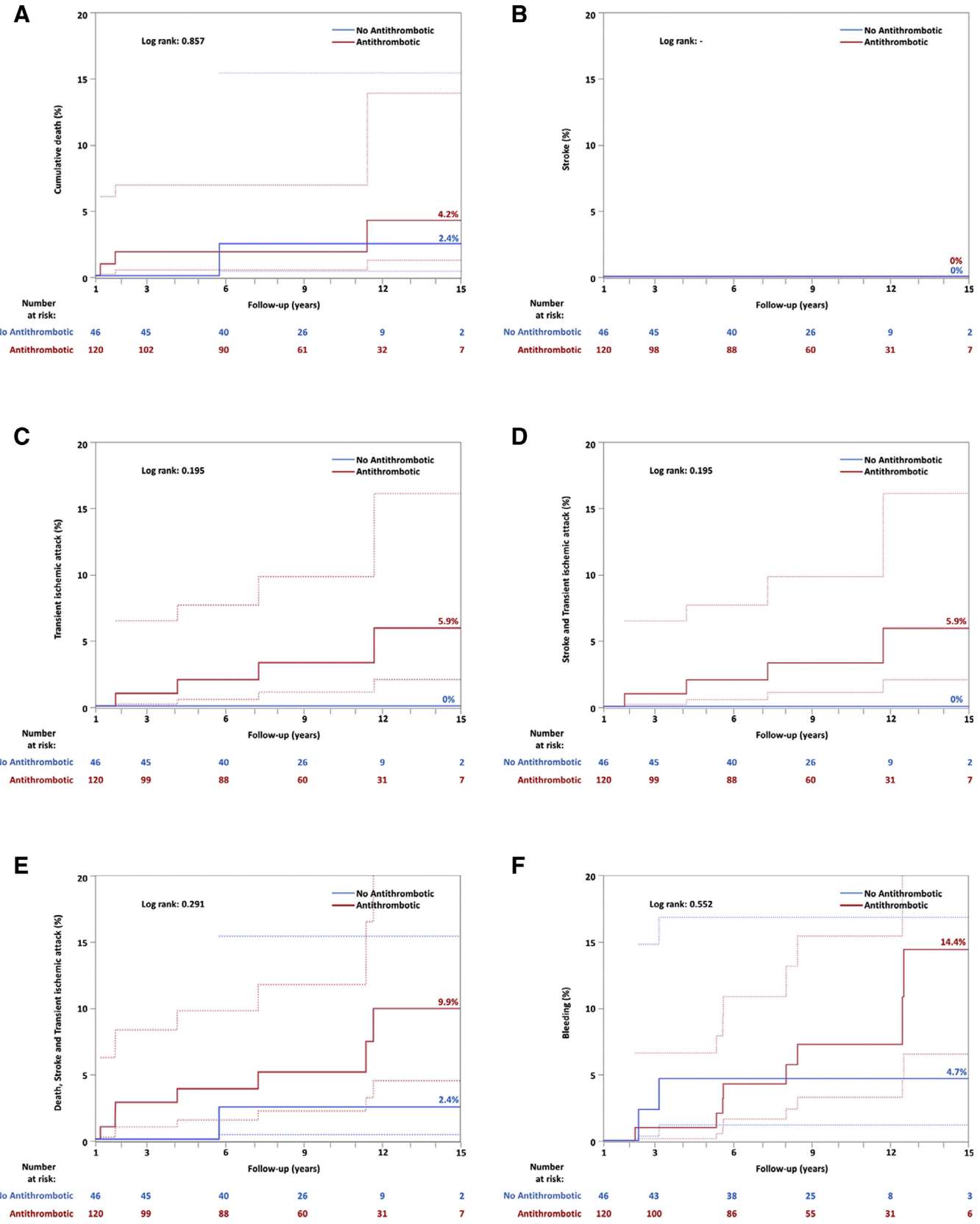

Figure 2. Kaplan-Meier estimates for clinical events up to 15-year follow-up in the propensity-matched cohort, according to antithrombotic therapy at 1-year follow-up. Kaplan-Meier plots showing cumulative death (A), stroke (B), transient ischemic attack (TIA) (C), stroke or TIA (D), death, stroke and TIA (E), and bleeding (F) over a 15-year follow-up with their 95% confidant interval's.

medication. However, no adjudication to the clinical events was performed. The echo data were site reported, and not analyzed in a central echocardiographic laboratory.

In conclusion, young patients with a cryptogenic ischemic event who underwent transcatheter PFO closure exhibited a low but clinically relevant risk of bleeding (overall and major bleeding) at long-term follow-up, eventually exceeding the risk of ischemic events. Importantly, all major bleeding events occurred in patients receiving antiplatelet therapy. Close to one fifth of the patients stopped the AT post-PFO closure, most of them during the year following the procedure. Antiplatelet therapy discontinuation was not associated with any increase in ischemic events, and could potentially translate into a lower rate of major bleeding events at longer term follow-up. These results suggest that, in patients without any other co-morbidities increasing the risk of stroke, shorter term ($\leq$1 year instead of lifelong) antiplatelet treatment could be a safe option following PFO closure. This study should inform the design of future randomized studies to determine the optimal duration of AT following PFO closure.

Disclosure

The authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.043.

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