Antithrombotic Therapy Duration after Patent Foramen Ovale Closure for Stroke Prevention: Impact on Long-Term Outcome

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1. Introduction

Recent randomized studies conducted with patients who had had cryptogenic stroke [1–4] have shown the positive impact of patent foramen ovale (PFO) closure vs. medical therapy to prevent recurrent ischemic stroke. In the periprocedural period, patients were mainly given antiplatelet therapy (single or dual) for a minimum of 3 months, which was continued for a highly variable duration of up to 5 years thereafter (Figure 1). After transcatheter atrial septal defect (ASD) closure, the European Society of Cardiology (ESC) guidelines [5] recommend an antiplatelet therapy for 6 months, which is the presumed time needed for endothelial coverage of the device [6]. Regarding PFO closure, a long-term antithrombotic therapy (ATT) is currently recommended, as for any patient in secondary prevention after an ischemic stroke [7, 8]. Yet, the optimal duration of ATT after PFO closure remains under debate.

Long-term medical therapy is supposed to improve thromboembolic protection, which could however be
counterbalanced by an increased risk of adverse events and bleedings, as observed with extended dual antiplatelet therapy after coronary angioplasty [9] or with low-dose aspirin in primary prevention [10].

The objective of the present study was to compare the long-term outcome in a cohort of consecutive patients undergoing PFO closure after cryptogenic stroke, who received antithrombotic agents for a short (6 months) vs. extended (>6 months) period after the procedure.

2. Methods

2.1. Patients. Between June 1999 and October 2018, 303 consecutive patients underwent PFO closure at our institution. Among these, 265 underwent the procedure to prevent recurrent cryptogenic stroke (Figure 2) after an extensive workup including cerebral magnetic resonance imaging (MRI), angio-MRI of the circle of Willis, echodoppler of cervical arteries, at least 24-hour Holter monitoring, and transesophageal echocardiography (TEE), all of which were normal excepting for the ischemic lesion at MRI and PFO at TEE. The right-to-left shunt was identified by TEE and/or transcranial Doppler, with blood tests for thrombophilia screening performed (protein C or S deficiency, antithrombin deficiency, antiphospholipid antibodies, activated protein C resistance, factor V Leiden mutation, lupus anticoagulant, and prothrombin G20210A mutation). The patients were all assessed by a stroke-team, including a vascular neurologist, hematologist, echocardiographer, and invasive cardiologist, in order to precise the diagnosis of cryptogenic stroke and confirm the indication of transcatheter PFO closure.

2.2. Study Protocol. All PFO closure procedures were performed under general anesthesia and TEE guidance. Procedural success was considered in case of proper transfemoral delivery of the prosthesis in the interatrial septum without significant residual shunt, defined as no more than 2-mm jet width at TEE color Doppler at the intervention’s end [11]. Periprocedural complications (from day 0 to hospital discharge) were defined according to the VARC-2 criteria [12]. Major complications included death, tamponade, myocardial infarction, disabling stroke, major bleeding (BARC 3 or 5) [13], major vascular damage, persistent arrhythmias (atrial fibrillation, conduction abnormalities), prosthesis embolization, and thrombosis. Minor complications included pericardial effusion not requiring surgery or drainage, minor bleeding (BARC 1 or 2), minor vascular damage, and nonpersistent (<24 hours) arrhythmias.

Before discharge, patients underwent clinical examination, 12-lead electrocardiogram, and transthoracic echocardiogram. Antithrombotic medications were prescribed at discharge for minimum 6 months. Patients with pre-existing thrombophilia received a preventive dosage of low-molecular-weight heparin associated with an antiplatelet agent for 1 month. A clinical and transthoracic echocardiographic follow-up was planned at 1, 6, and 12 months, and yearly thereafter. A TEE follow-up was recommended in case of recurrent stroke.

Late prosthesis dysfunction was defined as thrombus deposit, device dislocation/embolization, significant residual shunt, or pericardial effusion occurring during the follow-up period.

Clinical and procedural characteristics, periprocedural and long-term outcomes, as well as antithrombotic medications were prospectively collected into a dedicated database. Clinical events and ATT were determined from reviews of medical records or direct contact with the patient or referring physician. All neurological events were diagnosed by a neurologist and defined according to the relevant guidelines [14]. Informed consent was obtained from each patient, the study protocol was approved by our local ethics committee and conforms to the ethical guidelines of the 1975 declaration of Helsinki.

2.3. Statistical Analysis. Continuous variables were expressed as mean ± standard deviation when normally distributed, and as median and range when non-normally distributed. Categorical variables were presented as counts and percentages. Between-group comparisons were analyzed using the independent samples t-test for continuous variables and the chi-square or Fisher’s exact test, where appropriate, for categorical variables. Propensity score analysis and matching were built using the R software (version 4.0.3). Scores were computed using a 1:1 logistic regression model, with the response variable being the group of patients who stopped ATT at 6 months after PFO closure. The 5 covariables used to build the propensity score were age, hypertension, previous multiple stroke, factor V Leiden mutation, and antiphospholipid antibodies. The area under the receiver operating characteristic curve was 0.63 for the model built. The calculated propensity scores were then used to select pairs of patients with matched propensity scores in the 2 groups (1:1 match following the nearest neighbor matching rule) within a caliper of 0.15, using the matching package. Matched groups were compared using the paired t-test (absolute standardized differences test).

Estimates of freedom from death or adverse events were obtained using the Kaplan–Meier method. Univariate and multivariate analysis was carried out using the Cox proportional hazards method. A p value < 0.05 was considered statistically significant. Analyses were performed using the R software (version 4.0.3).

3. Results

3.1. Patients. The study included overall 259 consecutive patients (age 43 ± 10 years, 51% males) who underwent PFO closure after cryptogenic stroke and had a complete follow-up. Baseline characteristics are listed in Table 1.

Patients receiving ATT for a short period (6 months, Group short; N=88) were younger and suffered less frequently from hypertension and prior multiple strokes than those undergoing extended ATT (>6 months, Group long; N = 171).
Thrombophilia was observed in 7% of the cohort patients, with no difference between Groups short and long (9% vs. 6%, \( p = 0.47 \)).

After matching, 86 pairs of matched patients were identified, resulting in similar baseline characteristics.

3.2. Procedural Characteristics. Procedural success was achieved in all cases (in one patient, a significant residual shunt due to an additional ASD required a repeated procedure with successful second prosthesis implantation, resulting in final complete closure). The median delay
range: 1281–4690 days), resulting in 2314 patient-years, and the median value was 10 years (interquartile range: 3.3).

3.3. Follow-up. The mean duration of follow-up was 9 ± 5 years, and the median value was 10 years (interquartile range: 1281–4690 days), resulting in 2314 patient-years (Table 3).

During this follow-up period, four deaths occurred at a median time of 8 years after the procedure. The causes of death were cancer (N = 2), one suicide, and one ischemic stroke due to carotid occlusion occurring 4.4 years after PFO closure. Six additional patients experienced a recurrent ischemic stroke at a mean delay of 3.1 ± 1.5 years after the procedure. This means that the recurrent stroke rate was estimated at 0.3% patient-year. One was related to an atrial fibrillation, one was due to PFO-device thrombosis, whereas for four strokes, no cause could be identified. Therefore, the rate of recurrent cryptogenic stroke was estimated at 0.2% patient-year. A TEE investigation was performed in all these patients, which revealed a good position and function of the PFO device excepting for residual shunt detected in one case, and a device thrombosis occurring during cardiac arrest on account of anaphylactic shock at 9 months postprocedure. Five of these recurrent strokes (71%) were considered nondisabling. Details of recurrent strokes are provided in Table 4.

No major bleedings were observed during the follow-up period, while 48 minor bleedings occurred, yet without any significant difference between both groups (14 vs. 22% in Groups short and long, respectively, p = 0.17). The bleeding causes were subcutaneous hematoma (N = 31), epistaxis (N = 10), dental (N = 4), hemorrhage (N = 1), gynecologic (N = 1), and hemorrhoidal (N = 1) in nature.

Table 1: Baseline characteristics of patients.

| Characteristic                        | Before PS matching                                      | After PS matching                                      |
|---------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
|                                       | All N = 259                                             | Gr short N = 88                                        | Gr long N = 171                                        |
|                                       | Age (yrs) mean ± SD 43 ± 10                            | 40 ± 10                                                | 44 ± 10                                                | 0.0001 | 40 ± 10 | 41 ± 10 | 0.51 |
| Gender                               | Male 131 (51)                                           | 49 (56)                                                | 82 (40)                                                | 0.24   | 48 (56) | 37 (43) | 0.09 |
| Smoking                              | n (%) 105 (40)                                          | 33 (38)                                                | 72 (42)                                                | 0.48   | 32 (37) | 38 (44) | 0.35 |
| Hypertension                         | n (%) 48 (19)                                           | 10 (11)                                                | 38 (22)                                                | 0.03   | 10 (12) | 10 (13) | 1.0  |
| Diabetes                             | n (%) 6 (2)                                             | 1 (1)                                                  | 5 (3)                                                  | 0.37   | 1 (1)   | 3 (3)   | 0.31 |
| LDL-cholesterol (mg/dl)              | mean ± SD 123 ± 37                                      | 121 ± 36                                                | 124 ± 38                                                | 0.57   | 120 ± 36 | 122 ± 40 | 0.81 |
| Carotid artery disease               | n (%) 0                                                | 0                                                      | 0                                                      | —      | 0       | 0       | —    |
| Prior atrial fibrillation            | n (%) 1 (0.4)                                           | 0                                                      | 1 (1)                                                  | 0.47   | 0       | 0       | —    |
| Left ventricular ejection fraction <50% | n (%) 0                                                | 0                                                      | 0                                                      | —      | 0       | 0       | —    |
| Pulmonary hypertension               | n (%) 0                                                | 0                                                      | 0                                                      | —      | 0       | 0       | —    |
| Migraine                             | n (%) 103 (40)                                          | 35 (40)                                                | 68 (40)                                                | 1.00   | 35 (41) | 37 (43) | 0.76 |
| Protein C deficiency                 | n (%) 29 (11)                                           | 9 (10)                                                 | 20 (12)                                                | 0.72   | 8 (9)   | 8 (9)   | 1.0  |
| Protein S deficiency                 | n (%) 23 (9)                                            | 3 (3)                                                  | 20 (12)                                                | 0.03   | 3 (3)   | 0       | 0.08 |
| Factor V Leiden                      | n (%) 19 (7)                                            | 8 (9)                                                  | 11 (6)                                                 | 0.47   | 9 (10)  | 4 (5)   | 0.15 |
| Lupic Antibodies                     | n (%) 7 (3)                                             | 3 (3)                                                  | 4 (2)                                                  | 0.62   | 3 (3)   | 1 (1)   | 0.31 |
| Antiphospholipid Antibodies          | n (%) 4 (2)                                             | 1 (1)                                                  | 3 (2)                                                  | 0.7    | 1 (1)   | 1 (1)   | 1.0  |
| Prothrombin mutation                 | n (%) 2 (1)                                             | 1 (2)                                                  | 1                                                      | 0.05   | 2 (2)   | 0       | 0.16 |
| Antithrombin III                     | n (%) 5 (2)                                             | 1 (1)                                                  | 4 (2)                                                  | 0.51   | 1 (1)   | 1 (1)   | 1.0  |
| History of deep vein thrombosis      | n (%) 16 (6)                                            | 5 (6)                                                  | 11 (6)                                                 | 0.81   | 5 (6)   | 6 (7)   | 0.76 |
| Hormone therapy                      | n (%) 79 (31)                                           | 24 (27)                                                | 55 (32)                                                | 0.42   | 23 (27) | 32 (37) | 0.14 |

Gr = Group; LDL = low-density lipoprotein; PS = propensity score; SD = standard deviation; yrs = years.
ATT at last follow-up in Group long mainly comprised aspirin (90%), followed by anticoagulants (7%), dual antiplatelet therapy (2%), and clopidogrel (1%).

The duration of ATT was significantly shorter in Group short than in Group long (184 ± 27 vs. 2628 ± 1993 days, p < 0.001). Univariate analysis revealed that ATT discontinuation at 6 months following PFO closure was not associated with an increased risk of recurrent stroke (hazard ratio [HR]: 1.271 [95% CI: 0.247–6.551], p = 0.775). The only characteristic associated with an increased risk of recurrent stroke was thrombophilia, which was exclusively significant for the factor V Leiden mutation (HR: 15.64 [95% CI: 1.9–128.59], p = 0.01) and antiphospholipid antibody syndrome (HR: 39.76 [95% CI: 4.37–361.52], p = 0.001). Nevertheless, among these thrombophilia patients, a short-duration ATT did not increase the risk of recurrent stroke during follow-up (HR: 0.68 [95% CI: 0.043–10.977], p = 0.79).

Figure 3 illustrates the Kaplan–Meier analysis. At 10-year follow-up, overall survival and event-free survival were 99 ± 1% and 99 ± 2% in the total cohort and 100% and 99 ± 2% in the matched population, respectively, with no significant difference between Groups short and long (100 vs. 99 ± 1% and 98 ± 4 vs. 99 ± 3%, respectively, p = 0.25).

At systematic echocardiographic follow-up, four (two in each group) thrombotic deposits on the PFO prosthesis (three Cardia Star and one Occlutech PFO devices) were detected at a median time of 349 (interquartile range: 226–867) days after the procedure. Of these four patients, two were totally asymptomatic, whereas the two others suffered from a recurrent neurologic event, including one transient ischemic attack and one stroke. The thrombus resolved under anticoagulant therapy among three of them, whereas it was still persistent 6 months after treatment in one of these patients, eventually requiring surgery for extracting the thrombus and partially mal-apposed Cardia Star prosthesis. Three of these patients did not undergo any ATT at the time of thrombus discovery, while two of them displayed thrombophilia, including one protein S deficiency and one antiphospholipid antibody. Details of thrombotic deposits on the PFO prosthesis are provided in Table 5. Univariate analysis revealed that thrombophilia was associated with an increased risk of device thrombosis (HR: 16.96 [95% CI: 2.374–121.241], p = 0.005), whereas a short-duration ATT was not associated with the risk of device thrombosis either in the total population (HR: 0.50 [95% CI: 0.070–3.548], p = 0.48) or

### Table 2: Periprocedural outcome.

| Characteristic                                      | All N = 259 | Before PS matching | After PS matching | p value | p value |
|-----------------------------------------------------|-------------|--------------------|-------------------|---------|---------|
| Delay between stroke and cath (days)                | median [IQR]|                   |                   |         |         |
| Gr short N = 88                                     | 232 [137–420] | 214 [127–360]     | 241 [150–440]     | 0.46    | 0.46    |
| Gr long N = 171                                     |             |                   |                   |         |         |
| Attributable adverse neurological events             |             |                   |                   |         |         |
| Amplatzr; 25 [25–30]                                | n (%)       | 105 (41)           | 32 (26)           | 73 (43) | 0.35    |
| Cardia Star; 30 [25–30]                             | n (%)       | 99 (38)            | 37 (42)           | 62 (36) | 0.42    |
| Starflex; 28 [28–33]                                | n (%)       | 11 (4)             | 6 (7)             | 5 (3)   | 0.19    |
| Gore; 28 [25–30]                                    | n (%)       | 6 (2)              | 1 (1)             | 5 (3)   | 0.67    |
| Premere; 25 [25–25]                                 | n (%)       | 13 (5)             | 2 (2)             | 11 (6)  | 0.23    |
| Occlutech; 25 [25–30]                               | n (%)       | 23 (9)             | 9 (10)            | 14 (8)  | 0.65    |
| PFM Nit Occlud; 22 [22–25]                          | n (%)       | 2 (1)              | 1 (1)             | 1 (1)   | 1.00    |
| Prosthesis size (mm)                               | median [IQR]| 25 [25–30]         | 25 [25–30]        | 25 [25–30] | 0.21 |
| Complication                                        | n (%)       | 9 (3)              | 2 (2)             | 7 (4)   | 0.72    |
| Minor vascular                                      | n (%)       | 2 (1)              | 0                 | 2 (1)   | 0.55    |
| Minor bleeding                                      | n (%)       | 4 (2)              | 1 (1)             | 3 (2)   | 1.00    |
| Non disabling stroke                                | n (%)       | 1 (0.3)            | 0                 | 1 (1)   | 1.00    |
| Transient ischemic attack                           | n (%)       | 0                  | 0                 | 0       | 0.27    |
| Transient ST segment modification                   | n (%)       | 1 (0.3)            | 0                 | 1 (1)   | 1.00    |
| Death                                               | n (%)       | 0                  | 0                 | 0       | 0.27    |
| Antithrombotic treatment at discharge               | n (%)       | 1 (0.3)            | 1 (1)             | 0       | 1.00    |

Gr = Group; IQR = interquartile range; PS = propensity score.
among thrombophilia patients (HR: 0.60 [95% CI: 0.038–9.675], \( p = 0.72 \)). On multivariate analysis (Table 6), thrombophilia was an independent predictor of both, recurrent stroke (HR: 6.35 [95% CI: 1.22–32.98], \( p = 0.028 \)) and device thrombosis (HR: 29.07 [95% CI: 3.28–257.6], \( p = 0.002 \)).
During the follow-up period, neither delayed device dislocation/embolization nor pericardial effusion occurred. Overall, the rate of late prosthesis dysfunction was estimated at 0.2% patient-year, without any difference noted between Groups short and long (0.3% and 0.1% patient-year, respectively, \( p = 0.60 \)).

4. Discussion

The main findings of the current study (Figure 4. Central illustration) are, as follows:

1) In strongly selected patients undergoing transcatheter PFO closure due to cryptogenic stroke, the procedure is deemed safe and effective in stroke prevention (0.3% patient-year), and this up to 10 years of follow-up.

2) Discontinuation of ATT at 6 months after the procedure did not impair the clinical outcome, nor did it increase the risk of recurrent stroke.

3) Late prosthesis dysfunction is rare (0.2% patient-year), and it is not impacted by ATT cessation at 6 months after the procedure.

4.1. Safety and Efficiency of Transcatheter PFO Closure in Stroke Prevention at Long Term. The first randomized studies including patients affected by transient ischemic attack (TIA) and stroke [15, 16] failed to demonstrate a significant reduction in recurrent stroke after PFO closure, in comparison with medical therapy, while reporting a high rate of major procedural complications (>3%) and overall complications estimated at around 5%. In our study, there were only 3% of minor complications, and this rate was
significantly reduced after the first 100 patients (from 7% to 1.2%). This low rate of procedural complications is in line with more recent studies [1–4], clearly reflecting the operators’ learning curve. Randomized studies including only patients with cryptogenic stroke and excluding those with TIA [1–4] have demonstrated the superiority of PFO closure over medical therapy, with a variable impact on stroke rates. This is most likely due to the different types of devices used and their effective shunt closure capacities, but also to the follow-up duration, ranging from 2.8 to 5.9 years. The relevance of extended follow-up was highlighted by the RESPECT trial’s long-term analysis, [3] demonstrating a significant benefit in favor of PFO closure, whereas the first publications [17] failed to demonstrate such a difference. The latter is most probably related to the shorter patient follow-up (median value: 2.6 versus 5.9 years, respectively). Wintzer-Wehekind [18] reported a stroke rate estimated at 0.08% patient-year at 12-year follow-up among 201 unmatched patients, with a tendency of thrombophilia to effectively increase ischemic events. Likewise, our study revealed similarly low stroke (0.3% patient-year) and low cryptogenic stroke (0.2% patient-year) rates at 10 years, using propensity score matching of a cohort of 259 consecutive patients. Thrombophilia was observed in 7% of the population, which was significantly associated with an increased risk of recurrent stroke. These observations are similar to those reported by Liu et al. [19] that revealed thrombophilia to increase the risk of recurrent events (HR: 1.85), and PFO closure to be superior to medical therapy in terms of stroke prevention (HR: 0.25) in such patients. A meta-analysis including eleven studies [20] confirmed that thrombophilia was associated with an increased recurrence risk in PFO patients with cryptogenic stroke (OR: 2.41), and that this risk lost statistical significance after PFO closure (odds ratio (OR): 2.07, [95% CI: 0.95–4.48]).
The authors stated that the studies’ heterogeneity precluded strong conclusions to be drawn with respect to ATT duration following PFO closure.

4.2. Impact of ATT Discontinuation. ATT duration in randomized studies [1–4] ranged from 6 months to >5 years, and long-term ATT after PFO closure is currently recommended, even though the impact of discontinuing ATT after 6 months is not yet clear. In a histological analysis of explanted devices from human beings, Foth et al. [6] demonstrated that neo-endothelialization was observed in all specimens following implantation times of 10 weeks or more. Like in transcatheter ASD closure, for which ATT and endocarditis prophylaxis are given for 6 months, which is the presumed time needed for a complete endothelial coverage of the device, ATT could be stopped 6 months after PFO closure. In our study, patients underwent a strong selection process performed by a dedicated stroke-team in order to confirm the cryptogenic stroke. Therefore, our population was at very low cardiovascular risk, as they were younger and less frequently diabetics as respect to other series [2–4, 18]. After propensity score matching, the stroke rate was similarly low among those who stopped than among those who continued ATT at 6 months (0.3% and 0.4% patient-year, respectively, \( p = 1.00 \)) at 10 years of follow-up. Wintzer-Wehekind et al. [21] published a series of 46 matched patients who stopped ATT within one year of PFO closure, revealing no difference in ischemic events at 7 years of follow-up, of those who continued ATT at 6 months. This suggests that ATT discontinuation at 6 months postintervention did not increase the risk of recurrent strokes, nor did it impair the clinical outcome at up to 10 years of follow-up after PFO closure. Given that the procedure is usually performed among young patients, a lifelong ATT could potentially expose them to bleeding events and medications’ undesirable effects when given during such a long treatment period. These findings suggest that in strongly selected patients undergoing PFO closure due to cryptogenic strokes, ATT cessation at 6 months postintervention would be a quite reasonable strategy.

4.3. Late Prosthesis Dysfunction. The rate of prosthesis dysfunction was reported to be as high as 5% by Hornung et al. [23]. In their study, these authors randomized patients according to three different devices and showed significant differences in terms of thrombus and residual shunts, which were all in favor of the Amplatzer device, as compared with prolonged dual antiplatelet therapy [9], especially in high-bleeding-risk patients. These latter patients can be safely treated with one-month dual antiplatelet therapy following new-generation drug-eluting stent implantation [22]. Given in primary prevention to moderate-risk patients [10], low-dose aspirin prescribed as monotherapy was revealed to significantly increase the risk of bleeding, without any protective effect in terms of ischemic events. In our population of very-low-risk patients, it can be assumed that a successful PFO closure returns them to a primary prevention stage, without any additional benefit gained by pursuing long-term aspirin administration. It must be noted here that our observations clearly showed that ATT discontinuation at 6 months postintervention did not increase the risk of recurrent strokes, nor did it impair the clinical outcome at up to 10 years of follow-up after PFO closure. Given that the procedure is usually performed among young patients, a lifelong ATT could potentially expose them to bleeding events and medications’ undesirable effects when given during such a long treatment period. These findings suggest that in strongly selected patients undergoing PFO closure due to cryptogenic strokes, ATT cessation at 6 months postintervention would be a quite reasonable strategy.

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the Helex, CardioSEAL, and STARflex systems. Rigatelli et al. [24] reported a PFO-device thrombosis rate at 0.2% at 10 years of follow-up, while including 453 patients that were mainly treated with an Amplatzer device (75% cases) and ceased ATT after 6 months.

In the present study, late prosthesis dysfunction was similarly low (0.2% patient-year), including one significant residual shunt and four thromboses, which were more commonly observed among thrombophilia patients (11% vs. 0.8% in the absence of thrombophilia, \( p = 0.02 \)), yet without being impacted by ATT duration. All thrombus deposits were detected on non-Amplatzer devices. These observations suggest to be careful with thrombophilic patients undergoing PFO closure, and to treat them with low-thrombogenic devices.

4.4. Study Limitations. This is a retrospective analysis of a single center registry, with inherent limitations. This is a nonrandomized study on a small sample size with a low event rate, so underpowered, and bias still remains after propensity score matching.

At follow-up, the evaluation of residual shunting and device-thrombus was performed using transthoracic echocardiography, which may result in an underestimation of their actual incidences. Nevertheless, a TEE was performed in each patient that experienced a recurrent stroke, with only one significant residual shunt and one thrombus detected among these cases. Even if transthoracic echocardiographic follow-up is less complete and has a lower sensitivity than TEE, it is less invasive, more available, and properly reflects the way in which most patients are followed-up after PFO closure in real-life settings.

5. Conclusions

The current study has shown that among strongly selected patients at low cardiovascular risk, the rate of recurrent stroke and cryptogenic stroke after successful transcatheter PFO closure is very low (0.3 and 0.2% patient-year, respectively) at a 10-year follow-up. ATT discontinuation at 6 months versus extended ATT did not increase the risk of recurrent strokes, device thrombosis, nor did it impair the patient outcome.

Abbreviations

ASD: Atrial septal defect
ATT: Antithrombotic therapy
HR: Hazard ratio
MRI: Magnetic resonance imaging
PFO: Patent foramen ovale
TEE: Transesophageal echocardiography

Data Availability

The data that support the findings for this study are available from the corresponding author upon request.

Disclosure

The authors have no relationships relevant to this paper to disclose.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] J. L. Mas, G. Derumeaux, B. Guillou et al., “Patent foramen ovale closure or anticoagulation vs. Antiplatelets after stroke,” New England Journal of Medicine, vol. 377, no. 11, pp. 1011–1021, 2017.
[2] L. Sondergaard, S. E. Kasner, J. F. Rhodes et al., “Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke,” New England Journal of Medicine, vol. 377, no. 11, pp. 1033–1042, 2017.
[3] J. L. Saver, J. D. Carroll, D. E. Thaler et al., “Long-term outcomes of patent foramen ovale closure or medical therapy after stroke,” New England Journal of Medicine, vol. 377, no. 11, pp. 1022–1032, 2017.
[4] P. H. Lee, J.-K. Song, J. S. Kim et al., “Cryptogenic stroke and high-risk patent foramen ovale,” Journal of the American College of Cardiology, vol. 71, no. 20, pp. 2335–2342, 2018.
[5] H. Baumgartner, J. De Backer, S. Babu-Narayan et al., “2020 ESC Guidelines for the management of adult congenital heart disease,” European Heart Journal, vol. 42, pp. 1–83, 2021.
[6] R. Foth, T. Quentin, I. Michel-Behnke et al., “Immunohistochemical characterization of neotissues and tissue reactions to septal defect–occlusion devices,” Circulation: Cardiovascular Interventions, vol. 2, pp. 90–96, 2009.
[7] C. Pristipino, H. Sievert, F. D’Ascenzo et al., “European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism,” EuroIntervention, vol. 14, no. 13, pp. 1389–1402, 2019.
[8] D. O. Kleindorfer, A. Towfighi, S. Chaturvedi et al., “2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart association/American stroke association,” Stroke, vol. 52, no. 7, pp. e364–e467, 2021.
[9] S. Cassese, R. A. Byrne, T. Tada, L. A. King, and A. Kastrati, “Clinical impact of extended dual anti- platelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials,” European Heart Journal, vol. 33, no. 24, pp. 3078–3087, 2012.
[10] J. M. Gaziano, C. Brotons, R. Coppolecchia et al., “Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial,” The Lancet, vol. 392, no. 10152, pp. 1036–1046, 2018.
[11] C. Boutin, N. N. Musewe, J. F. Smallhorn, J. D. Dyck, T. Kobayashi, and L. N. Benson, “Echocardiographic follow-
up of atrial septal defect after catheter closure by double-umbrella device,” *Circulation*, vol. 88, no. 2, pp. 621–627, 1993.

[12] A. P. Kappetein, S. J. Head, P. Généreux et al., “Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document,” *The Journal of Thoracic and Cardiovascular Surgery*, vol. 145, no. 1, pp. 6–23, 2013.

[13] W. J. Powers, A. A. Rabinstein, T. Ackerson et al., “Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/ American stroke association,” *Stroke*, vol. 50, no. 12, pp. e344–e418, 2019.

[14] R. Mehran, S. V. Rao, D. L. Bhatt et al., “Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium,” *Circulation*, vol. 123, no. 23, pp. 2736–2747, 2011.

[15] A. J. Furlan, M. Reisman, J. Massaro et al., “Closure or medical therapy for cryptogenic stroke with patent foramen ovale,” *New England Journal of Medicine*, vol. 366, no. 11, pp. 991–999, 2012.

[16] B. Meier, B. Kalesan, H. P. Mattle et al., “Percutaneous closure of patent foramen ovale in cryptogenic embolism,” *New England Journal of Medicine*, vol. 368, no. 12, pp. 1083–1091, 2013.

[17] J. D. Carroll, J. L. Saver, D. E. Thaler et al., “Closure of patent foramen ovale versus medical therapy after cryptogenic stroke,” *New England Journal of Medicine*, vol. 368, no. 12, pp. 1092–1100, 2013.

[18] J. Wintzer-Wehekind, A. Alperi, C. Houde et al., “Long-term follow-up after closure of patent foramen ovale in patients with cryptogenic embolism,” *Journal of the American College of Cardiology*, vol. 73, no. 3, pp. 278–287, 2019.

[19] K. Liu, B. Song, I. F. Palacios et al., “Patent foramen ovale attributable cryptogenic embolism with thrombophilia has higher risk for recurrence and responds to closure,” *JACC: Cardiovascular Interventions*, vol. 13, no. 23, pp. 2745–2752, 2020.

[20] C. V. B. Hviid, C. Z. Simonsen, and A. M. Hvas, “Recurrence risk in patients with cryptogenic stroke, patent foramen ovale, and thrombophilia: a systematic review and meta-analysis,” *Thrombosis & Haemostasis*, vol. 119, no. 11, pp. 1839–1848, 2019.

[21] J. Wintzer-Wehekind, A. Alperi, C. Houde et al., “Impact of discontinuation of antithrombotic therapy following closure of patent foramen ovale in patients with cryptogenic embolism,” *The American Journal of Cardiology*, vol. 123, no. 9, pp. 1538–1545, 2019.

[22] M. Valgimigli, E. Frigoli, D. Heg et al., “Dual antiplatelet therapy after PCI in patients at high bleeding risk,” *New England Journal of Medicine*, vol. 385, no. 18, pp. 1643–1655, 2021.

[23] M. Hornung, S. C. Bertog, J. Franke et al., “Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale,” *European Heart Journal*, vol. 34, no. 43, pp. 3362–3369, 2013.

[24] G. Rigatelli, M. Zuin, F. Dell’Avvocata, L. Roncon, D. Vassilev, and N. Nghia, “Light anti-thrombotic regimen for prevention of device thrombosis and/or thrombotic complications after interatrial shunts device-based closure,” *European Journal of Internal Medicine*, vol. 74, pp. 42–48, 2020.