Percutaneous Left Atrial Appendage Closure Is a Reasonable Option for Patients With Atrial Fibrillation at High Risk for Cerebrovascular Events

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Background—Percutaneous left atrial appendage (LAA) closure is an emerging option for patients with atrial fibrillation at high risk for cerebrovascular events. The multicenter FLAAC registry (French Nationwide Observational LAA Closure Registry) was established to assess LAA closure outcomes in everyday practice.

Methods and Results—Four hundred thirty-six patients referred from April 2013 to September 2015 to 33 French interventional cardiology centers for percutaneous LAA closure were included prospectively in the FLAAC registry. Mean age was 75.4±0.4 years. The stroke risk was high (mean CHA_2DS_2–VASc score, 4.5±0.1) and most patients had experienced clinically significant bleeding (HAS-BLED score, 3.1±0.05). The device used was Amplatzer LAA occluder in 58% and the Watchman device in 42% of the patients. The procedural success rate was 98.4%. Median postprocedure follow-up was 12.0 (11.8–12.0) months and a single patient was lost to follow-up. During the periprocedural and subsequent follow-up period, procedure-related severe adverse events occurred in 21 (4.9%) and 10 (2.3%) patients, respectively. One-year cumulative incidences of ischemic stroke and cerebral hemorrhage were 2.9% (1.6–5.0) and 1.5% (0.7–3.2), respectively. Overall, 1-year mortality was 9.3% (6.9–12.5) with 7 of the 39 deaths related or possibly related to the device or procedure.

Conclusions—This nationwide prospective registry shows that, in the French population, LAA closure is mainly used in patients with high comorbidity rates and a poor prognosis. LAA closure in such patients seems reasonable to decrease the stroke rate. The overall health status of these patients should be taken into account during the preprocedural evaluation process.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT02252861.

Key Words: anticoagulants ■ atrial appendage ■ atrial fibrillation ■ cerebral hemorrhage ■ stroke

Population aging will contribute to an increase in the prevalence of atrial fibrillation (AF) in the coming years. Despite recent registry evidence of increased oral anticoagulant (OAC) use in patients with AF, approximately one-third of patients at moderate to high risk of stroke fail to receive guideline-recommended anticoagulants.[1,2] In the ORBIT-AF registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), the main factors associated with absence of OAC therapy in everyday practice were patient or physician preference, history of bleeding, and frailty.[3] Similarly, in the GARFIELD-AF registry (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation), an inverse relationship was found between OAC use and the HAS-BLED score.[4] Despite the development of new OAC,

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*A list of all FLAAC Investigators is given in the Appendix.

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WHAT IS KNOWN

- One-third of patients at moderate to high risk of stroke fail to receive guideline-recommended anticoagulants.
- PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy) randomized controlled trials compared left atrial appendage closure to warfarin in patients eligible for anticoagulant agents.

WHAT THE STUDY ADDS

- In a French group of patients not able to take long-term oral anticoagulation, left atrial appendage closure reduced the risk of thromboembolic events compared with the predicted risk.
- Left atrial appendage closure was associated with serious complications in some patients.
- Decision of left atrial appendage closure should be made on an individual basis and integrate a preprocedural clinical evaluation, assessment of risk/benefit ratio, and patient preference.

the prevention of thromboembolic events remains a major challenge in many patients with AF.

Alternatives to OAC treatment have been sought for years. Given that left atrial appendage (LAA) is the main source of thrombi in patients with AF,[5] self-expanding devices have been developed to achieve percutaneous LAA closure. Commercially available implants include the first- and second-generation Amplatzer LAA occluders (St Jude Medical, St. Paul, MN) and the Watchman device (Boston Scientific, Marlborough, MA), whose approval by national regulatory authorities differs across countries.

Only limited data are available to help physicians assess the risk/benefit ratio of LAA closure in the individual patient. The strongest evidence comes from 2 randomized controlled trials of LAA closure with the Watchman device as a potential alternative to long-term anticoagulation.[6,7] All included patients were potentially eligible for OAC therapy and, therefore, were perhaps not representative of the population treated with LAA closure in everyday practice. A few registries have reported the experience of expert centers.[8–10] However, some of these registries focused mainly on the periprocedural period.[11]

We established FLAAC registry (French Nationwide Observational LAA Closure Registry) to investigate the safety and efficacy of LAA closure in patients with AF managed in everyday practice in France. Here, the 1-year outcomes of 436 consecutive patients in this registry are reported.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

This multicenter, prospective, cohort study was conducted in 33 French interventional cardiology departments from April 2013 to September 2015. All cardiologists involved in the study followed a training program organized by the device manufacturers before performing their first procedure. Center selection was independent of previous experience with LAA closure to ensure that our patients were representative of everyday practice.

The study protocol was approved by the local institutional review committee and subjects gave informed consent. The study was conducted in compliance with the Declaration of Helsinki.

Inclusion criteria were the following: patients with nonvalvular AF referred to an interventional cardiology center for LAA closure for any reason. Each study cardiologist could choose among the devices commercially available in France, that is, first- or second-generation Amplatzer LAA occluders or Watchman. No recommendations were made about LAA size assessment or periprocedural care. Echocardiography or computed tomography follow-up and pharmacological treatment were at the discretion of the operators.

For each patient, the medical history, demographics, comorbidities, clinical and laboratory data, and echocardiographic characteristics were recorded prospectively by patient interview and medical record review.

This investigator-initiated study was funded by unrestricted grants from the device manufacturers, who had no role in the study design, data collection and interpretation, or writing of the article.

Patient Follow-Up

Follow-up data were collected during patient visits or phone calls 3, 6, and 12 months after LAA closure. The data were collected in a Microsoft Access Database. All severe adverse events (SAEs) were classified according to the definitions developed by the Valve Academic Research Consortium 2,[12] by an adjudication committee independent of the cardiologists caring for the patients. Bleeding events were classified as life-threatening or disabling, major, and minor. Vascular access-site complications were classified as major and minor. Procedure-related SAEs were defined as all events considered related or possibly related to the device or procedure.

Outcome Measures

The primary outcome was the proportion of patients with thromboembolic events (stroke or systemic embolism) during the first year after LAA closure. The predefined secondary outcome measures were the proportions of patients with SAEs related to the procedure (death, device embolization, pericardial effusion requiring intervention, stroke, systemic embolism, air embolism, and major bleeding), cardiovascular and unexplained deaths after LAA closure and pharmacological antithrombotic treatment after LAA closure. To allow comparisons of our results with previous data, we assessed complication rates over 2 periods, namely, the periprocedural period (from the day of the procedure to day 7 or discharge) and the follow-up period (up to 12 months).

Statistical Analysis

Descriptive results are displayed as mean±SEM or median (interquartile range) for continuous variables, according to the normality of the distributions as assessed by graphical study and Shapiro–Wilk tests. Categorical data are described as number (percentage). Categorical variables were compared using χ^2 tests. Continuous variables were compared using Student *t* tests or Mann–Whitney tests, depending on the normality of distributions. To assess the potential influence on the number of SAEs of the experience gained by centers over time and with the number of procedures performed, we conducted several complementary analyses, including (1) the comparison of the rates of SAE per center (defined by the raw number of SAEs occurred in a given center divided by the number of treated patients in this center) between high- and low-volume procedural centers (above or below the median number of procedures performed), (2) the evaluation of the association between the risk of having ≥1 SAE at the individual

level and the cumulative number of patients previously treated in the corresponding center, and finally (3) the evaluation of the association between the risk of having ≥1 SAE at the individual level and the increasing chronological time since study initiation. Overall survival and the cumulative incidence of thromboembolic events up to 1 year were calculated using Kaplan–Meier methodology for censored data; sensitivity analyses performed using the Fine and Gray competing-risks model yielded similar results. Two-sided P values<0.05 were considered statistically significant. Statistical analyses were conducted with Statview version 5.0 (JMP, Cary, NC) and Stata version 11.1 (StataCorp LP, College Station, TX).

Results

Study Population

A total of 436 consecutive patients referred to the 33 study centers for LAA closure were included in the registry. The median number of patients enrolled per center was 10.0 (6.0–16.0; range, 2–40). Table 1 reports their main baseline characteristics. Patients mean age was 75.4±0.4 and 62.2% were men. History of cardiovascular diseases and comorbidities were common. The mean CHA_2DS_2–VASc score (4.5±0.1) values indicated a high risk of stroke, and 38.5% of patients had a history of ischemic cerebral event. Most patients had experienced clinically significant bleeding (mean HAS-BLED score, 3.1±0.05).

The reason for LAA closure in 418 (95.9%) patients was a high thromboembolic risk in patients deemed unsuitable for OAC because of history or high risk of bleeding. Other reasons were a history of thromboembolic events despite adequate OAC therapy (n=15, 3.4%) and persistent asymptomatic LAA thrombus despite adequate OAC therapy (n=3, 0.7%).

Procedural Characteristics

LAA closure was successful in 429 (98.4%) patients, including 10 (2.3%) who required a second procedure after an initial failure (Table 2). The main reason for procedural failure was left atrial anatomy unsuitable for device implantation. Table 3 reports the characteristics of the implanted devices. The device selected initially after LAA sizing was usually adequate, and only 31 procedures used >1 device. First- or second-generation Amplatzer devices were implanted in 248 (57.8%) patients and the Watchman device in 181 (42.2%) patients. In 20 centers, all patients received the same type of device and in 13 both types were used. LAA closure was performed under general anesthesia in nearly all patients (n=431, 98.9%). Median procedure duration was 60 (45–75) minutes (fluoroscopy time: 12 [8–18] minutes). Median hospital stay after LAA closure was 2 (2–4) days.

Pharmacological Antithrombotic Treatment

The percentage of patients treated with anticoagulant agents was reduced after LAA closure compared with baseline (23.5% versus 32.2%, P<0.01). Treatment at discharge varied substantially between patients: 27.6% of the patients were discharged with single antiplatelet therapy, 45.6% with dual-antiplatelet therapy, and 23.5% with short-term anticoagulation. Only 3.3% of patients remained without any antithrombotic agent. Patients with anticoagulation at discharge were younger (73.4±0.9 versus 75.9±0.5 years, P=0.01) and

Table 1. Patient Characteristics

Patient Characteristics	
Age, y*	75.4±0.4
Male gender, n (%)	271 (62.2)
Atrial fibrillation, n (%)	285 (65.4)
Risk factors, n (%)	
Hypertension	374 (85.8)
Diabetes mellitus	130 (29.8)
Smoker (current or past)	123 (28.2)
Dyslipidemia	196 (45.0)
Cardiovascular history, n (%)	
Heart failure	113 (25.9)
Valvular surgery	15 (3.4)
Coronary artery disease	140 (32.1)
Myocardial infarction	45 (10.3)
Previous deep vein thrombosis/pulmonary embolism	44 (10.1)
Previous ischemic stroke, n (%)	168 (38.5)
Previous hemorrhagic event, n (%)	394 (90.4)
Hemorrhagic stroke	125 (28.7)
Subarachnoid hemorrhage	14 (3.2)
Epidural/subdural hematoma	46 (10.6)
Ischemic stroke with hemorrhagic transformation	21 (4.8)
Microbleeds	8 (1.8)
Gastrointestinal	113 (25.9)
Spontaneous hematoma	54 (12.4)
Other	63 (14.4)
Other comorbidities	
Cirrhosis, n (%)	20 (4.6)
Chronic obstructive pulmonary disease, n (%)	60 (13.8)
Thyroid dysfunction, n (%)	83 (19.0)
Creatinine at admission, µmol/L†	98 (80–127)
Creatinine clearance at admission, mL/min†	59.4 (45.1–77.0)
Hemoglobin at admission, g/dL†	12.9 (11.6–14.2)
Antithrombotic treatment at baseline	
Single antiplatelet therapy	141 (32.4)
Dual-antiplatelet therapy	14 (3.2)
Oral anticoagulant	99 (22.8)
Parenteral anticoagulant	41 (9.4)
No antithrombotic agent	140 (32.2)
CHA_2DS_2–VASc score*	4.5±0.1
0	0 (0.0)
1	8 (1.8)
2	37 (8.5)
3	67 (15.4)

(*Continued*)

Table 1. Continued

Patient Characteristics	
4	111 (25.5)
5	103 (23.6)
6	65 (14.9)
7	32 (7.3)
8	10 (2.3)
9	3 (0.7)
HAS-BLED score*	3.1±0.05
0	0 (0.0)
1	9 (2.1)
2	112 (25.7)
3	159 (36.5)
4	128 (29.4)
5	22 (5.0)
6	6 (1.4)
7	0 (0.0)
8	0 (0.0)
9	0 (0.0)

*Mean±SEM.
†Median (interquartile range).

had a less frequent history of hemorrhagic stroke (19.0% versus 32.3%, P=0.01).

Prescription of antithrombotic agents decreased over time. At the 12-month visit, 17.9% of the patients received no antithrombotic treatment, 63.6% a single antiplatelet therapy, 8.2% a dual-antiplatelet therapy, and 6.4% an anticoagulant agent. In patients treated with anticoagulation at discharge, a history of bleeding was a strong predictor of anticoagulation discontinuation before 1 year (86.8% versus 58.8% of anticoagulation discontinuation in patients with or without history of bleeding episode, P=0.01).

Primary Outcome Measure

Median follow-up in the 429 patients with successful LAA closure was 12.0 (11.8–12.0) months. A single patient was lost to follow-up (follow-up rate, 99.8%). Thromboembolic events occurred in 12 patients; of these 12 events, 3 occurred during the periprocedural period (on days 0, 1, and 4, respectively) and 9 during the subsequent follow-up (Figure 1A).

Table 2. Procedural Outcomes

Procedural Outcome	n (%)
Successful implantation	429 (98.4)
After first procedure	419 (96.1)
After second procedure	10 (2.3)
Failed implantation	7 (1.6)
Unsuitable anatomy	6 (1.4%)
Thrombus in the left atrial appendage	1 (0.2%)

Table 3. Implanted Devices

Implanted Device	n (%)
Amplatzer left atrial appendage occluder/ Watchman	248/181 (57.8/42.2)
No. of devices used per procedure	
1 device	398 (92.8)
≥2 devices	31 (7.2)
Watchman size, mm	
21	32 (7.5)
24	68 (15.9)
27	42 (9.8)
30	31 (7.2)
33	8 (1.9)
Amplatzer Cardiac Plug/Amplatzer Amulet, mm	
16	8 (1.9)
18	10 (2.3)
20	20 (4.7)
22	60 (14.0)
24	54 (12.6)
25	8 (1.9)
26	37 (8.6)
28	21 (4.9)
30	27 (6.3)
31	1 (0.2)
34	1 (0.2)

Most of the thromboembolic events occurred within the first 6 months after LAA closure. Thrombus was detected on the LAA closure device in only one of these patients. The 1-year cumulative incidence of thromboembolic events was 2.9% (1.6–5.0; Figure 1), a 57% decrease as compared with the annual thromboembolic event rate of 7.2% predicted by the CHA_2DS_2–VASc score without prophylaxis against thromboembolic events (Figure 1A and 1C).[13] This corresponds to a number needed to treat of 23 to prevent 1 thromboembolic event within 1 year (Figure 1D).

Procedure-Related SAEs

During the periprocedural and subsequent follow-up period, procedure-related SAEs occurred in 21 patients (4.9%; 22 SAEs) and 10 (2.3%) patients, respectively (Table 4). Major bleeding was the most common SAE and was mainly related to access-site complications. Device embolization occurred in 5 (1.2%) patients; among these events, 3 were asymptomatic and diagnosed during routine follow-up echocardiography on days 33, 38, and 39, respectively (Table 4). Pericardial effusion requiring pericardiocentesis occurred in 8 patients; among them, 4 developed progressive pericardial effusions requiring drainage on days 9, 64, 93, and 239, respectively.

Of the 32 procedure-related SAEs, 7 resulted in death, corresponding to a number needed to harm of 61 (for 1

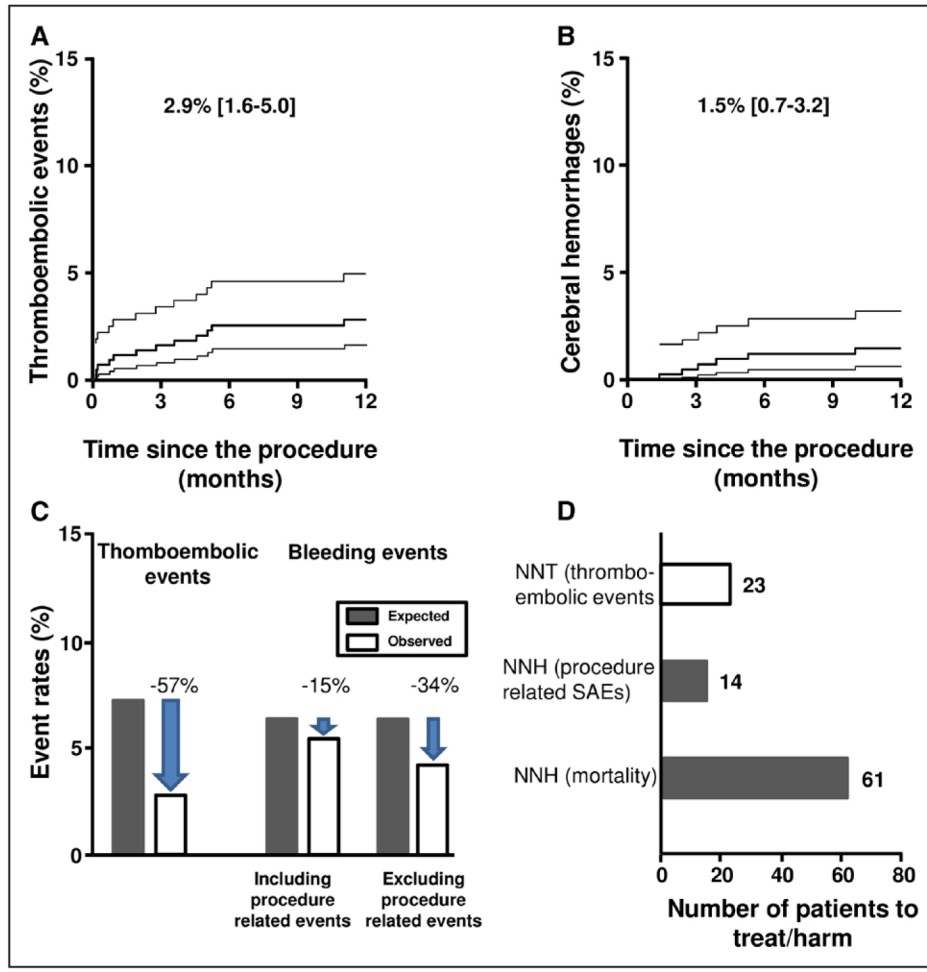

Figure 1. Risk/benefit ratio of left atrial appendage (LAA) closure. **A** and **B**, Cumulative incidence of thromboembolic events (**A**) and cerebral hemorrhagic events (**B**) at 1 year. The thin lines indicate the 95% confidence intervals. **C**, Observed thromboembolic and bleeding event rates 1 year after LAA closure compared with expected rates, based on CHA_2DS_2–VASc and HAS-BLED scores. LAA closure led to a decrease in the thromboembolic event rate and to a moderate reduction in the bleeding event rate. **D**, The white bar indicates the number needed to treat (NNT) to prevent 1 ischemic event within 1 year after LAA closure. Similarly, the grey bars indicate the number needed to harm (NNH; for all procedure-related severe adverse events and for deaths). SAEs indicates severe adverse events.

procedure-related death; Figure 1D). Four of these deaths occurred during the periprocedural period: device embolization with rupture of mitral chordae tendineae, pericardial effusion followed by an ischemic cerebral event, major access-site bleeding, and respiratory failure after anesthesia in a patient with chronic obstructive pulmonary disease. The causes of the 3 deaths during the subsequent follow-up period were device embolization with vascular lesion, gastrointestinal bleeding related to esophageal injury during transesophageal intraoperative echocardiography and device-related ischemic stroke (Table 5).

No statistically significant difference was found for the rate of SAEs per center (number of SAEs divided by number of patients treated) between high- and low-volume procedural centers (above or below the median number of procedures performed across FLAAC centers): mean (±SEM): 7.3±1.9% versus 10.2±3.2%, median: 6.5% (interquartile range, 0.0–9.8) versus 0.0% (interquartile range, 0.0–16.7), *P*=0.92. Furthermore, there was no association between the risk of having ≥1 SAE at the individual patient level and the cumulative number of patients previously treated in each center (odds ratio=0.98 per 1-patient increase [0.94–1.03], *P*=0.48) or the chronological time since study initiation (odds ratio=1.000 per 1-day increase [0.999–1.002], *P*=0.67) in a mixed effects logistic regression model.

Other Events During Follow-Up

During the follow-up period, 13 major bleeding episodes, not related to the procedure, occurred in 11 (2.6%) patients (Table 4). In addition, cerebral hemorrhage occurred in 6 (1.5%) patients, among whom 5 had a previous history of cerebral hemorrhage and 5 had a HAS-BLED ≥3 (Figure 1B). At the time of the bleeding event, 5 patients were taking antiplatelet agents and 1 patient no antithrombotic medication. This represents 15% fewer bleeding episodes than expected, based on the HAS-BLED score.[14] The decrease was 34% when procedure-related bleeding episodes were excluded (Figure 1C).

Among patients discharged alive, 35 (8.2%) died within the first year, including the 3 above-reported patients who died from procedure-related events (Table 5). The main reasons for death in the other 32 patients were preexisting

Table 4. Patients With Severe Adverse Event

	Periprocedural Period*	Subsequent Follow-Up
Procedure-related complications, n (%)		
Device embolization	2 (0.5)	3 (0.7)
Requiring surgery	1 (0.2)	2 (0.5)
Snared	1 (0.2)	1 (0.2)
Pericardial effusion requiring intervention	4 (0.9)	4 (0.9)
Subxyphoid pericardiocentesis	2 (0.5)	2 (0.5)
Surgical pericardiocentesis	2 (0.5)	2 (0.5)
Major vascular complication (access site)	13 (3.0)	1 (0.2)
Other major bleeding event	0 (0)	1 (0.2)
Air embolism	0 (0.0)	0 (0.0)
Adverse reaction to anesthesia	0 (0.0)	0 (0.0)
Systemic embolism	0 (0.0)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)
Other	1 (0.2)	0 (0.0)
Nonprocedure-related complications, n (%)		
Major bleeding	7 (1.6)	11 (2.6)
Gastrointestinal	6 (1.4)	9 (2.1)
Other	1 (0.2)	2 (0.5)
Anemia requiring blood transfusion	2 (0.5)	7 (1.6)

*From the day of the procedure to day 7 or discharge.

noncardiovascular comorbidities (n=14; 3.3%) and underlying cardiovascular disease (n=11; 2.6%). In all, of the 429 patients with successful LAA closure, 39 died within the first year, corresponding to a cumulative incidence of 9.3% (6.9–12.5; Figure 2).

Follow-Up of Patients With Procedural Failure

The 7 patients with failed LAA closure were followed for 1 year, during which no new attempt at LAA closure was performed. During follow-up, 3 of these patients died, including 1 from ischemic stroke.

Discussion

This nationwide prospective multicenter registry study collected the outcomes of LAA closure as performed in everyday practice in 436 consecutive patients in France. The frequency of thromboembolic events within the first year was 57% lower than expected. This result supports the use of percutaneous LAA closure as a reasonable option to decrease the thromboembolic event rate in high-risk patients with nonvalvular AF. However, the frequency of procedure-related SAEs, although rather low, deserves note and reflects the major risk factors in our population.

LAA closure was mainly used during this study in patients with a high burden of comorbidities and a poor prognosis, as

Table 5. Causes of Death

	Periprocedural Deaths	Deaths During Subsequent Follow-Up
Procedure-related complications, n (%)	4 (0.9)	3 (0.7)
Device embolization	1 (0.2)	1 (0.2)
Pericardial effusion	1 (0.2)	0 (0.0)
Device-related ischemic stroke	0 (0.0)	1 (0.2)
Procedure-related major bleeding (femoral artery, procedure-related esophageal lesion)	1 (0.2)	1 (0.2)
Postprocedural respiratory failure	1 (0.2)	0 (0.0)
Nonprocedure-related complications, n (%)	0 (0.0)	32 (7.5)
Ischemic stroke	0 (0.0)	1 (0.2)
Hemorrhagic stroke	0 (0.0)	3 (0.7)
Cardiovascular/unexplained death	0 (0.0)	11 (2.6)
Myocardial infarction	0 (0.0)	0 (0.0)
Heart failure	0 (0.0)	6 (1.4)
Sudden/unexplained death	0 (0.0)	5 (1.2)
Other major bleeding events	0 (0.0)	3 (0.7)
Gastrointestinal	0 (0.0)	2 (0.5)
Splenic hematoma	0 (0.0)	1 (0.2)
Noncardiovascular comorbidity	0 (0.0)	14 (3.3)

*From the day of the procedure to day 7 or discharge.

indicated by the 9.3% all-cause 1-year mortality rate.[6,7,9,15] Most of the deaths after successful LAA closure were related to the underlying cardiovascular disease and known comorbidities. For purposes of comparison, in an epidemiological survey conducted in the French general population, the annual mortality rate was 3.8% in patients with a similar age distribution.[16] The mortality after LAA closure varied substantially across previous studies. The all-cause 1-year mortality rate ranged from 3.0% in PROTECT-AF trial (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) to 9.8% in EWOLUTION (Registry on WATCHMAN Outcomes in Real-Life Utilization). These

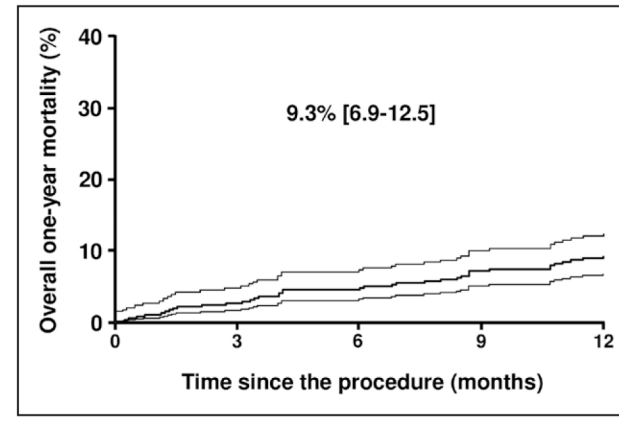

Figure 2. Cumulative incidence of overall 1-year mortality. The thin lines indicate the 95% confidence intervals.

differences may be explained, at least in part, by differences in comorbidities and patient characteristics. In EWOLUTION and FLAAC registries, comorbidities were common, as evidenced by the high CHA_2DS_2–VASc and HAS-BLED scores in these studies.

A post hoc analysis of data from the PROTECT-AF trial and CAP registry (Continued Access Program) suggests that the net clinical benefit of LAA closure may increase over time when the risk of periprocedural morbidity and mortality is taken into account.[17] Patients with multiple comorbidities and a short life expectancy may therefore derive only limited clinical benefits from LAA closure to prevent stroke.[18,19] Patients considered for LAA closure should thus undergo a comprehensive preprocedural evaluation. A formal assessment of frailty and comorbidities may be of assistance.

No randomized trial has quantified the effect of LAA closure in patients unsuitable for oral anticoagulation. In the FLAAC registry, the prevalence of stroke after LAA closure was relatively low, despite most of the patients were not able to take long-term OAC therapy. Our results suggest a 57% decrease in the annual thromboembolic event rate compared with the predicted rate, in keeping with previous registries of Watchman and Amplatzer devices.[9,10,15] Furthermore, a network meta-analysis of randomized controlled trials concluded that the Watchman device reduced the risk of thromboembolic events by 64% compared with a placebo.[20] Whether this protective effect is sustained over time remains to be assessed. Interestingly, the PROTECT-AF trial showed a low thromboembolic event rate after a follow-up of 3.8 years.[21] Furthermore, a subgroup analysis of the multicenter cohort reported by Tzikas et al[9] suggested a declining risk of thromboembolic events over time after LAA closure. The first direct evidence of long-term LAA closure effects will be provided by the ongoing 5-year randomized controlled ASAP-TOO trial (Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation) comparing the Watchman device to a single antiplatelet agent or no antithrombotic therapy in patients with contraindications to OACs.[22]

Assessment of the risk/benefit ratio of percutaneous LAA closure is of major importance to delineate the population eligible for this procedure. In the FLAAC registry population, LAA closure decreased the thromboembolic event rate but was associated with serious complications in some patients. The number needed to treat with LAA closure to prevent 1 thromboembolic event was 23, whereas the number needed to harm was 61 (procedure-related death). Decision of LAA closure should thus be made on an individual basis and integrate a preprocedural clinical evaluation, assessment of risk/benefit ratio, and patient preference.[18,19]

The procedure-related SAE rate in our registry was quite similar to that in PROTECT-AF, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy), and multicenter experience with ACP (AMPLATZER Cardiac Plug) studies but higher than in the EWOLUTION and Watchman US Post-Approval registries.[6–9,23] Differences in population characteristics may explain these findings, at least in part. Major bleeding was the most common SAE in our study, illustrating the high-risk profile of our patients. Furthermore, differences in study design may also have influenced the reporting of safety outcomes. Several previous registries collected data from public or manufacturer in-hospital databases, obtained during specific periods, usually defined as the time from the procedure to discharge.[11] The limited follow-up duration may have led to underestimation of procedure-related SAEs in some registries.[11,23] The recent European Society of Cardiology guidelines for the management of AF include a caution about possible reporting bias.[24] Several SAEs in our study, including device embolization and severe pericardial effusion, occurred several weeks or months after LAA closure. Occurrence of delayed SAEs after LAA closure has not been highlighted in previous registries. This finding indicates a need for specialized follow-up during the months after LAA closure, with clinical assessments, therapeutic management as needed, and routine imaging studies to detect asymptomatic device migration or pericardial effusion.[25]

Patient medical history influenced the antithrombotic treatment at discharge and during the follow-up period. LAA closure led to a moderate reduction in the bleeding rate compared with the predicted rate. Since anticoagulant agents were discontinued only several months after the procedure in some patients, we cannot exclude that the reduction of bleeding events will become more significant over time.

Our registry was designed to assess LAA closure in everyday practice on a nationwide scale and was fed by most of the French interventional cardiology centers. Other studies have reported the experience of high-volume centers in various countries.[8–10] Our registry may therefore be more representative of LAA closure outcomes in real-world practice. A learning curve has been described for several structural cardiac procedures. In PROTECT-AF and CAP studies, there was a reduction in the rate of SAEs with increasing operator experience. Interestingly, we did not find such association in the FLAAC registry. The lack of learning curve in our study may be explained by the support provided to low-activity centers. In centers with limited experience, procedures were performed by local investigators under supervision of a proctor. This highlights the importance of proper training of the operators to structural heart disease interventions because of the inherent risk of the procedures.

The reasons for LAA closure vary substantially across previous studies. In nearly all our patients, the reason was a need for alternative thromboembolic event prevention because of contraindications to long-term OAC therapy. In contrast, over one-fourth of patients in the ACP and EWOLUTION registries had LAA closure for other reasons.[8,9] Furthermore, in the PREVAIL and PROTECT-AF randomized controlled trials, a contraindication to warfarin was an exclusion criterion.[6,7] The 2016 European Society of Cardiology Guidelines for managing AF include a class IIb recommendation for LAA closure in patients with contraindications to OAC therapy.[24] Given the risk of severe complications demonstrated in our study, reserving LAA closure for patients with no other options for thromboembolic risk reduction would seem reasonable. However, data on such patients are scarce, and additional registries and adequately powered randomized trials will be required to fully

assess the usefulness of LAA closure in high-risk patients with contraindications to OAC therapy.

Limitations

This is a nationwide registry study with no control group. Therefore, we compared the annual thromboembolic event rate in our cohort to the rate predicted based on historical data. However, the reliability of the CHA_2DS_2–VASc score has been validated in several studies and supports a reduction of the thromboembolic risk after LAA closure.[13] Furthermore, our study patients were at high risk for thromboembolism and were not suitable for OAC therapy. Our findings may not apply to patient populations with other profiles.

Conclusions

In this nationwide prospective registry study, LAA closure performed in everyday practice was mainly used in patients at very high risk for cerebrovascular events. LAA closure seems reasonable in patients with no other option for thromboembolic risk reduction. The high percentage of deaths related to comorbidities suggests a need for a careful overall clinical evaluation to ensure optimal patient selection.

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Disclosures

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Appendix

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