Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial

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BACKGROUND Left atrial appendage (LAA) occlusion with WATCHMAN has emerged as viable alternative to vitamin K antagonists in randomized controlled trials.

OBJECTIVE EWOLUTION was designed to provide data in routine practice from a prospective multicenter registry.

METHODS A total of 1025 patients scheduled for a WATCHMAN implant were prospectively and sequentially enrolled at 47 centers. Indication for LAA closure was based on European Society of Cardiology guidelines. Follow-up and transesophageal echocardiography (TEE) were performed per local practice.

RESULTS The baseline CHA_2DS_2-VASc score was 4.5 ± 1.6; the mean age was 73.4 ± 9 years; previous transient ischemic attack/ischemic stroke was present in 312 (30.5%), 155 (15.1%) had previous hemorrhagic stroke, and 320 (31.3%) had a history of major bleeding; and 750 (73%) were deemed unsuitable for oral anticoagulation therapy. WATCHMAN implant succeeded in 1005 (98.5%) of patients, without leaks >5 mm in 1002 (99.7%) with at least 1 TEE follow-up in 875 patients (87%). Antiplatelet therapy was used in 784 (83%), while vitamin K antagonists were used in only 75 (8%). At 1 year, mortality was 98 (9.8%), reflecting the advanced age and comorbidities in this population. Device thrombus was

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observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen ($P = .14$). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) nonprocedure/device related.

CONCLUSION LAA closure with the WATCHMAN device has a high implant and sealing success. This method of stroke risk reduction appears to be safe and effective with an ischemic stroke rate as low as 1.1%, even though 73% of patients had a contraindication to and were not using oral anticoagulation.

KEYWORDS Stroke; Left atrial appendage; Atrial fibrillation; LAA closure; Bleeding

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Introduction

The left atrial appendage (LAA) has been implicated as the most common source of cardioembolic thrombi in nonvalvular atrial fibrillation (AF).[1] Left atrial appendage closure (LAAC) provides an attractive alternative to reduce the risk of stroke for those patients with a clinical rationale to prefer an alternative to long-term oral anticoagulation (OAC). Exclusion of the LAA for this reason has become part of cardiothoracic procedures such as valvular surgery or MAZE surgery for decades. The WATCHMAN technology is a permanent implantable device designed specifically for LAAC and provides a percutaneous catheter-based alternative for LAAC. In long-term follow-up of the randomized percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial (PROTECT AF trial), WATCHMAN LAAC was found to be superior to vitamin K antagonist (VKA) therapy in a selected patient population to prevent the combined end point of stroke, systemic embolism (SE), and cardiovascular or unexplained death.[2] It may also reduce the risk of life-threatening bleeding events such as hemorrhagic stroke by removing the need for long-term VKA or non-OAC (NOAC) therapy.[3]

In the United States, WATCHMAN LAAC has been approved for patients at high risk for stroke who are eligible for VKA therapy but who have reasons to seek an alternative. The latest European Society of Cardiology guidelines[4] recommend LAAC for patients at high risk for stroke who cannot use VKA or NOAC on a long-term basis, including those who are ineligible for OAC. There are, however, limited data available on the efficacy and safety of LAAC in the latter population and no data from randomized controlled trials. The European EWOLUTION study was designed to prospectively collect data on WATCHMAN LAAC performance in a real-world clinical setting in a high-risk patient cohort.

Methods

The outline of the study has been described in detail in the design article[5] and the first report on periprocedural outcomes.[6] The study adhered to international rules for scientific studies, the Helsinki principles, with local ethics committee approval in all participating centers per local regulations. All subjects provided informed consent before the procedure.

In brief, EWOLUTION was designed as a multicenter, prospective, nonrandomized cohort study aiming to include >1000 patients. Subjects were recruited at each participating center per physician's decision if they were eligible to receive the WATCHMAN device according to the appropriate local and international guidelines, were not participating in another trial, were not pregnant or of childbearing age, and were willing, able, and of legal age to provide informed consent. All implanting physicians underwent a thorough training and certification program to ensure an appropriate level of expertise in order to minimize patient risk.

Follow-up for subjects was not prespecified but based on each institution's standard practice, generally a clinical visit between 1 and 3 months postprocedure; LAA imaging to assess residual flow around the device; and annual follow-up visits. All data collection and adverse event reporting was performed directly by the individual sites and captured in a standardized central database. Adverse event adjudication was based on ISO 14155 and MEDDEV 2.7/3 12/2010 and included serious events such as perforation, tamponade, embolism, neurological events, thrombosis, and bleeding. Bleeding was scored according to the BARC criteria[7]; our definition of major bleeding (which includes fatal and life-threatening) aligns with the LAAC-specific modifications and refinements described by Tzikas et al[8] in the consensus document on definitions, end points, and data collection requirements. Stroke was classified in accordance to the criteria described by Leon et al.[9] All centers were monitored by an outside contract research organization on an ongoing basis, and all centers were visited between 1 and 4 times at the time of writing, depending on the number of patients enrolled and compliance review. Events and relevant source documents were also reviewed by the Sponsor Medical Safety Group (MSG). The MSG includes physicians with expertise in electrophysiology and/or cardiology as well as other health care professionals with the necessary therapeutic and subject matter expertise to evaluate the events. Centers were required to provide additional information in case of disagreement with the investigators' assessment of device-relatedness classification. For all patient deaths, source documents were requested at the sites and reviewed by the MSG.

Statistical analysis

The objective of the study was to obtain data on procedural success and complications and long-term patient outcomes, including bleeding and incidence of stroke/transient ischemic attack (TIA)/SE, and the sample size was based on the desire to obtain sufficiently precise estimates of rare adverse events

and not on power requirements for a formal hypothesis test. Rates of stroke/bleeding events are calculated as number of events per 100 patient-years. The individual patient annual risk of stroke and bleeding was recorded on the basis of each subject's CHA_2DS_2-VASc and HAS-BLED scores, and then the average risk score for the study population was calculated. The annual risk of stroke and bleeding was then extrapolated from the published risk score literature[10,11] in order to determine relative risk reductions. Mortality rate is calculated using the Kaplan-Meier method to account for censoring. The rate of device-associated thrombus is calculated using the Kaplan-Meier method, only taking into account patients with transesophageal echocardiography (TEE) performed. *P* values are based on log-rank tests for time-to-event analysis and Fisher exact test for binomial proportions.

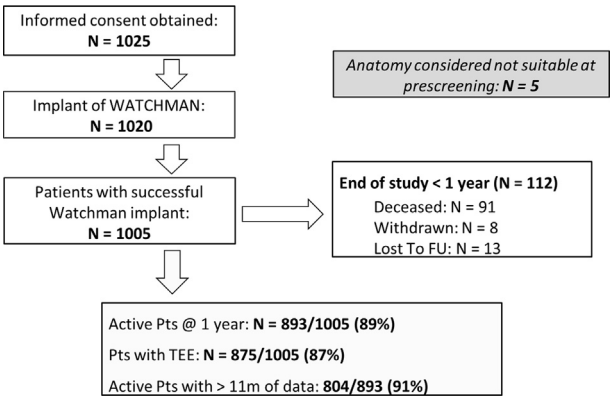

Figure 1 Flow chart of all patients included in EWOLUTION throughout 1-year follow-up. FU = follow-up; Pts = patients; TEE = transesophageal echocardiography.

Results

Patient characteristics

Enrollment opened in October 2013 and was completed in May 2015. A total of 1025 subjects were scheduled for implant in the study in a total of 47 centers in 13 countries (Figure 1). The inclusion rate ranged from 1 to 86 subjects, depending on center volume and local approval to start participation in the trial. Centers were encouraged to enroll consecutive patients to represent real-life practice and avoid selection bias. At least 39 of 47 sites (83%) enrolled consecutive patients. A comparison of serious adverse events (SAEs) in those 39 centers vs those with nonconsecutive enrollments (n = 3[6.4%]) or unknown (n = 5[10.6%]) did not show any difference regarding occurrence of SAEs ($P = .253$).

Implanting physicians and centers with varying levels of experience with the device participated in the registry. Seventy-eight percent of the implanting physicians had <2 years of experience with the WATCHMAN device and performed 75% of the study procedures. The distribution of experience across implanters is shown in Table 1.

Five patients signed the informed consent but eventually did not undergo an attempt at the implant procedure.

Baseline and acute implant data are, respectively, available for 1025 and 1020 subjects, as 5 patients were withdrawn from the study after giving informed consent with no attempt at LAAC as reported before.[6] The baseline demographic characteristics and risk factors are summarized in Table 2. The baseline CHA_2DS_2-VASc score was 4.5 ± 1.6 (estimated stroke risk of 7.2% per patient-year in the absence of therapy[10]) and HAS-BLED score 2.3 ± 1.2 (estimated bleeding risk of 5% per patient-year in the presence of VKA therapy[11]). A HAS-BLED score of ≥3 was present in 40% of patients. The mean age was 73.4 ± 8.9 years; previous ischemic stroke/TIA was present in 30.5%, 15.1% had previous hemorrhagic stroke, and 31.3% had a history of major bleeding; and 73.3% of patients were deemed contraindicated for OAC. Data are not always provided on the reasons for that contraindication. It is possible that some of these patients may have had relative vs absolute contraindications to the drugs, but nevertheless they were deemed unsuitable for short- or long-term OAC treatment at the time of implant.

Procedural outcomes

An initial report on procedural outcomes has been published previously.[6] Briefly, WATCHMAN implant succeeded in 1005 of 1020 patients (98.5%), without procedural leaks >5 mm in 99.8%. Procedure- and/or device-related SAEs within the first 7 days occurred at a rate of 2.8%. There were 4 cases of death within 7 days of the procedure: 1 because of cerebral air embolism on the day of the procedure and 3 reported as not associated with the device or procedure. There were no procedural stroke, SE, or myocardial infarction events. Table 3 summarizes the periprocedural events.

Periprocedural anticoagulation and device thrombus

The anticoagulation use directly after the procedure was as follows: VKA 16%, NOAC 11%, dual antiplatelet therapy 60%, single antiplatelet therapy 7%, and no anticoagulation in 6%. During follow-up, discontinuation of clopidogrel and (N)OAC occurred, resulting in 84% of patients receiving antiplatelet therapy (55% single and 28% dual) and 9% taking no medications (Figure 2). The average time to discontinue dual antiplatelet therapy was 6 months, but a large proportion of subjects (25%) used a short dual antiplatelet therapy regimen (≤3 months).

At the time of the data snapshot, 91% of active patients had ≥11 months of follow-up and 875 patients (87%) had at least 1 TEE examination during their follow-up. The average time to first TEE was 77 days, and the average time to last TEE was 225 days. Adequate sealing (no leaks >5 mm) was observed in 99% of patients. Device thrombus was present in 28 patients (3.7%) and was not correlated with the drug regimen ($P = .14$). Medications were adjusted in 22 patients, while no action was taken in the remaining 6. At the next follow-up visit, 24 cases had

Table 1 Level of experience with the WATCHMAN device among EWOLUTION implanters

WATCHMAN experience	Implanters	Cases
<6 mo	14 (22)	149 (15)
6 mo to 2 y	36 (56)	611 (60)
>2 y	14 (22)	260 (25)
Total	64 (100)	1020 (100)

Values are presented as n (%).

completely resolved, including 5 where no action was taken. The remaining 4 cases are unknown, as the patients had no TEE performed after thrombus was discovered. In patients with thrombus detected at routine TEE, there were no subsequent reports of adverse events such as stroke, TIA, or embolism. In patients with stroke in whom TEE or computed tomography (CT) was performed, 1 instance of device thrombus was observed.

Mortality, stroke, embolism, and bleeding through 1-year follow-up

At 1 year, 91 patients had died (mortality of 9.8%), reflecting the advanced age and considerable comorbidities in this population mostly contraindicated for VKA/NOAC use. The cause of death was known in 77 of 91 patients and included 24% cardiovascular and 60% noncardiovascular deaths, while in 15% patients the cause of death was not retrieved in the registry at the time of writing. In the events with a known cause of death, there were no late complications of the procedure or the device.

The annual rate of ischemic stroke was 1.1% (15 of 1325 patient-years), which translates into an 84% risk reduction, as compared with the calculated stroke rate of 7.2% without the use of anticoagulation for similar CHA_2DS_2-VASc scores (Figure 3). There were no occurrences of periprocedural strokes, and there were no hemorrhagic strokes during follow-up. Combining ischemic stroke with TIA and systemic thromboembolism, the annual rate is 1.5% (20 of 1318), translating into an 84% risk reduction (Figure 3).

The annual rate of major bleeding in the study (periprocedural and follow-up) was 2.6% (34 of 1303 patient-years), which corresponds to a 48% risk reduction (Figure 4), as compared with the rate that would have been expected during VKA therapy based on a comparable HAS-BLED score.

The majority of the bleeding events occurred outside the periprocedural period. The rate of major bleeding events, excluding procedural bleedings, is 2.3% (30 of 1307 patient-years), which corresponds to a 54% reduction (Figure 4).

No differences in death, stroke, or bleeding rates were observed between patients with or without a contraindication for anticoagulation, and there was no relation with the type of anticoagulant used. Half of the subjects with stroke were still on their discharge medication, and half had changed to a lower form of anticoagulation. At the time of stroke, 9% were on VKA, 27% on dual antiplatelet therapy, 55% on single antiplatelet therapy, and 9% on no medication.

Discussion

EWOLUTION is the largest prospective real-world registry on WATCHMAN, and the only study reporting on 1-year follow-up outcomes of LAA closure to date. In a previous publication (*European Heart Journal*), we described device deployment was successful in 98.5% of patients, with no flow or minimal residual flow achieved in 99.8% of implanted patients. The procedural through 7-day SAE rate was 2.8%, including all device- and procedure-related SAEs, with a mortality rate of 0.3% at 7 days. These procedural outcome data are the best that have been reported for any WATCHMAN study.[12] The present article contains outcome data of all patients, showing a stroke/TIA/SE rate as low as 1.5 per 100 patient-years, which is 85% lower than the expected 10.1 based on the findings of Friberg et al.[10] Retrospective registry data from 1000 patients with a similar risk profile treated with the AMPLATZER Cardiac Plug (St. Jude Medical, LLC, St. Paul, MN) indicated a similarly low annual rate of systemic thromboembolism of 2.3% per 100 patient-years.[13]

Ischemic stroke/SE compared to other WATCHMAN LAAC studies

A meta-analysis of the PROTECT AF and prospective randomized evaluation of the WATCHMAN left atrial

Table 2 Baseline patient characteristics (N =1025)

Characteristic	Value
Contraindicated	751/1024 (73.3)
Age at the time of consent (y)	73.4 ± 8.9
Age ≥75 y	520/1025 (50.7)
Sex: female	411/1025 (40.1)
CHA_2D_2-VASc score	4.5 ± 1.6
≤1	19/1024 (1.9)
2–3	257/1024 (25.1)
≥4	748/1024 (73.0)
HAS-BLED score	2.3 ± 1.2
<3	614/1024 (60.0)
≥3	410/1024 (40.0)
Congestive heart failure	350/1024 (34.2)
NYHA class	
I	36/348 (10.3)
II	194/348 (55.7)
III	111/348 (31.9)
IV	7/348 (2.0)
LVEF ≤40%	135/1022 (13.2)
Vascular disease	429/1024 (41.9)
Abnormal renal function	162/1024 (15.8)
Abnormal liver function	44/1024 (4.3)
Hypertension	885/1024 (86.4)
Diabetes	304/1024 (29.7)
Previous ischemic stroke/TIA	312/1024 (30.5)
Previous hemorrhagic stroke	155/1024 (15.1)
History of major bleeding	320/1024 (31.3)
History of major bleeding or predisposition to bleeding	396/1024 (38.7)

Values are presented as mean ± SD or as n/N (%).

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack.

Table 3 Listing of all major cardiac adverse events within 7 d of implant and other device-/procedure-related serious adverse events

Major adverse cardiac events* ≤7 d	18 (1.8%)
All deaths (0–7 d)†	4
Major bleeding	9
Cardiac tamponade/significant PE	3
Device embolization requiring surgery	1
Device embolization snared	1
Stroke	None
Systemic embolism	None
Myocardial infarction	None
Other events requiring surgery/major intervention	None
Other periprocedural serious adverse events ≤7 d	15 (1.5%)
Vascular complications @ groin	4
Air embolism (coronary)	2
Minor pericardial effusion (untreated)	2
Reinterventions due to incomplete seal	2
Minor bleeding (untreated)/hematoma	2
TIA	1
Hypotension	1
Adverse reaction to anesthesia	1

PE = pericardial effusion; TIA = transient ischemic attack.
*Major cardiac adverse events include 5 events (3 deaths and 2 major bleeding events) that are deemed unrelated to the procedure, yet we include them in the list because of their proximity to the implant procedure.
†One event >7 d but originating at the procedure.

appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL randomized trials using this device in patients eligible for long-term OAC showed comparable efficacy and postprocedure ischemic stroke/SE rates vs VKA (hazard ratio [HR] 0.79, $P = .22$ and HR 1.56, $P = .21$, respectively) while significantly reducing rates of hemorrhagic stroke, cardiovascular death, and postprocedural bleeding (HR 0.22, $P = .004$; HR 0.48, $P = .006$; and HR 0.51, $P = .002$).[14] Patients in the Continued Access to PROTECT AF Registry had similarly high CHA_2DS_2-VASc scores (mean 3.9) and age (74 years), demonstrating ischemic stroke rates of 1.3 per 100 patient-years, which aligns with the EWOLUTION annual rate of 1.1%.[15] Using a similar comparison method for an imputed benefit, Hanzel et al[16] calculated an 83% reduction in ischemic stroke events vs expected rates based on risk scores, matching the present findings of 84% reduction compared to historical control group. In left atrial appendage closure in patients with contraindications to oral anticoagulation (ASAP) trial, a WATCHMAN study of 150 subjects with VKA contraindications managed with aspirin combined with 6 months of clopidogrel without VKA transition after the LAAC procedure, patients with a mean CHA_2DS_2-VASc score of 4.4 showed an observed ischemic stroke rate of 1.7 per 100 patient-years after 2 years of follow-up and 1.8 per 100 patient-years after 5 years of follow-up.[17] Most patients enrolled in EWOLUTION were also deemed contraindicated to OAC and had more severe comorbidities than did patients enrolled in previous trials, yet the ischemic stroke rate of 1.1 per 100 patient-years compares favorably to outcomes from all aforementioned literature, further supporting the consideration of LAAC for this subset of high-risk patients.

Impact of anticoagulation eligibility and use on outcomes

The bleeding risk of the cohort was high with a mean HAS-BLED score of 2.3, conferring an expected 5% annual rate of major bleeding. The observed relative reduction >50% may be somewhat overestimated for this population, as the expected rate is calculated assuming VKA use, thus limiting the utility in calculating an imputed benefit in patients that otherwise cannot tolerate OAC.

A recent meta-analysis, including primarily studies using VKA in the first months after implant, found a 3.4% incidence of device thrombus for WATCHMAN.[18] An unintended consequence with lower use of postprocedural anticoagulation could be device thrombus, which could be perceived as a risk factor for impending stroke or embolism. Chun et al[19] described TEE data from 38 patients with WATCHMAN LAAC with 6 weeks of VKA transition or dual antiplatelet therapy after which only aspirin was used. They found thrombus in 7.9% of patients at 6 weeks, which

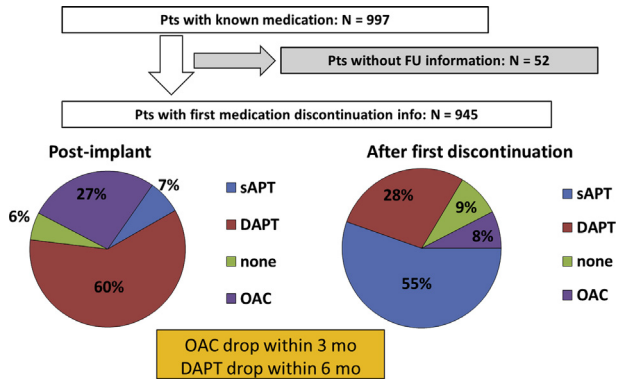

Figure 2 Flowchart of anti-coagulation drugs used after WATCHMAN implant throughout 1-year follow-up. DAPT = dual antiplatelet therapy; FU = follow-up; OAC = oral anticoagulation; Pts = patients; sAPT = single antiplatelet therapy.

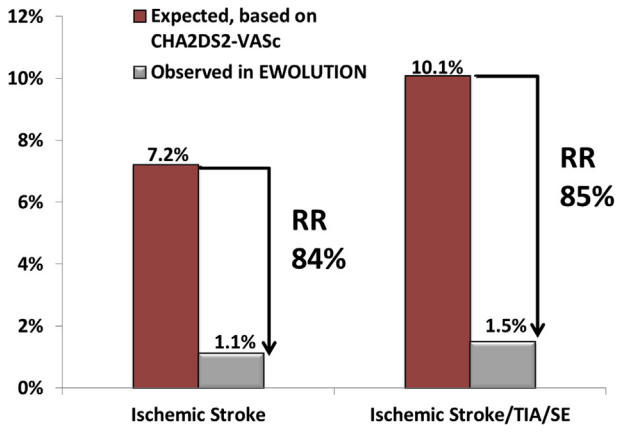

Figure 3 Actual stroke rate, and calculated stroke risk based on CHA_2DS_2-VASc score, and the relative risk reduction for the total EWOLUTION patient cohort after 1-year follow-up. RR = relative risk; SE = systemic embolism; TIA = transient ischemic attack.

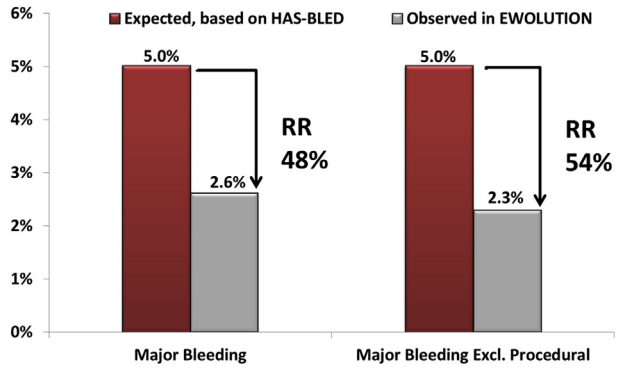

Figure 4 Actual major bleeding rate excluding procedural bleeding events, and calculated major bleeding risk based on HAS-BLED score, and the relative risk reduction for the total EWOLUTION patient cohort after 1-year follow-up. RR = relative risk; SE = systemic embolism; TIA = transient ischemic attack.

had dissolved in all at 12 weeks. During routine TEE follow-up in 875 EWOLUTION patients, thrombus was seen in 28 patients (3.7%), of which only 1 was detected at the time of hospitalization for a stroke. While the association is weak, the absence of device thrombus does not eliminate the possibility of thrombus embolization. Conversely, the presence of thrombus on the WATCHMAN device does not exclude a different etiology for stroke. However, no statistical relation was observed between thrombus, stroke, and use of anticoagulation. As a large cohort of the study group did not transition with VKA/NOAC and many even used single antiplatelet therapy or nothing, lower use of anticoagulation does not seem to lead to increase in device thrombus or stroke. This finding is encouraging and will be studied further in the ongoing randomized controlled trial in VKA-intolerant patients: ASAP-TOO.[20]

Patient selection

The mortality rate at 1 year was 9.8%, which may be perceived as high, given both LAAC and anticoagulation aim at long-term stroke prevention. Mortality rates during short-term follow-up were 3 per 100 patient-years in PROTECT AF and ~2.5 per 100 patient-years in PREVAIL, but these cohorts included patients eligible for VKA/NOAC with lower comorbidity profiles. During long-term follow-up, mortality in patients with WATCHMAN LAAC was significantly lower than that in patients on VKA (HR 0.66; $P = .04$), primarily because of significant reductions in fatal hemorrhagic strokes.

Patients ineligible to OAC would seem to be the most likely candidates to benefit from LAAC, but often turn out to have a higher comorbidity profile and higher mortality rate that may temper the long-term benefit of therapy. In the present study, comorbidity was indeed significant as witnessed by the highest CHA_2DS_2-VASc and HAS-BLED scores of all large WATCHMAN trials so far. More than half of the patients were older than 75 years, ~40% had a high risk of bleeding or a history of major bleeding, 35% with a history of ischemic/hemorrhagic stroke, 42% had evidence for vascular disease, >85% had hypertension, 34% had heart failure, 40% had diabetes, and >20% had liver and/or kidney disease. WATCHMAN LAAC in many of these patients was probably used as a last resort. As the European Society of Cardiology guidelines skew LAAC in the direction of last-resort patients, the absolute benefit of the therapy regarding mortality may not reach its full potential; however, relative stroke reductions over no therapy make LAAC an attractive strategy for these patients in most need of an alternative treatment.

Study limitations

Although this is a prospective registry with outside monitoring for data completeness, the primary clinical follow-up and responsibility of complete reporting lies with the participating centers. The postprocedural antithrombotic regimen was not uniform but at the physician's discretion, as was the time frame of follow-up and performing TEE or CT follow-up. In 13% of patients, follow-up and TEE or CT follow-up were not available for evaluation, which may influence the absolute numbers of device thrombus or sealing rates. Detailed information on the management and resolution of device thrombus was not systematically captured in the database.

The lack of a control arm limits the full assessment of therapy benefit in this patient population. HAS-BLED predicted bleeding rates from literature are based on samples of patients taking VKA. Although the majority of patients in this study were contraindicated to VKA, extreme caution should be exercised when interpreting relative reductions in major bleeding with the LAAC strategy in these VKA-ineligible patients.

Conclusion

In a large real-world cohort of 1025 patients with AF who had a high risk for stroke, of whom 73% were deemed unsuitable for OAC therapy, WATCHMAN LAAC was found to have a low annual stroke rate of 1.1%. Although most patients did not use VKA/NOAC transition but only antiplatelet therapy or nothing, this did not appear to affect the occurrence of stroke or other thromboembolic events during follow-up.

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