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ORIGINAL ARTICLE

Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology

Final 2-Year Outcome Data of the EWOLUTION Trial Focusing on History of Stroke and Hemorrhage

See Editorial by Turagam et al

BACKGROUND: Left atrial appendage occlusion with WATCHMAN has emerged as viable alternative to vitamin K antagonists in randomized controlled trials. Evaluating real-life clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology was designed to collect prospective multicenter outcomes of thromboembolic events, bleeding, and mortality for patients implanted with a WATCHMAN in routine daily practice.

METHODS: One thousand twenty patients with a WATCHMAN implant procedure were prospectively followed in 47 centers. Left atrial appendage occlusion indication was based on the European Society of Cardiology guidelines. Follow-up and imaging were performed per local practice up to a median follow-up of 2 years.

RESULTS: Included population was old (age 73.4±8.9 years), at high risk for stroke (311 prior ischemic stroke/transient ischemic attack and 153 prior hemorrhagic stroke) and bleeding (318 prior major bleeding), with CHA_2DS_2-VASc score ≥5 in 49%, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, Labile international normalized ratio, elderly, drugs/alcohol concomitantly ≥3 in 40% and oral anticoagulation contraindication in 72%. During follow-up, 161 patients (16.4%) died, 22 strokes were observed (1.3/100 patient-years, 83% reduction versus historic data), and 47 major nonprocedural bleeding events (2.7/100 patient-years, 46% reduction versus historic data). Stroke and bleeding rates were consistently lower than historic data in those with prior ischemic (–76% and –41%) or hemorrhagic (–81% and 67%) stroke and prior bleeding (–85% and –30%). Lowest bleeding rates were seen in patients with early discontinuation of dual antiplatelet therapy. Patients with early discontinuation of antithrombotic therapy showed lower bleeding rates, while they were highest for those with prior bleeding. Device thrombus was observed in 34 patients (4.1%) and was not correlated to drug regimen during follow-up (P=0.28).

CONCLUSIONS: During the complete 2-year follow-up of Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology, patients with a WATCHMAN left atrial appendage occlusion device had consistently low rates of stroke and nonprocedural bleeding, although most were contraindicated to oral anticoagulation and used only single antiplatelet therapy or nothing.

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Key Words: atrial appendage ■ atrial fibrillation ■ contraindications ■ hypertension ■ stroke

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WHAT IS KNOWN?

- The left atrial appendage is the most important source of thromboembolism and stroke in patients with nonvalvular atrial fibrillation.
- Mechanical closure with WATCHMAN has been proven an effective alternative to vitamin K antagonists for stroke-protection in randomized controlled trials.

WHAT THE STUDY ADDS?

- Evaluating real-life clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology confirms favorable outcomes during 2-year follow-up in 1020 routine clinical practice patients, most of them with a contraindication for anticoagulation.
- Thromboembolism and bleeding rates are low, even in high-risk patient cohorts with prior stroke, prior intracranial hemorrhage, and prior bleeding.
- Further lowering of anticoagulation reduces bleeding rate while retaining efficacy.

Over the last decade, left atrial appendage occlusion (LAAO) has become an attractive alternative to reduce the risk of stroke in patients with nonvalvular atrial fibrillation (AF), especially when long-term oral anticoagulation (OAC), either a vitamin K antagonist (VKA) or a novel agent (NOAC), is not suitable or hazardous. The recent meta-analysis of the final 5-year outcome data of the randomized controlled trials PROTECT-AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy) shows that WATCHMAN LAAO (Boston Scientific Corporation, St Paul, MN) was noninferior to warfarin therapy for the prevention of stroke, while nonprocedural bleeding and mortality were lower in the device arm.[1] Based on these randomized controlled trial and smaller registry data, WATCHMAN LAAO has become part of routine reimbursed health care options for stroke prevention in many countries around the world, including large geographies such as the United States and Germany.

In clinical guidelines, however, LAAO still has a class 2b indication and is primarily recommended for those patients who have survived or are deemed at risk for life-threatening bleeding in the European Society of Cardiology guidelines of 2012 and 2016.[2] Evidence for the benefits of LAAO in this population only came from small registries such as the ASAP trial (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology), that showed >70% lower stroke rate in 150 patients with WATCHMAN compared with expected if OAC would have been used.[3] The prospective multicenter, multinational EWOLUTION registry (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) was designed to obtain periprocedural and outcome data over a 2-year time frame from >1000 patients with nonvalvular AF at high risk for stroke in everyday clinical practice outside of controlled trials.[4] Periprocedural outcome data showed a high implant success with low adverse events rates, while the 1-year interim analysis showed promising outcomes for efficacy and safety.[5,6] The present article reports on the complete 2-year follow-up data for the entire patient cohort. Overall safety and efficacy are presented, as well as for subgroups at very high risk for stroke and bleeding including patients with prior ischemic and hemorrhagic stroke and those with a prior major bleeding.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The outline of the study has been described in detail in the design article[4] and the first report on periprocedural outcomes[5] and 1-year outcome data.[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. Boston Scientific Corporation provided funding for the study. In brief, EWOLUTION was designed as a multicenter, prospective, nonrandomized cohort study aiming to include over 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 when 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 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 and thrombus on the device, and annual follow-up visits. All data collection and adverse event reporting were performed directly by the individual sites and captured in a standardized central database. Adverse event adjudication was based on ISO 14155 and the 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 (Bleeding Academic Research Consortium) criteria,[7] aligning with definition of major bleeding (which includes fatal and life threatening) 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 data and events were adjudicated and entered into the central database by the local investigators. Events and relevant source documents

were additionally reviewed by the Sponsor Medical Safety Group. The Medical Safety Group includes physicians with expertise in Electrophysiology and Cardiology, as well as other healthcare professionals with the necessary therapeutic and subject matter expertise to evaluate the events. Centers were required to provide additional information in case of disagreement. At study end, the adjudication by the investigators and the Medical Safety Group was 100% aligned. All centers were also monitored by an outside contract research organization on an ongoing basis. One center with only one patient enrolled was only visited once. All other centers received onsite monitoring between 2 and 5 times depending on number of patients enrolled and compliance review. Data review in the study database was performed for 100% of forms. Source data verification was performed at onsite visits and for relevant adverse events source documents were requested at the sites and reviewed remotely. These included at a minimum all-cause death, all strokes, transient ischemic attack (TIA), systemic embolism (SE), and all adverse events occurring within 7 days of the implant, regardless of whether event was judged serious and whether related or not to the device/procedure. Boston scientific provided supervision over the trial and the source data (E. Vireca), as well as statistical support. The 2 coauthors employed by Boston Scientific (E. Vireca and Dr Stein) were involved in trial design and review of the article. Individual sites reported on transesophageal echocardiography (TEE) findings. TEE images from the implant and first follow-up were sampled in 25% of sites and about 10% of patients by the sponsor, to rule out discrepancies with the database content. As no irregularities were detected no additional review was performed.

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/TIA/SE, and the sample size was based on a 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 a number of events per 100 patient-years. The individual patient annual risk for stroke and bleeding was recorded based on each subject's CHA_2DS_2-VASc (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; left ventricular ejection fraction) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score and then the average risk score for the study population was calculated. Annual risk of stroke and bleeding was then extrapolated from published risk score literature[10,11] to determine relative risk reductions (RRRs). For stroke, TIA, and SE, this was compared with patients not using any form of anticoagulation matched for CHADS-VASc score,[10] while for bleeding this was compared with patients using VKAs matched for HAS-BLED score.[11] Mortality rate is calculated via the Kaplan-Meier method to account for censoring. Rate of device-related thrombus (DRT) is calculated as a proportion of patients who had LAA imaging available. *P* values are based on log-rank tests for time-to-event analysis and Fisher exact test for binomial proportions. Three separate higher-risk cohorts were defined as being patients with a history of stroke or TIA, patients with a history of hemorrhagic stroke and patients with a history of major bleeding. These cohorts were also compared against the same historical control data.

RESULTS

Patient Characteristics

Enrollment opened in October 2013 and was completed in May 2015. Details of the periprocedural outcomes and 1-year interim data were published previously.[5,6] A total of 1020 subjects underwent a WATCHMAN implant procedure in a total of 47 centers in 13 countries (Figure 1). The inclusion rate ranged from 1 to 86 enrolled subjects per site, and at least 39/47 sites (83%) enrolled consecutive patients, with no apparent differences about occurrence of SAEs (P=0.253).[6] Seventy-eight percent of the implanting physicians had <2 years of experience with the WATCHMAN device and performed 75% of the study procedures. The median follow-up in the study was 732 days (interquartile range: 677–757).

Baseline demographics and risk factors are summarized in Table 1. Baseline CHA_2DS_2-VASc was 4.5±1.6 (historic stroke risk of 7.2% per patient-years in the absence of anticoagulation therapy[10]) and HAS-BLED 2.3±1.2 (historic bleeding risk of 5.0% per patient-years in the presence of VKA therapy[11]). A HAS-BLED score ≥3 was present in 40% of patients. Mean age was 73.4±8.9 years, prior ischemic stroke/TIA was present in 30.5%, 15.1% had previous hemorrhagic stroke, and 31.3% had a history of major bleeding; 72.2% of patients were deemed contraindicated for OAC. Data were not always provided on the reasons for a contraindication. It is possible that some of these patients may have had relative versus absolute contraindications to the drugs, but nevertheless, they were deemed unsuitable for short- or long-term OAC treatment at the time of implant.

Mortality During 2-Years Follow-Up

Of the 1020 patients that underwent a WATCHMAN LAAO implant procedure, 161 (Kaplan-Meier event rate 16.4%, CI, 13.8%–19.3%) died as depicted in Figure 1. A list of the reasons for death is provided in Table 2. Noncardiovascular reasons were miscellaneous and most common (7.4%), while 4.5% had a cardiovascular reason (most common heart failure), 1.0% had a fatal bleeding, and 2.9% remained unknown. In the 10 patients with death because of bleeding, 6 were gastrointestinal while the other 4 were cerebral. These patients were most commonly on dual antiplatelet therapy (DAPT; 7), while 1 was on single antiplatelet therapy (SAPT), 1 on VKA, and 1 was using no anticoagulation at the time of the event.

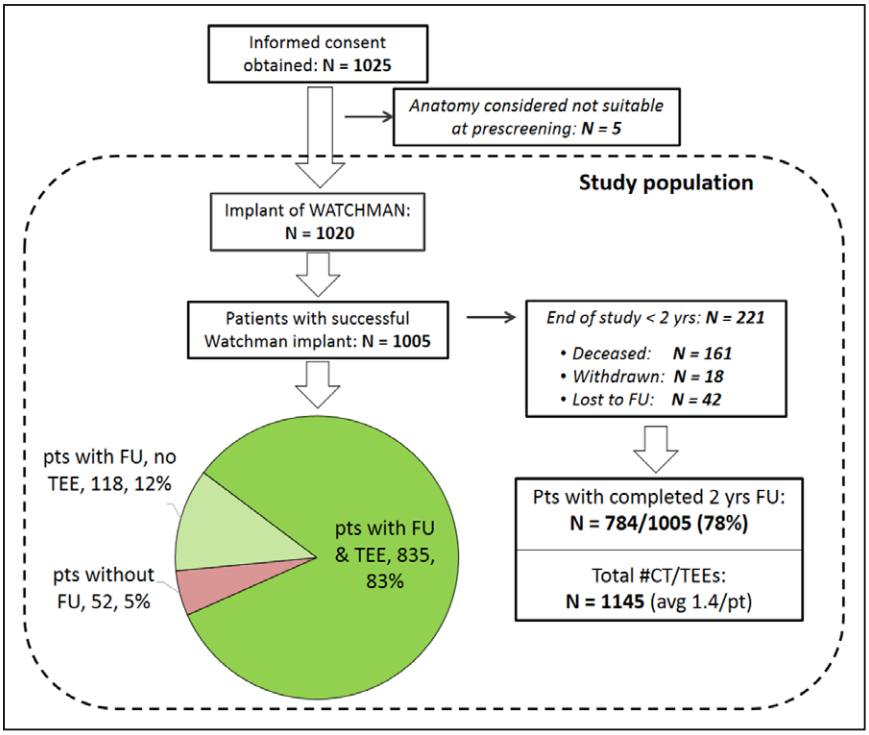

Figure 1. Flowchart of the patients in the EWOLUTION study (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology).
CT indicates computed tomography; FU, follow-up; pts, patients; TEE, transesophageal echocardiography; and yrs, years.

Antithrombotic Regimen

At hospital discharge after successful WATCHMAN LAAO, 16% of patients were using VKA, 11% NOAC, 60% DAPT, 7% SAPT, and 6% no anticoagulation at all (Figure 2A). After the first discontinuation of anticoagulants only 8% remained on VKA or NOAC, while 26% were on DAPT, 58% on SAPT, and 8% were using nothing. The median (interquartile range) time to discontinue OAC was 68 (50–102) days, for DAPT it was 158 (74–195) days. At the final follow-up of 2 years, 8% of active patients were still on OAC, 7% were on DAPT, 71% were on SAPT, while 14% were not using any anticoagulant. The timing of conversion to a final treatment of SAPT or nothing is shown in Figure 2B: 46% had switched at 6 months, 75% at 1 year, and 95% at 2 years. Table 3 shows the antithrombotic medication for the higher-risk cohorts with prior ischemic and hemorrhagic stroke and major bleeding.

The use of different drug types was fairly consistent for all subgroups directly after the implant. Only in patients with prior hemorrhagic stroke less patients were on OAC and more were on SAPT/nothing. At 2 years, in all cohorts, the use of OACs and DAPT was only around 15%.

Device Thrombus

The main reason to use any type of anticoagulant after a WATCHMAN implant is the risk of DRT, which could in turn be related to thromboembolic events. In the 835 patients with imaging of the LAA, a total of 34 cases of DRT (4.1%) were observed with an average 1.4 per patient TEE or computed tomography imaging procedures. Of these 34 cases, 31 were observed at first imaging usually within 90 days after the procedure (median 54 days, interquartile range 42–111). The majority (21, 2.5%) were nonmobile laminar type of thrombus, some (9, 1.1%) were mobile and pedunculated, and a few (4, 0.5%) were not specified. No statistical relation could be found between DRT and type of anticoagulation (Figure 3), although only patients on NOAC, VKA, or DAPT had laminar nonmobile types, and mobile types were seen in all but VKA patients.

Treatment of DRT was initiated in 21/34 of patients while no action was taken in the remaining 13. Resolution was confirmed in 18/21 of treated patients and 9/13 of untreated. The outcome of 6 DRT is unknown, as the patients had no LAA imaging performed after thrombus was discovered, however, no thromboembolic event occurred in these patients. One DRT was not resolved at the time of study end, the thrombus was detected at first TEE (90 days) while on warfarin and treatment remain unchanged throughout the study, but did not solve the thrombus.

One patient experienced a major gastrointestinal bleeding because of the medication change (rivaroxaban 15 mg added to preexisting DAPT), which resolved within 10 days.

In all patients with thrombus detected at routine LAA imaging, there were no subsequent reports of adverse events such as stroke, TIA, or embolism during a median follow-up period of 21 months (interquartile range, 16–23) following DRT detection. In 21 patients with stroke in whom LAA imaging was performed, 1

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (N=1025)
Contraindicated	72.2% (740/1025)
Age at time of consent, y	
Mean±SD	73.4±8.8
Age >75	50.7% (520/1025)
Sex (Female)	40.1% (411/1025)
CHA_2DS_2-VASc score	4.5±1.6
<1	1.8% (1811025)
2–3	25.2% (258/1025)
≥4	73.1% (749/1025)
HAS-BLED score	2.3±1.2
<3	60.0% (615/1025)
≥3	40.0% (410/1025)
NYHA class	
I	10.3% (36/348)
II	55.5% (193/348)
III	32.2% (112/348)
IV	2.0% (7/348)
CHF	34.1% (350/1025)
LVEF ≤40%	13.2% (135/1023)
Vascular disease	42.2% (433/1025)
Abnormal renal function	15.8% (162/1025)
Abnormal liver function	4.3% (44/1025)
Hypertension	86.6% (888/1025)
Diabetes mellitus	29.7% (304/1025)
Prior major bleeding or predisposition to bleeding	38.6% (396/1025)

CHA_2DS_2-VASc indicates CHF, hypertension, 75 y of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65–74 y of age, female; CHF, congestive heart failure; EWOLUTION, Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

Table 2. Summary of Fatal Events at 2-Year Follow-Up

Type of Death	Total No. of Events
Bleeding	10 (1.0%)
Gastrointestinal bleeding	6
Hemorrhagic stroke	2
Cranial bleed	1
Subdural hematoma	1
Cardiovascular	46 (4.5%)
Heart failure	19
Myocardial infarction	5
Cardiac arrest	4
Cardiogenic shock, low-output syndrome	4
Pulmonary embolism	3
Aortic dissection	2
Cerebral air embolism*	1
Aortic stenosis	1
Peripheral vascular disease	1
Ventricular fibrillation	1
Ventricular tachycardia	1
Noncardiovascular	75 (7.4%)
Pulmonary	18
Systemic infection	14
Cancer	11
Multiorgan failure	10
Gastrointestinal	8
Renal	7
Integumentary	3
Neurological	1
Physical trauma	1
Musculoskeletal	1
Immune	1
Unknown	30 (2.9%)
Total	161 (15.8%)

*Related to implant of the device.

instance of DRT was observed. No significant difference in annual rates of stroke/TIA/SE was observed in patients with or without DRT (DRT 1.7 versus no-DRT 2.2, P=0.805).

Bleeding Events

During the 2-year follow-up, a nonprocedural major bleeding was observed in 47 patients, of which 10 were fatal events. Compared with a historical bleeding risk of 5.0 with the EWOLUTION distribution of HAS-BLED scores, the actual bleeding rate of 2.7/100 patient-years conferred a 46% RRR (Figure 4A). In patients with HAS-BLED <3 (Figure 5) the reduction was slightly larger (612 patients, historic 3.6 versus actual 1.8 per 100 patient-years, RRR 50%) than in those with HAS-BLED of 3 or more (408 patients, historic 7.1 versus actual 4.2 per 100 patient-years, RRR 41%).

A propensity-adjusted analysis was performed of the patients prescribed DAPT postimplant to assess the impact of DAPT duration on bleeding and thromboembolic events. The cohort was separated in patients discontinuing DAPT ≤105 days (189 patients) versus those that switched >105 days (379 patients). Propensity matching was performed for CHA_2DS_2-VASc score, HAS-BLED score, total number of partial device recaptures across all attempted devices, number of full device recaptures, left ventricular ejection fraction

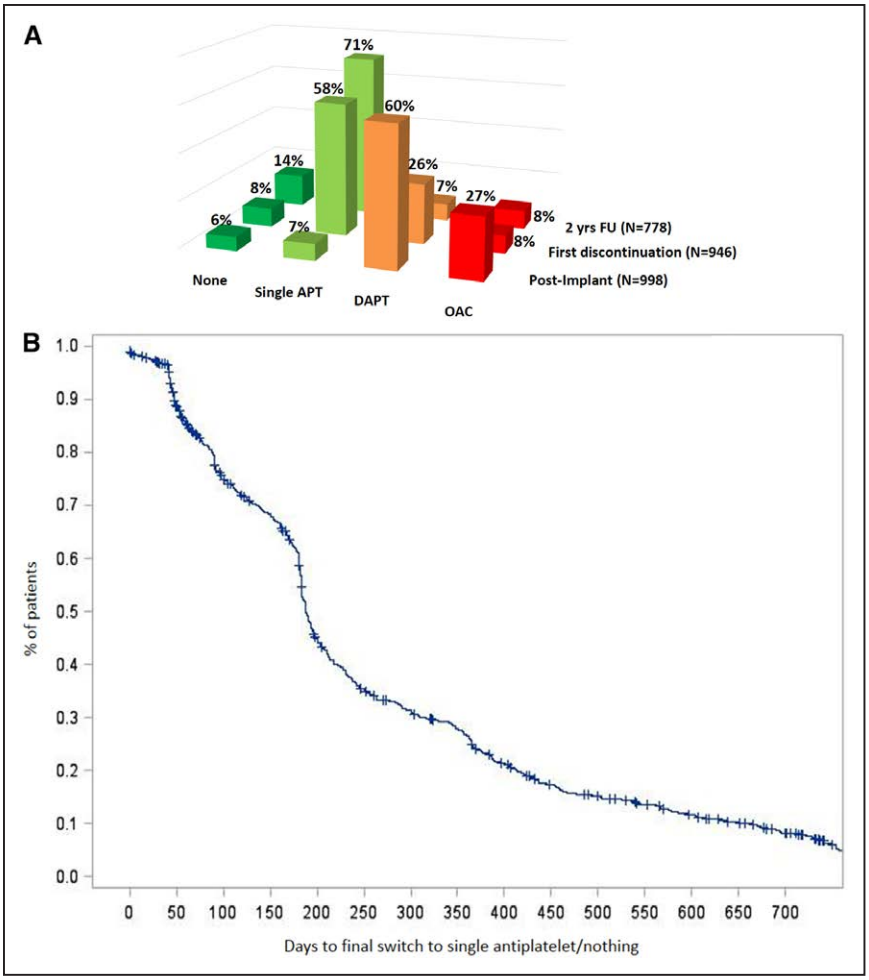

Figure 2. Overview of anticoagulation use during the EWOLUTION study (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology).
A, Anticoagulation after WATCHMAN left atrial appendage occlusion (LAAO) during 2-y follow-up; (**B**) timing of final switch to single antiplatelet therapy (SAPT) or nothing after WATCHMAN LAAO. DAPT indicates dual antiplatelet therapy; FU, follow-up; and OAC, oral anticoagulation.

(<30%, 30%–50%, or >50%), AF pattern (paroxysmal, persistent, permanent, paced, sinus rhythm, and other), and postimplant LAA seal (complete seal, jet size ≤5 mm, or jet size >5 mm). In patients with early lowering of anticoagulation, propensity-adjusted bleeding rates were lowest at 1.1%, while bleeding rates were higher for late discontinuation with 3.5%, while there was no difference in the combined rates of ischemic stroke, TIA, SE, and DRT in the 2 cohorts (3.9% and 3.7%). Although this propensity-adjusted analysis did not reach statistical significance (*P*=0.122), it suggests that a shorter DAPT duration may be as safe as a longer course, and it could be a preferred strategy in very high-risk patients to minimize the risk of bleeding events.

Stroke, TIA, and SE

The event rates for ischemic stroke, TIA, and SE can be seen in Figures 6A and 7A. The complete cohort had a historical ischemic stroke risk of 7.2/100 patient-years and composite risk of ischemic stroke/TIA/SE of 10.1/100 patient-years. The observed stroke rate was

Table 3. Summary of Risk Factors and Postimplant Medications for the Entire EWOLUTION Population and the 3 Higher-Risk Cohorts: Prior Stroke/TIA, Prior Hemorrhagic Stroke, Prior Major Bleeding

Group	N	CHA_2DS_2-VASc	HAS-BLED	Postimplant meds		
				OAC	SAPT/None	DAPT
EWOLUTION full cohort	1020	4.5	2.3	27%	14%	60%
Hx ischemic stroke/TIA	311	5.5	2.6	35%	15%	50%
Hx hemorrhagic stroke	153	5.4	2.8	11%	27%	62%
Hx major bleeding	318	4.8	3.2	15%	17%	67%

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, 75 y of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65–74 y of age, female; DAPT, dual antiplatelet therapy; EWOLUTION, Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; Hx, history; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation; SAPT, single antiplatelet therapy; and TIA, transient ischemic attack.

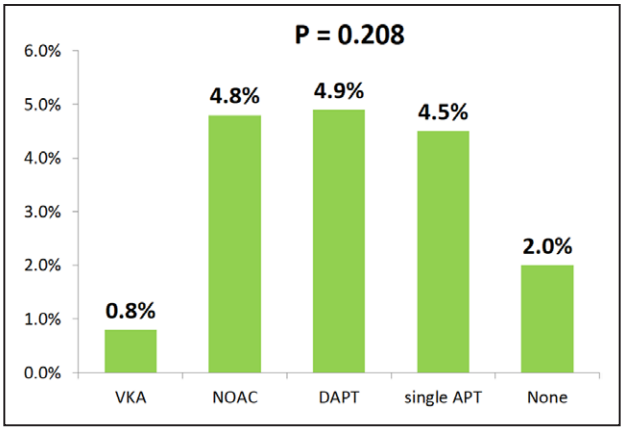

Figure 3. Rate of device-related thrombus by anticoagulant use.
(D)APT indicates (dual) antiplatelet therapy; NOAC, novel oral anticoagulation; and VKA, vitamin K antagonist (warfarin).

1.3/100 patient-years, conferring a reduction of 83%. For the combined end point, ischemic stroke/TIA/SE, the observed rate was 2.0/100 patient-years, conferring a risk reduction of 80%. Of interest, when the cohort was divided in those with lower (n=118) and those with higher risk (n=902), no ischemic strokes, TIA, or SE were observed in any patient with a CHA_2DS_2-VASc score of <3 (Figure 8). In the group with a CHA_2DS_2-VASc score of 3 or more, the ischemic stroke rate was 82% lower than expected (7.9 versus 1.4/100 patient-years), while the composite of ischemic stroke/TIA/SE was 79% lower than expected (11.1 versus 2.3 per 100/patient-years).

Overall, 46 thromboembolic events occurred in 35 patients, of which 22 were ischemic stroke (5 disabling), 23 were TIA, and 1 was an SE. At the time of the first thromboembolic event, 17% were on (N)OAC, 26% on DAPT, 43% on SAPT, and 14% on no medications. In 43% of the index events, anticoagulation was intensified by starting a (N)OAC or adding (stronger) APT, while in the remainder the type of anticoagulation remained unchanged (48%) or was lowered/stopped (9%) despite the event, possibly to prevent hemorrhagic transformation. Nine patients had subsequent events, regardless of intensifying (4), keeping (3), or stopping anticoagulation (2). Two patients even had 3 events, despite remaining on DAPT in one, and switching from OAC plus acetylsalicylic acid (ASA) to OAC plus clopidogrel in the other. No significant relationship could be established between the events or the type of drug use.

Outcomes in Higher-Risk Patient Subgroups

Specific subgroups of interest were patients with a history of either stroke/TIA, or hemorrhagic stroke, or major bleeding. Prior stroke/TIA was present in 311 of the 1025 patients (30.5%) and compared with the rest of the study population was less common in the elderly over 65 years (76.0% versus 83.8%, *P*=0.004), while CHA_2DS_2-VASc of 5.5±1.4 and HAS-BLED scores of 2.6±1.3 were high. The observed ischemic stroke rate was 2.3/100 patient-years (76% less than historic controls), with a rate of ischemic stroke/TIA/SE of 3.9/100 patient-years (71% less than historic controls). Nonprocedural major bleeding rate of 3.2/100

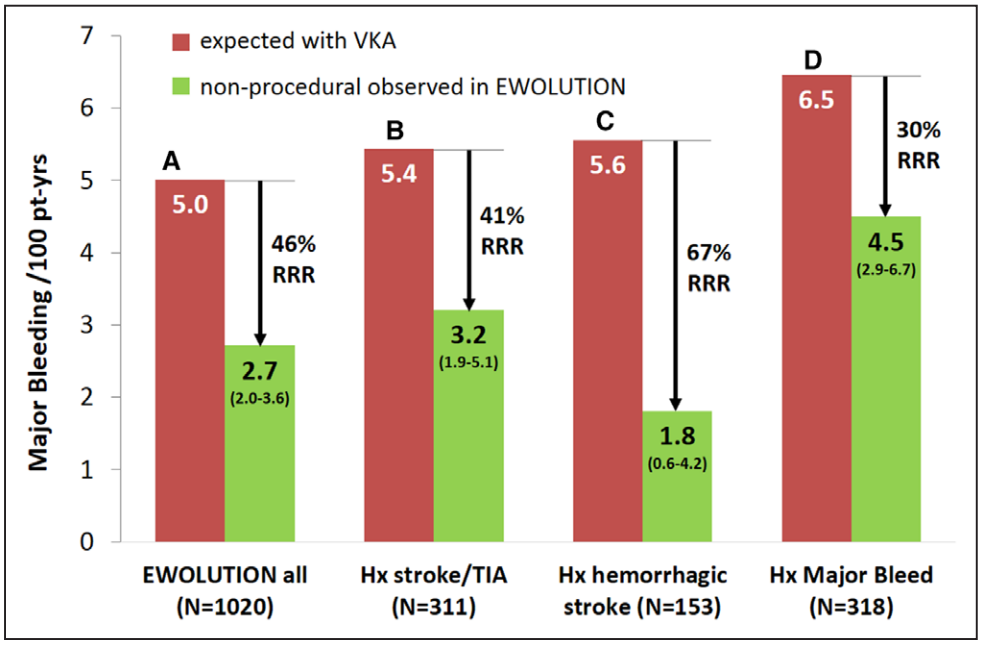

Figure 4. Major bleeding rates for the overall population and high risk subgroups.
A, Overall population; (**B**) patients (pts) with history of stroke/transient ischemic attack (TIA); (**C**) pts with history of hemorrhagic stroke; and (**D**) pts with history of major bleed. EWOLUTION indicates Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; Hx, history; RRR, relative risk reduction; and VKA, vitamin K antagonist.

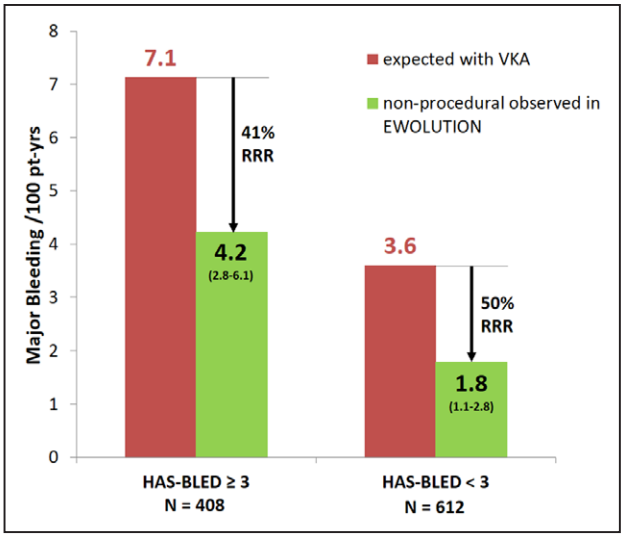

Figure 5. Major bleeding after WATCHMAN left atrial appendage occlusion (LAAO) by hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) score censored at 3.
EWOLUTION indicates Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; RRR, relative risk reduction; and VKA, vitamin K antagonist.

patient-years was 41% lower than expected (Figures 4B, 6B, and 7b).

Compared with the rest of the population, the patients with a prior hemorrhagic stroke (n=153) were more often male (69.7% versus 58.2%, *P*=0.008) and were older (age>65 years, 91.0% versus79.8%, *P*=0.001), had less LV dysfunction (7.1% versus 14.3%, *P*=0.014), less vascular disease (33.5% versus 43.8%, *P*=0.0174), and less prior major bleeding/predisposition to bleed (25.2% versus 41.0%, *P*=0.0002). This cohort also had a high CHA_2DS_2-VASc (5.4±1.2) and HAS-BLED score (2.8±0.9). Nevertheless, the observed rates for stroke, embolism, and bleeding were as low as 1.8/100 patient-years (81% RRR), 2.6/100 patient-years (80% RRR), and 1.8/100 patient-years (67% RRR) (Figures 4C, 6C, and 7C).

The final cohort to discuss is the one with 318 patients with a prior major bleeding. Their CHA_2DS_2-VASc score was 4.8 with a HAS-BLED of 3.2, conferring a very high risk of both stroke and bleeding. At 2 years, actual stroke rate was 1.2/100 patient-years (85% RRR), stroke/TIA/SE rate was 1.9/100 patient-years (82% RRR), while bleeding occurred at a rate of 4.5/100 patient-years (30% RRR; Figures 4D, 6D, and 7D).

DISCUSSION

EWOLUTION is the largest prospective real-world registry on WATCHMAN and the only study in its kind reporting on 2-year follow-up outcomes of LAA closure to date. The results reinforce the data observed after 1-year follow-up,[6] showing a low overall stroke, TIA, and SE rate, which was 80% lower than predicted based on historic data in patients with a similar risk profile not using anticoagulation. When we compare the outcome data for stroke to prior WATCHMAN trials, such as PROTECT-AF, PREVAIL, and the CAP registries, these are completely in line and consistently low.[1]The discontinuation of DAPT and (N)OAC in 85% of the patients at 2 years was accom-

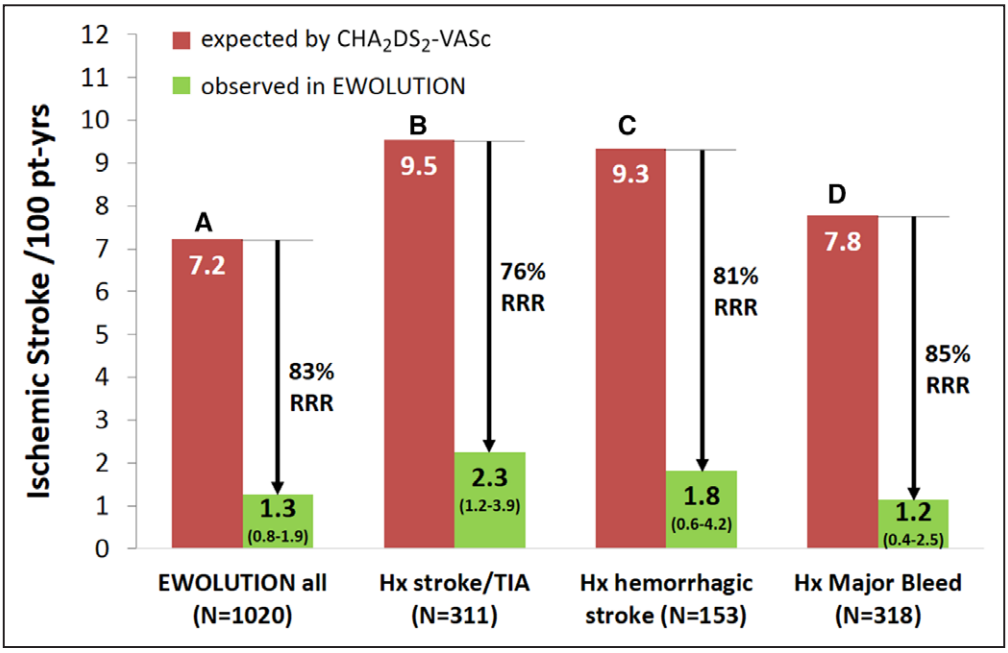

Figure 6. Ischemic stroke rates for the overall population and high risk subgroups.
A, Overall population; (**B**) patients (pts) with history of stroke/transient ischemic attack (TIA); (**C**) pts with history of hemorrhagic stroke; and (**D**) pts with history of major bleed. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, 75 y of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65–74 y of age, female; EWOLUTION, Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; Hx, history; and RRR, relative risk reduction.

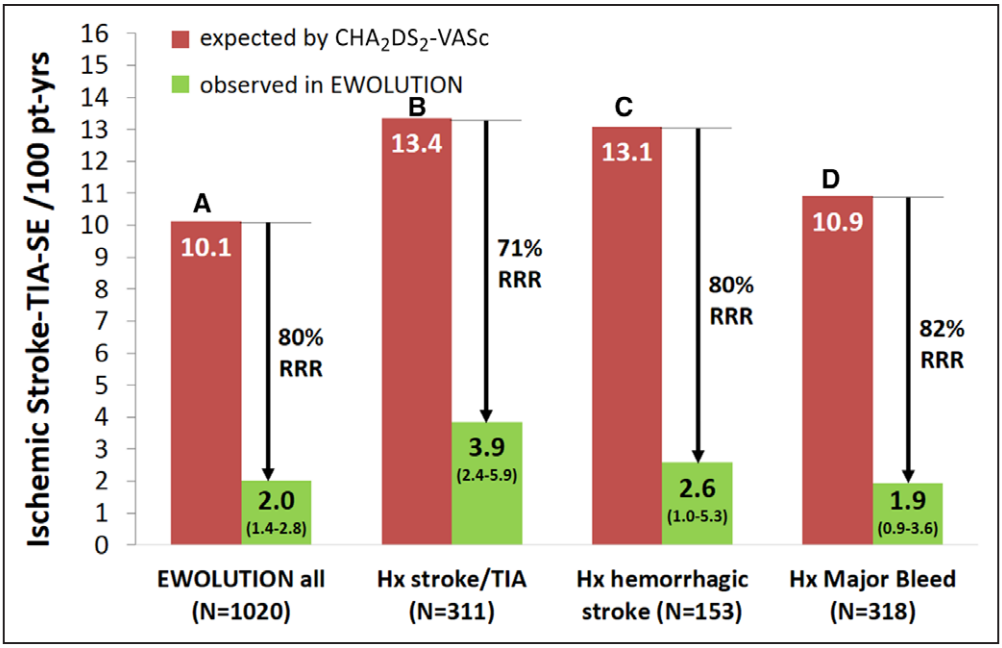

Figure 7. Ischemic stroke/transient ischemic attack (TIA)/systemic embolism (SE) rates for the overall population and high risk subgroups.
A, Overall population; (**B**) patients (pts) with history of stroke/TIA; (**C**) pts with history of hemorrhagic stroke; and (**D**) pts with history of major bleed. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, 75 y of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65–74 y of age, female; EWOLUTION, Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; Hx, history; and RRR, relative risk reduction.

panied by a 46% lower major bleeding rate compared with historic controls. Not surprisingly for this higher-risk patient population contraindicated for anticoagulation, 161 patients died (15.7%), 1.8% withdrew, and 4.1% of patients were lost to follow-up during the 2-year study period. There were no late events like secondary leakage, device embolization, or other events associated with the device. In the AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment),[12] warfarin contraindicated AF patients with a lower CHA_2DS_2-VASc score had a stroke rate of 1.6% on apixaban, while in the recent GARFIELD registry (Global Anticoagulation Registry in the Field),[13] AF patients with a CHA_2DS_2-VASc of 3.0 showed a stroke rate of 1.3 per 100 patient-years. Despite differences in design and population, these outcomes are comparable to EWOLUTION, and show that in this real-world cohort of all-comers, WATCHMAN LAAO is a very effective and safe alternative for prevention of thromboembolic events in patients with nonvalvular AF at high risk for stroke and bleeding.

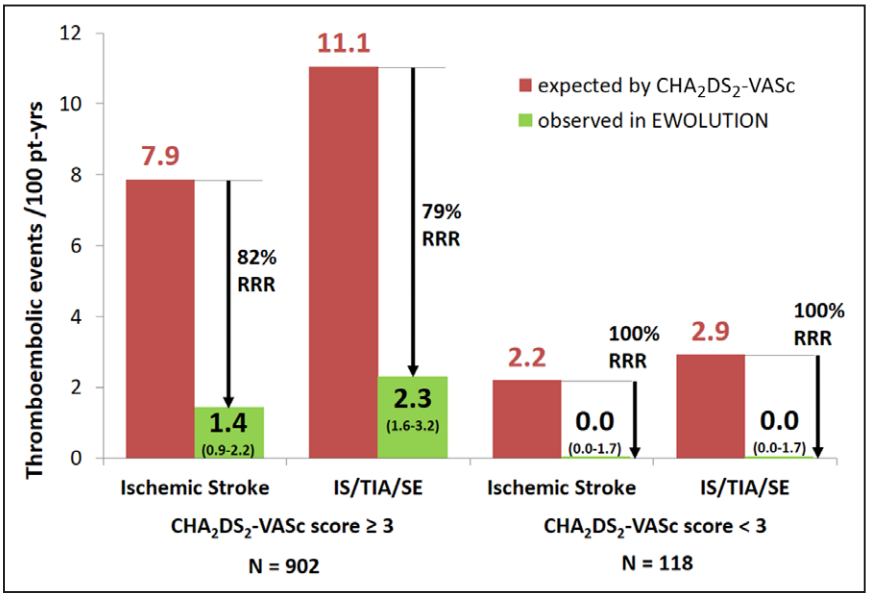

Figure 8. Overall rates for stroke, transient ischemic attack (TIA), and systemic embolism (SE) by congestive heart failure, hypertension, 75 y of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 y of age, female (CHA_2DS_2-VASc) score censored at 3.
EWOLUTION indicates Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology.

Anticoagulation and Thromboembolism

The evidence that WATCHMAN LAAO can be a safe alternative to OAC comes from the randomized controlled trials PROTECT-AF and PREVAIL showing noninferiority for stroke, TIA, and SE in patients that were tolerant to OAC treatment but had reason to seek for an alternative in the long-term.[1] The patients in the LAAO arm used ASA and warfarin for 45 days, then DAPT until 6 months, and then ASA for life. In real-world populations, LAAO is usually sought as an alternative dictated by necessity in patients with a contraindication for OAC, which is the only recommended indication in the European Society of Cardiology guidelines.[2] Such patients cannot adopt a harsh anticoagulation scheme and usually end up using only APT or nothing at all. In EWOLUTION, 72% of patients were deemed unsuitable for OAC and switched to (D)APT or nothing immediately after WATCHMAN implant. After 3 to 6 months, 66% changed to SAPT or nothing, while at study end 84% of the active patients were using SAPT or nothing. Despite this lower anticoagulation scheme, outcomes for thromboembolism were favorable and preserved over time. Based on the data from EWOLUTION, the recommended anticoagulation scheme after WATCHMAN implant outside of the United States has been lowered to a minimum of 3 months of DAPT and ASA up to 1 year.

The main reason to eliminate OAC and further decrease APT is the evidence that this has a positive effect on major bleeding rates. In post hoc analyses of PROTECT-AF, PREVAIL, and the CAP registries, it was observed that after discontinuation of warfarin at 45 days, bleeding rates in the WATCHMAN arm were only half of those in the warfarin arm, and dropped another 50% after discontinuation of DAPT.[14] As reduction of bleeding events is a major goal of WATCHMAN LAAO treatment, it seems desirable to minimize any form of anticoagulation. Conversely, reduction of the periimplant anticoagulation could adversely affect DRT formation, which is feared as possible hallmark of embolic events. In a recent meta-analysis,[15] an average of 3.7% DRT was observed with WATCHMAN and AMULET devices, with no clear predictors or underlying mechanisms. In PROTECT-AF, the rate of WATCHMAN DRT under optimal anticoagulation was 5%, while a recent reevaluation of the TEE data suggested a relationship between stroke and DRT.[16] In the French RELAXAO registry (Registry on Real-Life Experience With Left Atrial Appendage Occlusion),[17] DRT was observed in up to 7.7%, while 4 patients with DRT also had later stroke and 1 patient with stroke also had later DRT. In EWOLUTION, DRT in 4.1% of patients was never related to later stroke, and only 1 patient with a stroke was found to have a DRT. Of note, in EWOLUTION most DRT were of the nonmobile laminar type which may account for the lower embolic propensity compared with the other studies.[16,17] No relationship was observed between intensity of anticoagulation during the first 3 to 6 months and the presence of DRT. Similar small cohort registries observed similar favorable outcomes with a shorter period of dual antiplatelet [(D)APT] (ie, 6 weeks) or single APT [(S)APT] right after implant particularly in patients with high bleeding risk.[18,19] Future randomized studies are needed to show if APT can even be lower and shorter with both low thromboembolic and low DRT rates.

Patients with AF who have suffered a prior ischemic stroke constitute a special population as they are the living proof of the increased thromboembolic risk. Patients with AF and prior hemorrhagic stroke are living proof of the risks involved in classic stroke prevention, especially if it occurred while using anticoagulants. Although there may be competing risks that are not treated by LAAO, both patient categories could benefit from LAAO as alternative or adjunctive therapy to anticoagulation. In EWOLUTION, 311 patients had history of ischemic stroke or TIA and 153 had history of hemorrhagic stroke. Despite having a high stroke risk, the actual stroke rate in both groups was very low and in line with the total cohort. Interestingly, in the ischemic stroke cohort, slightly more patients were on (N)OAC therapy in the first period after implant, although most of them also changed to APT/nothing over time. The stroke reduction was slightly lower than for the total population, which could be because of competing stroke risk factors. It seems conceivable that in this cohort a future hybrid strategy of LAAO with low dose (N)OAC could combine the best of both worlds and reduce stroke rates even further.

In the hemorrhagic stroke cohort, for obvious reasons (N)OAC use after implant and during follow-up was much lower than for the total population, while stroke rate reduction was the same and major bleeding rate was 67% less than historic data. In this patient population, the optimal stroke prevention strategy with anticoagulation is the topic of ongoing debate among neurologists. Although recurrence of hemorrhagic stroke can be up to 9%, (N)OAC therapy is often reinstated after recovery of the index event.[20] Conversely, many patients are prescribed with APT or nothing as in some forms of cerebral disease the risk of recurrence is considered too high. Randomized studies like APACHE-AF (Apixaban Versus Antiplatelet Drugs or No Antithrombotic Drugs After Anticoagulation-Associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation)[21] are ongoing to determine the efficacy and safety of NOAC or ASA strategies. Nonetheless, some patients seem to become exposed to a bleeding risk again, while others may remain unprotected for ischemic stroke. Recent propensity-matched data from Nielsen-Kudsk et al[22] suggested that the combination of

LAAO with SAPT therapy had a strikingly lower stroke risk as well as hemorrhagic stroke recurrence, compared with conventional therapy ranging from (N)OAC to APT to nothing. More evidence in this population will be coming from the randomized STROKECLOSE study (Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage) that is ongoing.

Bleeding and Anticoagulation

In EWOLUTION actual major bleeding rates of 2.7 per 100 patient-years were almost half compared with historic data based on HAS-BLED scores with nonvalvular AF patients on warfarin therapy.[11] Bleeding risk was highest during the more intense phase of OAC. Although the low major bleeding rate appears favorable, it seems desirable to achieve even lower bleeding rates by further diminishing the use of anticoagulants. Interestingly, an analysis of the DAPT cohort in EWOLUTION showed that early DAPT discontinuation preserved the stroke rate reduction, while lowering the rate of bleeding at 1 year by 69%.[23] However, aside from the perceived risk of DRT, one should realize that there are competing comorbidities necessitating the concomitant use of even DAPT in many patients.

In view of the favorable results on stroke reduction with lower bleeding risks in the large NOAC against warfarin trials, some argue that there is a need to repeat randomized trials against LAAO. However, especially in those with a contraindication to anticoagulation that currently constitute the main LAAO population, there are ethical and practical considerations that make this difficult. In the AVERROES trial,[12] AF patients with a contraindication (60%) or discontinued use of warfarin (40%) showed higher stroke reduction by apixaban with similar bleeding risk compared with ASA. However, the recent NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source)[24] in patients without AF and stroke of unknown origin was terminated prematurely because rivaroxaban had an excessive bleeding rate compared with ASA. In EWOLUTION, major bleeding rates were low, although there was a difference between subgroups. Patients with prior hemorrhagic stroke had a 67% lower rate than expected and had the lowest use of (N)OAC and DAPT, while patients with prior ischemic stroke had a 41% reduction but more patients on (N)OAC and DAPT. Patients with a history of a major bleeding had a somewhat protracted risk reduction of 30% compared with the highest historic HAS-BLED score in the study. Some argue that the inability to reduce bleeding by continued use of ASA is the Achilles heel of LAAO therapy. However, by their nature, some bleeding conditions will continue to cause events even without any use of OACs, and any reduction in events should be considered favorable. Current studies do not provide evidence of bleeding burden reduction by using APT instead of (N)OAC, but a strategy of the lower-the-better seems the most logical option.

Limitations

Although this is a prospective registry with outside monitoring for data completeness, the clinical indications, clinical follow-up, and imaging were center dependent and the responsibility of local investigators. The lack of a control arm limits the full assessment of therapy benefit in this patient population. Although the indication to install stroke prevention in daily practice is also based on CHA_2DS_2-VASc and HAS-BLED outcome data in historical patient cohorts, direct comparison to the current findings for WATCHMAN LAAO should be done with caution. The continued use of any form of OAC in 92% of the patients may also play a role in stroke/TIA/SE prevention.

Conclusions

The final 2-year follow-up of EWOLUTION shows that WATCHMAN LAAO is an effective and safe alternative to OAC in a population of nonvalvular AF patients at high risk for stroke and bleeding. The favorable effect was consistently observed even in patients with prior ischemic or hemorrhagic stroke and patients with a history of major bleeding, in the presence of a much lower use of anticoagulation compared with prior randomized controlled trials on WATCHMAN, as in this cohort 73% were deemed unsuitable to use (N)OAC.

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Dr Boersma reports fees to the Cardiology Department from Boston Scientific, Medtronic, outside the submitted work. Dr Ince is a proctor for Boston Scientific and received personal fees from Boston Scientific, outside the submitted work. Dr Schmidt reports personal fees from Boston Scientific and St Jude Medical, outside the submitted work. Dr Betts reports personal fees from Boston Scientific, outside the submitted work. Dr Mazzone is a proctor for Boston Scientific and consultant for St Jude Medical. Dr Grygier is a Boston Scientific advisory board member, proctor, receives honoraria for lectures and is a proctor for Medtronic. E. Vireca and Dr Stein are employees and shareholders at Boston Scientific. Dr Bergmann reports personal fees from Boston Scientific, St Jude Medical, Biosense Webster and Johnson & Johnson, outside the submitted work. Dr Sievert reports personal fees from Abbott, Aptus, Atrium, Biosense Webster, Boston Scientific, Carag, Cardiac Dimensions, CardioKinetix, CardioMEMS, Cardiox, Celonova, CGuard, Coherex, Comed B.V., Contego, Covidien, CSI, CVRx, ev3, FlowCardia, Gardia, Gore, GTIMD Medical, Guided Delivery Systems, Hemoteq, InSeal Medical, InspireMD,Kona Medical, Lumen Biomedical, Lifetech, Lutonix, Maya Medical, Medtronic, Occlutech, pfm Medical, Recor, Trireme, Trivascular, Valtech, Vascular Dynamics, Venus Medical, Veryan, Vessix, outside the submitted work; and he reports stock options in Cardiokinetix, Access Closure, Coherex, SMT, outside the submitted work. The other authors report no conflicts.

APPENDIX

The following investigators and institutions participated in the EWOLUTION study. Investigators are listed after centres in alphabetic order: Al Qassimi Hospital: Arif Al Nooryani, Asklepios Klinik Saint Georg: Felix Meincke, Asklepios Klinik Weissenfels: Thomas Fiedler, Ospedale di Cirie: Gaetano Senatore, Beaumont Hospital: David Foley, Cardioangiologisches Centrum Bethanien: Boris Schmidt, CHRU de Lille: François Brigadeau, CHU Grenoble Hopital Michallon: Pascal Defaye, CHU Henri Mondor: Emmanuel Teiger, CHU La Timone Hospital: Jean-Louis Bonnet, Dominikus- Krankenhaus: Christof Wald, Elisabeth Krankenhaus Essen: Thomas Schmitz, Erasmus MC - University Medical Center Rotterdam: Tamas Szili-Torok, Evangelisches Krankenhaus Bielefeld: Wladimir Tschishow, Fondazione Centro San Raffaele: Patrizio Mazzone, Freeman Hospital: David Crossland, Herzkatheter Asklepios Wandsbek: Martin W. Bergmann, Hôpital Bichat: Alec Vahanian, Hospital Clinico Salamanca: Ignacio Cruz-Gonzalez, Hospitaux du Haut Leveque: Jean-Benoit Thambo, Johannes Gutenberg Universitaet Mainz: Tommaso Gori, John Radcliffe Infirmary Oxford II: Timothy Betts, King Fahed Medical City Prince Salman Cardiac Center: Faisal Al Smadi, Klinikum Neuperlach: Harald Mudra, Krankenhaus Barmherzige Bruder: Robin Molitoris, Medisch Centrum Leeuwarden: Richard Folkeringa, Medisch Spectrum Twente: Yorick Stevenhagen, NCN Nouvelles Cliniques Nantaises: Daniel Gras, Onze Lieve Vrouw Ziekenhuis: Tom De Potter, Ospedale Ferrarotto: Corrado Tamburino, Ospedale Sacro Cuore Don Calabria: Giulio Molon, Regional Vascular Center: Vladimir Protopopov, Royal Victoria Hospital: Mark Spence, University of Medical Sciences: Marek Grygier, Santa Maria: Eduardo Infante Oliveira, St. Antonius Ziekenhuis: Lucas Boersma, St. Katharinen Krankenhaus: Horst Sievert, State Cardiology Research Center: Evgeny Merkulov, State Research Institute of Circulation Pathology: Evgeny Pokushalov, Szpital Uniwersytecki: Adam Sukiennik, The Brompton Hospital: Tom Wong, Universitatsmedizin Greifswald: Mathias Busch, University Berlin, Charite Virchow Standort: Leif-Hendrik Boldt, University KH Bonn: Georg Nickenig, University Leipzig: Martin Neef, Vivantes Klinikum Am Urban: Hüseyin Ince, Vivantes Klinikum im Friedrichshain: Stephan Kische.

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