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CLINICAL RESEARCH
Atrial fibrillation: non-pharmacological management

Real-world clinical outcomes with a next-generation left atrial appendage closure device: the FLXibility Post-Approval Study

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Aims The FLXibility Post-Approval Study collected data on unselected patients implanted with a WATCHMAN FLX in a commercial clinical setting.

Methods and results Patients were implanted with a WATCHMAN FLX per local standard of care, with a subsequent first follow-up visit from 45 to 120 days post-implant and a final follow-up at 1-year post-procedure. A Clinical Event Committee adjudicated all major adverse events and TEE/CT imaging results were adjudicated by a core laboratory. Among 300 patients enrolled at 17 centres in Europe, the mean age was 74.6 ± 8.0 years, mean CHA2DS2-VASc score was 4.3 ± 1.6, and 62.1% were male. The device was successfully implanted in 99.0% (297/300) of patients. The post-implant medication regimen was DAPT for 87.3% (262/300). At first follow-up, core-lab adjudicated complete seal was 88.2% (149/169), 9.5% (16/169) had leak <3 mm, 2.4 (4/169) had leak ≥3 mm to ≤5 mm, and 0% had >5 mm leak. At 1 year, 93.3% (280/300) had final follow-up; 60.5% of patients were on a single antiplatelet medication, 21.4% were on DAPT, 5.6% were on direct oral anticoagulation, and 12.1% were not taking any antiplatelet/anticoagulation medication. Adverse event rates through 1 year were: all-cause death 10.8% (32/295); CV/unexplained death 5.1% (15/295); disabling and non-disabling stroke each 1.0% (3/295, all non-fatal); pericardial effusion requiring surgery or pericardiocentesis 1.0% (3/295); and device-related thrombus 2.4% (7/295).

Conclusion The WATCHMAN FLX device had excellent procedural success rates, high LAA seal rates, and low rates of thromboembolic events in everyday clinical practice.

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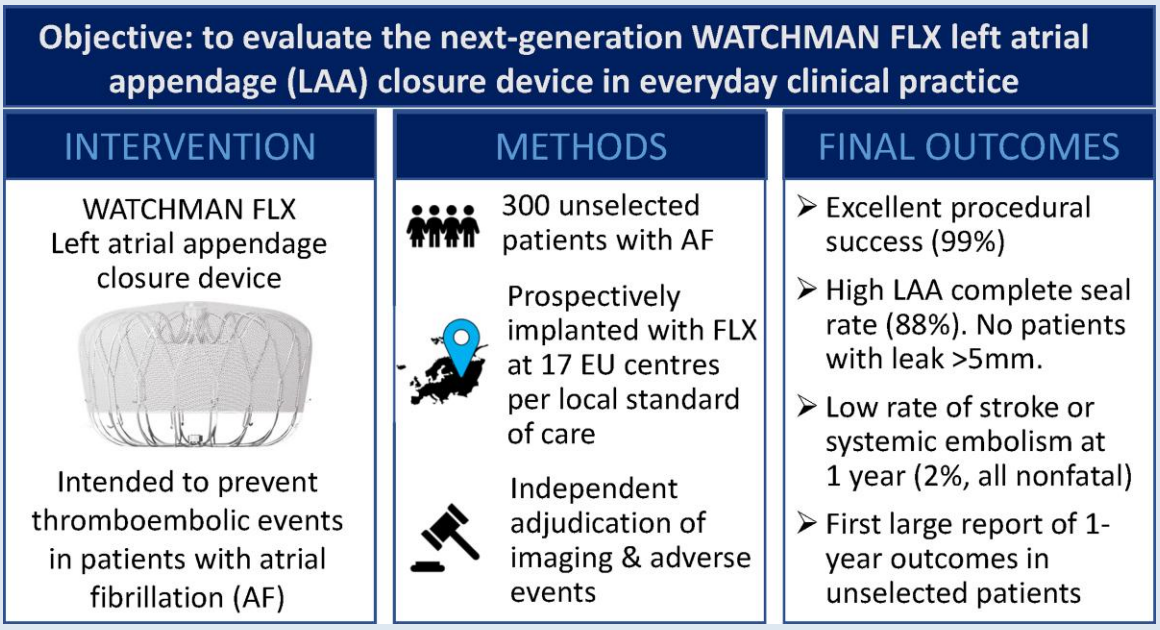
Graphical Abstract



Keywords Atrial fibrillation • Left atrial appendage closure • Left atrial appendage obstruction • WATCHMAN FLX • Stroke prevention (limit 6)

What's new?

- In this prospective, multicentre, post-approval registry, the next-generation WATCHMAN FLX device had excellent procedural success rates, high rates of left atrial appendage seal, and low rates of thromboembolic events through 1 year of follow-up.
- These results confirm and extend the efficacy reported for WATCHMAN FLX in the pivotal PINNACLE FLX study and show that they can be replicated in everyday clinical practice.
- To our knowledge, this is the first large report of 1-year outcomes with this new device in unselected patients treated in a commercial clinical setting.

Introduction

Left atrial appendage (LAA) closure is an approved treatment for the prevention of thromboembolic events in patients who have atrial fibrillation and who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy. The first-generation WATCHMAN device was extensively tested in multiple studies [1–7] and shown to be effective at reducing thromboembolic events.

The next-generation WATCHMAN FLX (Boston Scientific, Marlborough, MA, USA) device was designed to provide improved safety and ease of implantation compared with the predicate WATCHMAN device. The WATCHMAN FLX device received CE-mark based on data from the pivotal PINNACLE FLX study.[8] The objective of this FLXibility Post-Approval Study was to evaluate 'real-world' safety and performance of the next-generation WATCHMAN FLX device in a commercial setting.

Methods

Study design, device, and patients

The FLXibility Post-Approval Study was a prospective, post-market, observational, multi-centre, single-arm study designed to assess outcomes in patients implanted with the next-generation WATCHMAN FLX device in a commercial clinical setting. This study was sponsored and funded by Boston Scientific Corporation (Marlborough, MA, USA), and adhered to the principles of the Declaration of Helsinki and all relevant local and internal regulations. The FLXibility study is registered at www.clinicaltrials.gov (NCT02654470). The data and study protocol for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

The next-generation WATCHMAN FLX™ LAA Closure Device (WATCHMAN FLX) builds on the safety and efficacy established for the predicate WATCHMAN device, and incorporates design modifications intended to improve control, flexibility, sealing ability, and safety. Specifically, the modifications include an atraumatic tip for advancing and repositioning deeper in the LAA, a fluoroscopic marker for enhanced procedural visibility, a shorter overall device length to facilitate treatment of complex shallow LAA anatomies, and a greater range of device size options. In addition, the number of contact points between the WATCHMAN FLX Device and LAA ostium were increased to minimize potential leaks, and the overall metal surface area was reduced to promote endothelialization of the proximal face.

Participants aged ≥18 years who were eligible to receive a WATCHMAN FLX device according to currently approved indications and guidelines were eligible for enrolment. Exclusion criteria included patients who were currently enrolled in another investigational study that would directly interfere with the current study, who planned to have concomitant procedures with the WATCHMAN FLX implant (i.e. cardiac ablation, transcutaneous valve procedures, cardioversions, etc.), patients who

were unable or unwilling to comply with study requirements, patients of childbearing potential who were or planned to become pregnant during the study, or patients who had a documented life expectancy of < 1 year. Patients were considered enrolled in the study when informed consent was signed by the patient or a guardian.

Enrolled patients who had an attempted WATCHMAN FLX implant, defined as having had a WATCHMAN Access Sheath inserted, were categorized as 'Attempt' (if implant attempt was ultimately unsuccessful) or 'Implant' (if device implantation was successful). All implant procedures were performed per local standard of care. For analysis purposes, total procedure time was defined as the difference between WATCHMAN Access System Transeptal crossing time and WATCHMAN Access Sheath removal time.

A first follow-up visit that included echocardiographic imaging of the device was mandated to occur from 45 to 120 days post-implant, and a final clinical visit was mandated to occur at 365 ± 30 days. This study was conducted during the first waves of the COVID-19 pandemic and travel restrictions prevented some patients from physically attending clinic visits and, especially, having a routine echocardiogram performed within the allowed first follow-up visit window. In those cases, patients were followed-up with virtual appointments and asked to return to the clinic for in-person verification when feasible. Sites were additionally asked to record all deaths and protocol deviations that may have been related to COVID-19 infection. All data collected, even if out of window, was considered and reported as required according to the trial protocol and applicable regulations.

Endpoints

Protocol-specified endpoints included: procedural success, procedural complications, device seal and thrombus rates, and the incidence of strokes post-implantation (including type and severity). In accordance with the observational post-market nature of this study, no formal pre-specified statistical hypothesis was defined. An independent Core Laboratory reviewed and adjudicated all LAA imaging collected at protocol-required timepoints during the study, and an independent Clinical Events Committee adjudicated key adverse events.

Statistical methods

Descriptive statistics were used for baseline, procedural, and follow-up data collected throughout the study. Categorical variables were expressed as per cent (n/N) and continuous variables as mean ± SD (range).

All patients with an attempted implant ('Attempt/Implant' population) were included in procedural and outcomes analyses. Binary event rates (proportions) were calculated on a per-patient basis. For time-to-event analyses, event-free patients were censored at the date of their last follow-up. All statistical analyses were performed using SAS Software (Cary, North Carolina, USA), version 9.3 or higher.

Results

Patient characteristics and disposition

A total of 301 patients were enrolled at 17 sites in Europe between July 2019 and July 2020. The mean age at enrolment was 74.6 ± 8.0 years, among whom 54.2% (163/301) were aged ≥75 years; mean baseline CHA_2DS_2VASc score was 4.3 ± 1.6; mean HAS-BLED score was 2.6 ± 1.0; and 37.9% (114/301) were female (*Table 1*). One enrolled patient did not meet the eligibility criteria and did not undergo an attempted implant; thus, the Attempt/Implant population consisted of 300 patients. Patient disposition is shown in *Figure 1*.

Due to COVID-19-related travel restrictions and non-essential hospital procedure closures, not all patients were able to have an in-person clinical visit and mandated echocardiography. Virtual appointments were used for clinical visits, where possible, with outcomes confirmed at any subsequent in-person visits. At the first follow-up visit, 14 patients died before follow-up and a further 3 missed the visit (2 of the 3 had a later follow-up visit performed). The mean ± SD time of the first follow-up visit was 6.7 ± 4.5 months (range, 0–15.9 months), and TEE assessment of LAA closure was available for 181 patients. At final, 1-year follow-up, 32 patients died prior to 365 days, and a further 20 did not have clinical follow-up performed at 1 year, primarily because of loss to follow-up ($n = 11$). A total of 64 patients had echocardiographic assessment completed between 120 days and 1 year.

Table 1 Baseline patient demographics and characteristics

Variable	Enrolled patients ($N = 301$)
Age, years	74.6 ± 8.0 (301)
Female	37.9 (114/301)
CHA_2DS_2-VASc score	4.3 ± 1.6 (301)
HAS-BLED score	2.6 ± 1.0 (301)
History of major bleeding	70.8 (213/301)
Prior ischaemic stroke or TIA	24.6 (74/301)
Ischaemic stroke	17.9 (54/301)
TIA	10.0 (30/301)
History of systemic thromboembolism	2.3 (7/301)
Prior hemorrhagic stroke	17.3 (52/301)
Carotid artery disease	9.3 (28/301)
Coronary artery disease	31.3 (89/284)
Congestive heart failure	24.6 (74/301)
Peripheral vascular disease	8.0 (24/301)
Type of atrial fibrillation	
Paroxysmal	40.2 (121/301)
Persistent	6.0 (18/301)
Long-term persistent	13.6 (41/301)
Permanent	40.2 (121/301)
Indications for LAA closure	
History of major or minor bleeding (with or without OAC therapy)	79.4 (239/301)
Increased risk for bleeding due to physical condition and/or comorbidities	25.6 (77/301)
Inability to take OACs for reasons other than high risk for bleeding	8.6 (26/301)
Thromboembolic event or documented presence of thrombus in the LAA despite adequate OAC therapy	8.0 (24/301)
Left ventricular ejection fraction, %[a]	55.9 ± 8.8 (269)
LAA ostium diameter, mm[b]	19.7 ± 3.5 (287)
LAA length, mm[b]	27.7 ± 6.3 (283)
Number of LAA lobes[b]	
1	80.7 (192/238)
2	19.3 (46/238)
≥3	0.0 (0/238)

Values are per cent (*n*/*N*) or mean ± SD (*n*).
[a]Value is per site assessment.
[b]Value is per core-lab adjudication.
INR, international normalized ratio; LAA, left atrial appendage; OAC, oral anticoagulant medication; TIA, transient ischaemic attack.

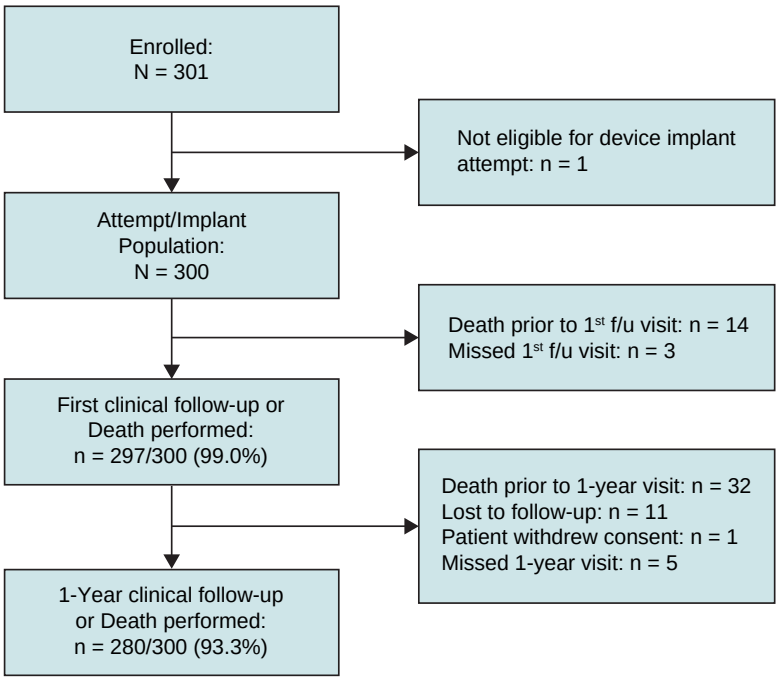


Figure 1 Patient disposition. Patient flow throughout the study. One enrolled patient did not meet the eligibility criteria and did not undergo an attempted implant; thus, the Attempt/Implant population consisted of 300 patients.

Procedural results

Procedural success, defined as successful deployment and release of the device was 99.0% (297/300). In the three patients who were not successfully implanted, two had unsuitable anatomy for device implantation and the third was implanted too proximally to meet the device release criteria; the device was removed and no other implant attempt was conducted. Procedural characteristics are provided in *Table 2*. Approximately 20% of implant procedures were conducted using ICE and the rest used TEE for implant guidance. The most commonly implanted device size was 27 mm and overall mean final device compression was 19%. Nearly 10% of patients each were implanted with the 20 and 35 mm devices—two sizes that were not available with the prior-generation device. In total, 97% of patients had successful implant of the first attempted device and nearly three-quarters of patients did not require any device recaptures to achieve successful implantation.

Antiplatelet/anticoagulation medications

Antiplatelet and anticoagulation medications were prescribed at physician discretion, per local standard of care and the WATCHMAN FLX Instructions for Use. Most patients were discharged on DAPT (87.3% [262/300]) (*Figure 3*), with the remainder on SAPT (7.0% [21/300]) or a direct oral anticoagulant medication (DOAC) (4.7% [14/300]). At final follow-up, the majority of patients were on SAPT (60.5% [150/248]), followed by DAPT (21.4% [53/248]), and no antiplatelet/OAC (12.1% [30/248]).

Left atrial appendage closure

LAA closure was assessed using transesophageal echocardiography at the first follow-up visit, which was mandated to occur between 45 and 120 days, per protocol. Core-lab adjudicated results among 169 patients with evaluable echocardiograms are shown in *Figure 2*; an additional 11 patients had echocardiograms performed that could not be reliably assessed by the core lab. More than 88% (149/169) of patients had complete seal; of the remaining patients, 9.5% (16/169) had peridevice leak <3 mm, and an additional 2.4% (4/169) had leak ≥3 but ≤5 mm. No patients had leak >5 mm. An additional 64 patients had echocardiography assessment beyond 120 days. Of these, 86.4% (51/59) had complete seal and the remaining 13.6% had leak <3 mm (four additional patients had echocardiograms that were not assessable by the core lab).

One-year clinical follow-up

Adverse events rates are shown in *Table 3*. No patients died or had a stroke within 7 days post-procedure. Three patients had pericardial effusions requiring intervention (1 via surgery and 2 via pericardiocentesis) on the day of procedure; all three were successfully resolved and there were no additional pericardial effusions through 1 year of follow-up. One device embolization occurred in a patient implanted with a 27 mm Watchman FLX device. Per Core Lab assessment, the device compression was less than 10% and a mild device tilt was noted after implant release. One day after the procedure, a CT was performed for unrelated medical reasons and showed that the Watchman device had embolized into the left ventricle. The endovascular removal procedure was complicated by damage to the mitral apparatus, resulting in severe mitral regurgitation, surgical repair, and multiorgan failure with death occurring at 13 days post-procedure. At 1 year, all-cause mortality was 10.8% (32/295), of which 10 (31.3% of total deaths) were cardiovascular and 5 (15.6% of total deaths) were unexplained. Two of the 10 deaths were considered related to COVID-19 infection by the site investigators. Overall stroke rate at 1 year was 2.0% (6/295), all of which were non-fatal ischaemic strokes; half (3/6) were non-disabling. Device-related thrombus was detected in 7 (2.4%) patients through 1 year; all were detected during routine imaging. One patient with a small DRT detected by cardiac CT on

Table 2 Procedural characteristics

Parameter	Implant/attempt patients (*N* = 300)
Procedural imaging type used	
Transoesophageal echocardiography	78.3% (220/281)
Intracardiac echocardiography	21.7% (61/281)
Device size implanted	
20 mm	9.1% (27/297)
24 mm	29.6% (88/297)
27 mm	32.0% (95/297)
31 mm	20.5% (61/297)
35 mm	8.8% (26/297)
Implanted device compression (%)	19.1 ± 6.2 (290) (4.2, 41.9)
Total fluoroscopy time (minutes)	8.8 ± 5.8 (299) (1.3, 39.0)
Total procedure time (minutes)	25.1 ± 13.7 (299) (4.0, 120.0)
Number of implanted/attempted WATCHMAN devices (patient-based)	1.0 ± 0.2 (298) (1.0, 2.0)
Number of implanted device recaptures	
0 Recapture	71.4% (212/297)
1 Recapture	14.1% (42/297)
2 Recaptures	6.4% (19/297)
3 Recaptures	3.4% (10/297)
4 Recaptures	2.4% (7/297)
5 Recaptures	0.7% (2/297)
6 Recaptures	0.3% (1/297)
≥7 Recaptures	1.3% (4/297)

Values are per cent (*n*/*N*) or mean ± SD (*n*) (range).

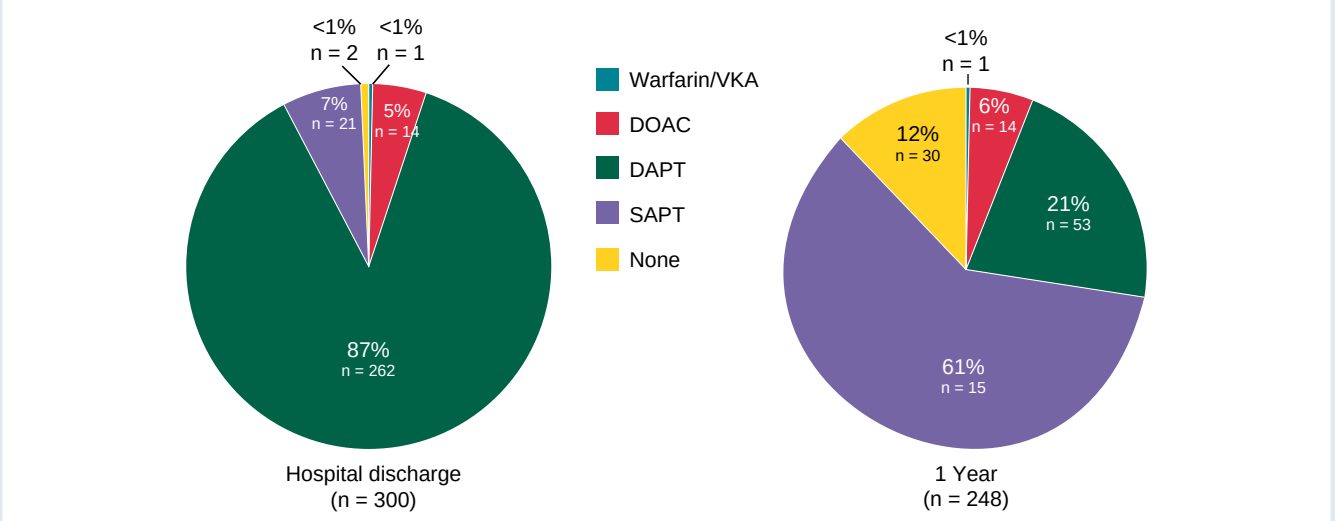


Figure 2 Left atrial appendage seal at first follow-up visit (45–120 days). Results are core-lab adjudicated assessment by transoesphageal echocardiography.

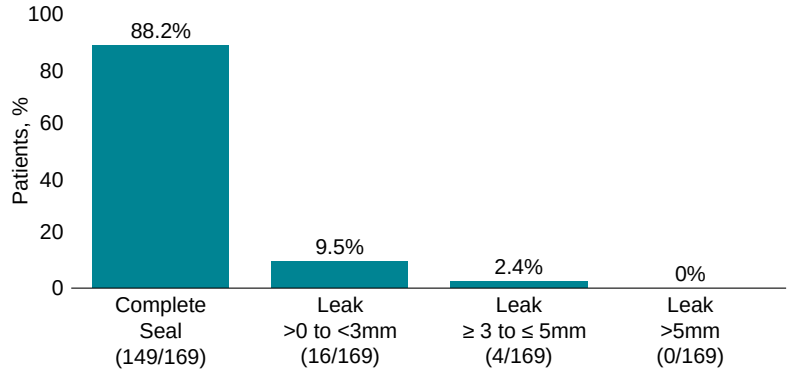


Figure 3 Antiplatelet/anticoagulation medications at hospital discharge and 1 year. DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; SAPT, single antiplatelet therapy; VKA, Vitamin K antagonist.

Table 3 CEC-adjudicated adverse events through 7 days and 1 year (implant/attempt population: $N = 300$)

Event	0–7 Days	0–365 Days
All-cause mortality	0.0% (0/300)	10.8% (32/295)
Cardiovascular	0.0% (0/300)	3.4% (10/295)
Non-cardiovascular	0.0% (0/300)	5.8% (17/295)
Unexplained	0.0% (0/300)	1.7% (5/295)
Stroke	0.0% (0/300)	2.0% (6/295)
Ischaemic	0.0% (0/300)	2.0% (6/295)
Hemorrhagic	0.0% (0/300)	0.0% (0/295)
Disabling stroke	0.0% (0/300)	1.0% (3/295)
Non-disabling stroke	0.0% (0/300)	1.0% (3/295)
Fatal stroke	0.0% (0/300)	0.0% (0/295)
Transient ischaemic attack	0.3% (1/300)	0.7% (2/295)
Systemic embolism	0.0% (0/300)	0.0% (0/295)
Major open cardiac and/or endovascular surgery through 7 days or hospital discharge (whichever is later)	0.7% (2/300)	0.7% (2/295)
Serious adverse events related to the device or procedure	2.0% (6/300)	2.0% (6/295)
Major bleeding (BARC 3 or 5)	3.7% (11/300)	8.5% (25/295)
BARC 3	3.7% (11/300)	7.8% (23/295)
BARC 5 (fatal bleeding)	0.0% (0/300)	0.7% (2/295)
Non-procedural major bleed	1.3% (4/300)	6.8% (20/295)
Pericardial effusion requiring surgery	0.3% (1/300)	0.3% (1/295)
Pericardial effusion requiring pericardiocentesis	0.7% (2/300)	0.7% (2/295)
Device-related thrombus	0.0% (0/300)	2.4% (7/295)
Device migration	0.0% (0/300)	0.0% (0/295)
Device embolization	0.3% (1/300)	0.3% (1/295)

Values are per cent (*n*/*N*). BARC, bleeding academic research consortium scale.

day 358 post-procedure had experienced a non-disabling ischaemic stroke on day 244 with symptoms of aphasia (90-day post-stroke mRS score = 1); no cardiac imaging had been performed at the time of the stroke. Throughout the study, there were no reported systemic embolisms and no device migrations.

Discussion

In the prospective, multicentre, post-approval FLXibility registry, the next-generation WATCHMAN FLX device had excellent procedural success rates, with 99% procedural success. Post-implant, more than 87% of patients were treated with DAPT. In addition, we observed high rates of LAA seal at mandated 45- to 120-day follow-up, with 88% of patients demonstrating complete LAA seal, and an additional 10% demonstrating leak <3 mm. No patients had leak >5 mm. At 1-year post-procedure, all-cause death occurred in 10.8% of patients, disabling, and non-disabling stroke each occurred in 1.0% (3/295, all non-fatal), device-related thrombus was detected in 2.4% (7/295) (all asymptomatic), and no patients had a systemic embolism. To our knowledge, this is the first large report of 1-year outcomes with this new device in unselected patients treated in a commercial clinical setting.

These results confirm and extend the efficacy reported for WATCHMAN FLX in the pivotal PINNACLE FLX study, which reported a 98.8% implant success rate and 83% complete seal at first follow-up visit, with no leak >5 mm, and are also comparable or improved vs. 1-year rates reported in registries of the prior-generation WATCHMAN 2.5 device (*Table 4* and Supplementary material online, *Figure S1*).[8–10] Similarly, rates of all stroke and ischaemic stroke at 1 year in FLXibility (2.0% and 2.0%, respectively) were comparable to or lower than those observed in PINNACLE FLX (2.6% and 2.6%, respectively), as well as in other studies of LAAC devices, which have reported 1-year ischaemic stroke rates ranging from 1.1% to 2.6%.[8–12] Interestingly, nearly 90% of patients in this study of everyday clinical practice were discharged from the hospital on DAPT therapy, whereas the PINNACLE FLX study protocol required DOAC treatment for 45 days post-procedure before commencing DAPT. The overall comparable rates of ischaemic events and bleeding between the two studies suggests that DAPT may be a reasonable alternative to DOAC treatment post-LAAC, although this remains to be conclusively proven.

Table 4 Summary of key 1-year outcomes in WATCHMAN device studies

	WATCHMAN 2.5 registries		WATCHMAN FLX studies	
	EWOLUTION[10] (*N* = 1025)	NCDR registry[9] (*N* = 36 681)	PINNACLE FLX[8] (*N* = 400)	FLXiblity (*N* = 300)
Patients				
Mean age, years	73 ± 9	76 ± 8	74 ± 9	75 ± 8
Female sex	40.1%	41.1%	36%	38%
CHA_2DS_2-Vasc score	4.5 ± 1.6	4.8 ± 1.5	4.2 ± 1.5	4.3 ± 1.6
HAS-BLED score	2.3 ± 1.2	3.0 ± 1.1	2.0 ± 1.0	2.6 ± 1.0
1-Year outcomes				
All-cause mortality	9.8%	8.5%	6.6%	10.8%
All stroke	1.1%	2.1%	2.6%	2.0%
Ischaemic	1.1%	1.5%	2.6%	2.0%
Hemorrhagic	0%	0.5%	0%	0%
Systemic embolism	NR	0.7%	0.3%	0%
Major bleeding	2.6%	6.9%	7.9%	8.5%
DRT	NR	NR	1.8%	2.4%

Values are mean ± SD or per cent. DRT, device-related thrombus; NR, not reported.

One notable and novel finding from our study was the high number of single deployments and single device use in unselected patients; these results may be related to the improved deliverability of WATCHMAN FLX vs. the predicate device, although this is speculative. Moreover, even though this study was not designed to evaluate cost-effectiveness, this high number of single deployments and devices has the potential to improve cost-effectiveness and should be further investigated.

Mortality at 1 year was higher in this study than in recent controlled studies of LAAC devices such as AMULET or PINNACLE FLX,[1,2,8] which range from 4% to 7%, but is in line with other registries of unselected patients treated with WATCHMAN (*Table 4*).[9,10] This observation is consistent with a recent patient-level meta-analyses of post-LAAC outcomes in everyday clinical practice vs. clinical trials, which showed higher mortality in registry patients, primarily due to increased non-cardiovascular deaths.[13] It is also worth noting that patients with atrial fibrillation in general tend to be older, frailer, and have more comorbidities. For this reason, the NHS England guidelines mandate that some form of frailty assessment and life expectancy (3 years) is warranted in selecting patients for this therapy.[14]

Some limitations of this study must be acknowledged. First, this was a single-arm, open-label study with mid-term (1 year) follow-up. Nonetheless, it represents the largest study of 1-year outcomes published to date in everyday clinical practice with WATCHMAN FLX. Additional research will be needed to assess longer-term outcomes with this next-generation device. Second, due to pandemic travel restrictions, we had a lower rate of echocardiographic follow-up than anticipated at the time of study design; however, the outcomes observed here are consistent with those observed in the pivotal PINNACLE FLX study, [8] which suggests that the outcomes were not strongly affected by the limited imaging availability, although this remains to be definitively determined.

In conclusion, when used in everyday clinical practice, the next-generation WATCHMAN FLX LAA closure device had an excellent rate of procedural success, high effective LAA closure rates, and low rates of thromboembolic events.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data and study protocol for this clinical trial may be made available upon request to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

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