



# Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device

## Results From the PINNACLE FLX Trial

**BACKGROUND:** Left atrial appendage (LAA) occlusion provides an alternative to oral anticoagulation for thromboembolic risk reduction in patients with nonvalvular atrial fibrillation. Since regulatory approval in 2015, the WATCHMAN device has been the only LAA closure device available for clinical use in the United States. The PINNACLE FLX study (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) evaluated the safety and effectiveness of the next-generation WATCHMAN FLX LAA closure device in patients with nonvalvular atrial fibrillation in whom oral anticoagulation is indicated, but who have an appropriate rationale to seek a nonpharmaceutical alternative.

**METHODS:** This was a prospective, nonrandomized, multicenter US Food and Drug Administration study. The primary safety end point was the occurrence of one of the following events within 7 days after the procedure or by hospital discharge, whichever was later: death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery. The primary effectiveness end point was the incidence of effective LAA closure (peri-device flow  $\leq 5$  mm), as assessed by the echocardiography core laboratory at 12-month follow-up.

**RESULTS:** A total of 400 patients were enrolled. The mean age was  $73.8 \pm 8.6$  years and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASC score was  $4.2 \pm 1.5$ . The incidence of the primary safety end point was 0.5% with a 1-sided 95% upper CI of 1.6%, meeting the performance goal of 4.2% ( $P < 0.0001$ ). The incidence of the primary effectiveness end point was 100%, with a 1-sided 95% lower CI of 99.1%, again meeting the performance goal of 97.0% ( $P < 0.0001$ ). Device-related thrombus was reported in 7 patients, no patients experienced pericardial effusion requiring open cardiac surgery, and there were no device embolizations.

**CONCLUSIONS:** LAA closure with this next-generation LAA closure device was associated with a low incidence of adverse events and a high incidence of anatomic closure.

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## Clinical Perspective

### What Is New?

- The PINNACLE FLX study (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) evaluated a next-generation left atrial appendage closure device in patients at high thromboembolic risk with nonvalvular atrial fibrillation who were eligible for anticoagulation therapy.
- The device implantation was successful without prohibitive safety issues and displayed effective appendage closure on transesophageal echocardiography imaging at 12 months.

### What Are the Clinical Implications?

- The left atrial appendage closure device met the primary safety end point with 0.5% (2/400) of patients experiencing a safety end point event within 7 days postprocedure or at hospital discharge.
- The next-generation left atrial appendage closure device met the primary effectiveness end point with a left atrial appendage closure incidence (<5 mm peri-device flow) of 100.0% at both 45 days and 1 year after the procedure ( $P<0.0001$  versus pre-specified performance goals for both end points).

**T**rascatheter left atrial appendage (LAA) closure has emerged as a minimally invasive therapeutic option to prevent thrombus embolization from the LAA in patients with nonvalvular atrial fibrillation (NVAf). Several clinical trials and observational studies have established the safety and clinical effectiveness of the first-generation WATCHMAN LAA closure device for risk reduction of atrial fibrillation (AF)-related embolic strokes in patients at high risk.<sup>1–3</sup> Although the first-generation device is associated with a relatively low procedure-related complication incidence of 2.2% in current practice,<sup>4</sup> there are still some limitations of the device regarding the size matrix, ability to fully recapture the device, risk of perforation, device-related thrombus (DRT) formation, and peri-device leak. In addition, further improvements in procedural safety with a similar or superior incidence of anatomic closure might improve the long-term net clinical benefit of LAA closure compared with oral anticoagulation. The WATCHMAN FLX (Boston Scientific, MN; hereafter referred to as next-generation LAA closure device) is a next-generation LAA closure device designed to address these limitations, enhance procedural performance, and expand the eligible patient population with respect to treatable LAA anatomy. In a US Food and Drug Administration Investigational Device Exemption clinical study, we evaluated the safety and anatomic effectiveness of this next-generation device in patients with NVAf with clinical indications for LAA closure.

## METHODS

The PINNACLE FLX study (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02702271) is a single arm, prospective, nonrandomized study across 29 investigational centers in the United States. This study was approved by an institutional review committee and the patients gave informed consent. The data and study protocol for this clinical study may be made available to other researchers in accordance with Boston Scientific's Data Sharing Policy (<http://www.bostonscientific.com/enUS/data-sharing-requests.html>). Patients were eligible for the study if they had NVAf and a CHA2DS2-VASc score of  $\geq 2$  for men or  $\geq 3$  for women, were able to take the prescribed postimplant antithrombotic medication regimen, had a rationale for a nonpharmacological approach to stroke prevention, and had no other diagnoses that would require long-term anticoagulation. Full inclusion/exclusion criteria are listed in [Table 1 in the Data Supplement](#).

To allow physicians to gain experience with the implant procedure, all sites were required to enroll 2 roll-in patients before enrollment in the main study cohort. The main study cohort represents the analysis population.

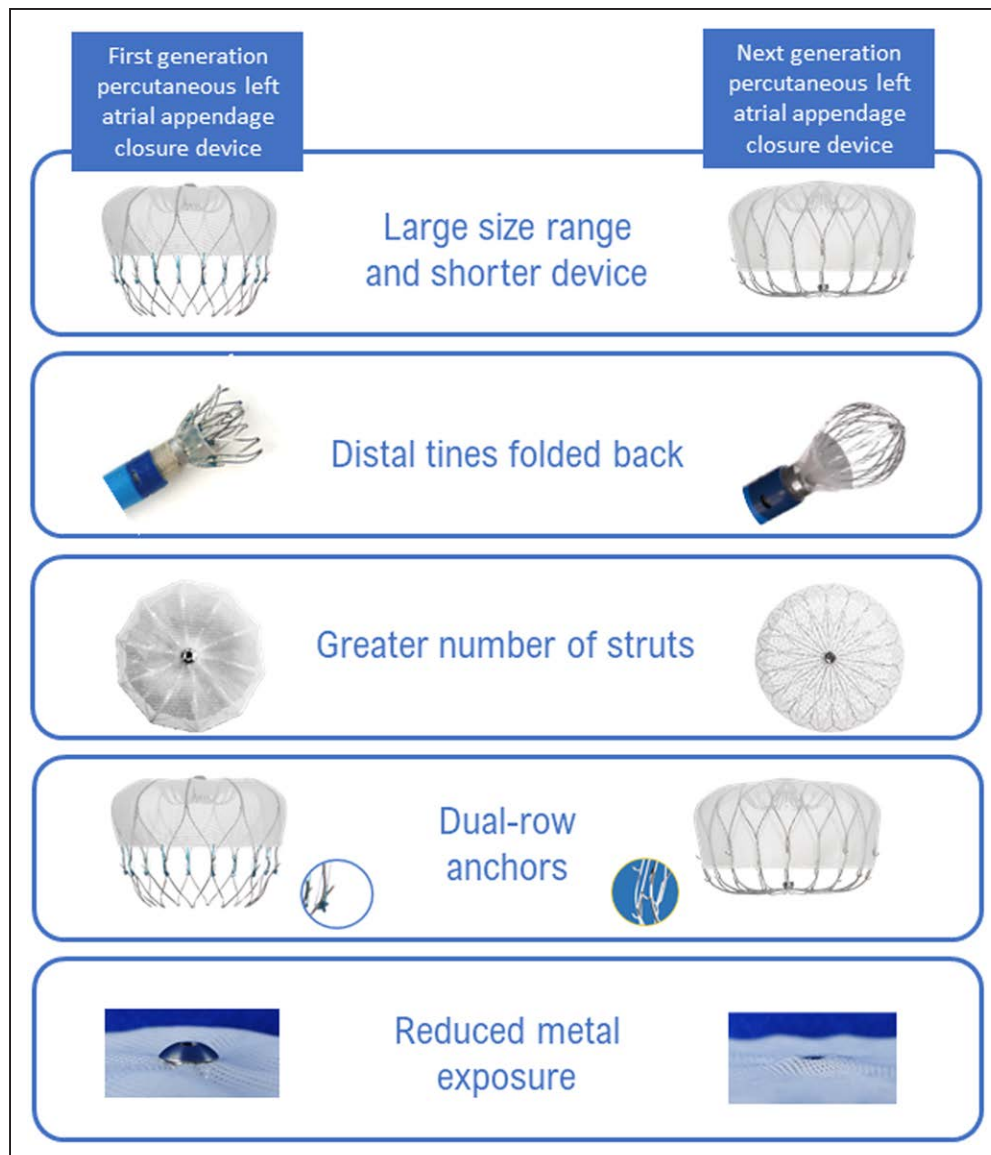
An independent clinical events committee adjudicated end point events. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. The study was sponsored by Boston Scientific Corporation and registered with ClinicalTrials.gov. All patients gave written informed consent.

## Procedure Description

The basic steps of the procedure were similar to the implantations of the current-generation device regarding the use of general anesthesia, femoral venous access for the transseptal puncture, use of guide wire and pigtail for sheath guidance and positioning, and device selection based on transesophageal echocardiography (TEE) and angiography.<sup>5</sup> The next-generation device was deployed into the LAA first by forming "a ball" (Figure 1) and either (1) unsheathing while maintaining the position of the ball, similar to the current device technique; (2) advancing the device distally out of the sheath until it was fully deployed; or (3) a combination of both of these techniques. Once the device was deployed, the operator applied forward pressure on the delivery cable for at least 10 seconds to engage fixation barbs and allow the device to conform to the appendage. If position were not optimal, the device could be partially or fully recaptured and repositioned both proximally or distally using the "ball." Conformation of Position, Anchor, Size, and Seal criteria were assessed, and the device was released similarly to the current-generation implant.

## Postprocedure Management

After device placement, treatment with a direct oral anticoagulant (DOAC) was required through at least a 45-day follow-up, with apixaban or rivaroxaban strongly recommended. Patients were also prescribed concomitant low-dose (81–100 mg) aspirin. On evidence of adequate LAA seal (leak  $\leq 5$  mm) at the 45-day TEE evaluation, patients were directed to discontinue



**Figure 1. WATCHMAN and WATCHMAN FLX device comparison.**

Changes from the first-generation to the next-generation LAA closure device include an 18-strut frame for improved conformability, a single-component device preloaded into a delivery catheter to allow both full or partial recapture during implant, dual-row J-shaped anchors to maximize device stability, a low-profile threaded insert covered by a permeable polyester fabric to minimize metal exposure and reduce healing time, an atraumatic tip for advancement and maneuverability within the appendage, and a shorter length and wider sizing matrix to treat a wider variety of anatomies. Image provided courtesy of Boston Scientific. ©2021 Boston Scientific Corporation or its affiliates. All rights reserved.

DOAC therapy and begin a dual antiplatelet therapy regimen of clopidogrel (75 mg) plus low-dose aspirin until 6 months postimplant, followed by low-dose aspirin indefinitely. If a leak  $>5$  mm was measured at the 45-day follow-up, patients continued DOAC plus aspirin and were reevaluated at 6 months postimplant. If there were no leaks  $>5$  mm at the subsequent follow-up visit, patients could forego dual antiplatelet therapy and proceed straight to lifelong low-dose aspirin.

Postimplant follow-up visits were required at 45 days, 6, 12, 18, and 24 months.

## Outcome Measures

The primary safety end point was the occurrence of one of the following events between the time of implant and within 7

days after the procedure or by hospital discharge, whichever was later: death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, arteriovenous fistula repair, or another major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications were excluded from this end point.

The primary effectiveness end point was the incidence of effective LAA closure, defined as any peri-device flow with jet size  $\leq 5$  mm per core laboratory–assessed TEE at 12 months. The secondary effectiveness end point was the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. Because not all patients had completed 24-month

follow-up at the time of this report, data on the secondary effectiveness end point are not presented here. Other clinical events sent to the independent Clinical Events Committee for review and adjudication included all-cause death, stroke/transient ischemic attack, systemic embolism, major bleeding events (Bleeding Academic Research Consortium 3 or Bleeding Academic Research Consortium 5), device embolization, device thrombus, device migration, or pericardial effusion resulting in an invasive intervention (eg, open cardiac surgery or pericardiocentesis/pericardial puncture).

## Statistical Methods

Descriptive statistics are provided for patient demographic and baseline characteristics, procedural characteristics, and medication compliance. The incidence of major clinical events, device- or procedure-related serious adverse events, and the incidence of LAA closure are also provided.

For the primary safety end point, a performance goal was established based on a clinically acceptable margin added to a composite event incidence of 1.68% derived from the observed safety event incidence in the cohort of patients receiving a device in the combined PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation versus Long Term Warfarin Therapy)<sup>2,6</sup> and CAP2 (Continued Access to PREVAIL AF Registry)<sup>3,7</sup> studies with CHADS<sub>2</sub> score  $\geq 2$  or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$ . These 2 studies were used to support Food and Drug Administration approval of the previous generation LAA closure device. A margin of 2.53% was added to establish the performance goal of 4.21%, corresponding to a maximum observable incidence of 2.5%. This margin was deemed clinically acceptable on the basis of the observed incidence of procedural complications. Assuming a 1-sided  $\alpha$  of 0.05, a sample size of 400 patients provided a power of 92%; if using a 2-sided  $\alpha$  of 0.05, the power would be 77%. For the primary effectiveness end point, the expected incidence of effective LAA closure was 99.4%, based on the incidence observed in the combined PREVAIL and CAP2 device patients with a CHADS<sub>2</sub> score  $\geq 2$  or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$ . A  $\Delta$  of 2.3% was then subtracted from the expected incidence of effective LAA closure to establish the performance goal of 97.0%, representing a minimum observable incidence of 98.8%. Assuming an incidence of attrition of 20% (ie, patients who do not have a 12-month TEE) and a 1-sided  $\alpha$  of 0.05, a sample size of 400 patients provided 92% power; if using a 2-sided  $\alpha$  of 0.05, the power would be 81%.

## RESULTS

### Study Population and Procedural Characteristics

A total of 400 patients were enrolled between May 2018 and November 2018. Baseline demographic information is provided in Table 1. The mean age was 73.8 $\pm$ 8.6 years, 35.5% of the patients were women, and most were White (94%). More than half of the patients presented with paroxysmal AF. The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 4.2 $\pm$ 1.5 and the mean HAS-BLED score was 2.0 $\pm$ 1.0 (Table II in the Data Supplement).

**Table 1. Baseline Demographic and Clinical Characteristics**

Measure	N=400
Age	73.8 $\pm$ 8.6 (400) [44.0, 98.0]
Female sex	35.5% (142/400)
Race/ethnicity	
American Indian or Alaska native	0.3% (1/382)
Asian	0.5% (2/382)
Black or African heritage	4.7% (18/382)
White	93.7% (358/382)
Hispanic or Latino	2.6% (10/382)
Native Hawaiian or other Pacific Islander	0.0% (0/382)
Other	0.0% (0/382)
Atrial (AF) pattern	
Paroxysmal AF	51.8% (207/400)
Persistent AF	36.5% (146/400)
Permanent AF	10.5% (42/400)
Paced Rhythm	1.3% (5/400)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	4.2 $\pm$ 1.5 (400) [2.0, 9.0]
HAS-BLED score	2.0 $\pm$ 1.0 (400) [0.0, 5.0]

Data are mean $\pm$ SD (N) [min, max] or % (n/N). Note: Subjects were not required to disclose race/ethnicity; subjects were allowed to choose >1 entry in this category. AF indicates atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, 75 years of age and older, diabetes, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly.

Implant procedure success, defined as the successful delivery and release of a device into the LAA, was achieved in 395 patients (98.8%). The most common reason for an unsuccessful attempt (3 of 5 patients) was unsuitable anatomy (eg, attributable to excessive vascular tortuosity, inadequate positioning, or insufficient anchoring). Two attempts were unsuccessful because adequate compression and seal could not be achieved.

Procedural characteristics are shown in Table 2. All 5 available device sizes were implanted successfully in the study, with the 27-mm device being the most commonly used. A broad range of anatomies were treated, with 11.4% of patients treated with a 20-mm device and 7.8% treated with a 35-mm device, sizes that are not available for the predicate device. The average number of devices used was 1.2 $\pm$ 0.4 per procedure. The number of partial- or full-device recaptures during implantation, defined as partial or complete withdrawal of the device back into the delivery sheath, was 1.8 $\pm$ 2.8 and 0.4 $\pm$ 1.1, respectively.

### Postimplant Antithrombotic Therapy

The most frequently prescribed DOAC postprocedure were apixaban (76.7%) and rivaroxaban (20.3%). Based on TEEs interpreted by the sites, 96.2% (379/394) of patients had an adequate seal and discontinued DOAC



**Table 2. Procedural Characteristics**

Parameter	N=400
Implant success	98.8% (395/400)
Unsuitable anatomy	3/400
Device did not meet release criteria	2/400
Procedure time, min	37.9±21.9 (400) [11.0, 174.0]
Number WATCHMAN FLX devices used per case	1.2±0.4 (400) [1.0, 4.0]
Final device size, mm	
20	11.4% (45/395)
24	26.8% (106/395)
27	31.1% (123/395)
31	22.8% (90/395)
35	7.8% (31/395)

Data are mean±SD (N) [min, max] or % (n/N).

at 45 days. Of the remaining 15 patients (3.8%) who continued DOAC after the 45-day visit, an additional 7 patients were found to have adequate seal and discontinued their DOAC after the 6-month TEE. The remaining 8 patients (2.0%) continued anticoagulation therapy beyond 6 months based on physician discretion. On the basis of core laboratory analysis of the 45-day TEE, no patient showed a peri-device leak >5 mm, and all evaluable patients were therefore eligible to discontinue oral anticoagulation. As per protocol, nearly all patients (99.5%) were treated with aspirin at hospital discharge; most patients (96.7%) then transitioned to dual antiplatelet therapy after the 45-day follow-up through 6 months, and 85.9% of patients were on aspirin monotherapy at 12 months.

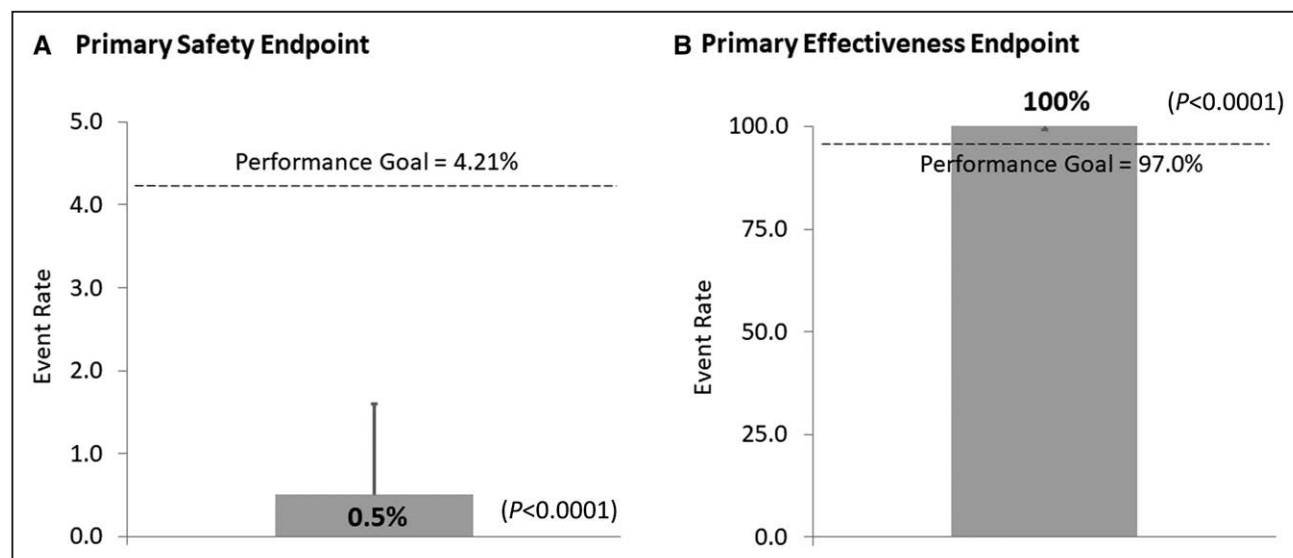
## Clinical and Echocardiographic Outcomes

### Primary Safety End Point

The incidence of the primary safety end point was 0.5%. The upper 1-sided 95% CI was 1.6%, below the performance goal of 4.21% ( $P<0.0001$ ; Figure 2); the 2-sided 95% CI was 1.8%. Two patients had a primary safety end point event. One patient had an ischemic stroke 1 day after an unsuccessful LAA closure procedure. Multiple instrumentations of the LAA without successful device deployment was likely the cause of the stroke. Imaging confirmed multiple small emboli in the brain. The second patient had difficulty in writing and finding words 2 days after the procedure. Imaging was suggestive of a subacute ischemic stroke attributable to intracranial atherosclerotic disease, and the patient was discharged 4 days later with minimal residual symptoms. There were no pericardial effusions requiring intervention before discharge or up to 7 days after the procedure. Figure 3 compares the safety results of the next-generation LAA closure device compared with the first-generation device used in the initial Food and Drug Administration trials: PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), CAP (Continued Access to PROTECT AF registry), PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), and CAP2 (Continued Access to PREVAIL).

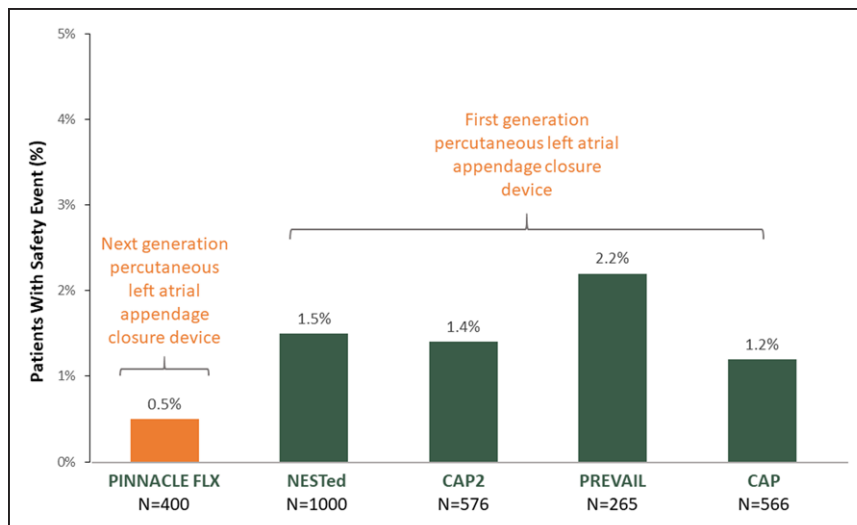
### Primary Effectiveness End Point and LAA Closure Incidence

The incidence of the primary effectiveness end point of LAA closure was 100%. The lower 1-sided 95% CI



**Figure 2. PINNACLE FLX primary end point analysis.**

The composite primary safety end point (A) was met with an incidence of 0.5% and upper 1-sided 95% CI=1.6%, which was below the performance goal of 4.21% ( $P<0.0001$ ). The primary effectiveness end point (B) was met with an incidence of 100.0% and lower 1-sided 95% CI=99.1%, which was above the prespecified performance goal of 97.0% ( $P<0.0001$ ). PINNACLE FLX indicates Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology.



**Figure 3. Safety event comparison.**

The next-generation left atrial appendage occlude device event incidence in PINNACLE FLX was 0.5%. This compares favorably with the previous generation device used commercially in NESTed and in the previous Food and Drug Administration approval trials CAP, PREVAIL, and CAP2. CAP indicates Continued Access to PROTECT AF registry; CAP2, Continued Access to PREVAIL AF Registry; NESTed, New Enrollment Post Approval Surveillance Analysis Plan; PINNACLE FLX, Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology; and PREVAIL, Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation versus Long Term Warfarin Therapy.

was 99.1%, above the performance goal of 97.0% ( $P < 0.0001$ ; Figure 2); the 2-sided 95% CI was 98.9%. Table 3 shows LAA closure incidence for all implant, 45-day, and 12-month TEEs analyzed by the core laboratory. At 45-day follow-up, 97.3% of patients (389/400) had evaluable TEEs, all of whom (389/389; 100%) exhibited adequate LAA closure. The peri-device leak was  $0.03 \pm 0.22$  mm and  $0.57 \pm 1.26$  mm at implant and 45 days, respectively. In all the cases where a device was implanted but the TEE was not evaluable by the core laboratory, peri-device flow was assessed as  $\leq 5$  mm by the site. Core laboratory 12-month follow-up data were available and evaluable for 344 patients, and, likewise, the incidence of LAA closure was 100% (344/344). No patients had a jet size  $> 5$  mm and 90% had no detectable peri-device leak as assessed by the core laboratory.

### Major Clinical Events

The Kaplan-Meier event incidence was calculated for Clinical Events Committee–adjudicated major clinical events (Table 4). Clinical follow-up was available for 100% (400/400) of patients at 45 days after the procedure, and 95.4% (355/372) of eligible patients at 12 months. A total of 4 patients experienced a pericardial effusion requiring intervention, representing a 12-month Kaplan-Meier incidence of 1.0%. Three effusions occurred between 7 and 45 days after the

procedure, and the 4th effusion occurred at 340 days after the procedure after a cardiac ablation. A total of 25 deaths and 10 strokes occurred through 12-month follow-up; the 12-month Kaplan-Meier–estimated incidence for all-cause mortality and stroke was 6.6% and 2.6%, respectively (additional detail on deaths available in Table III in the Data Supplement). There were no hemorrhagic strokes. There was 1 systemic embolism (0.3%), and no device embolizations. The trial is ongoing through 24-months of follow-up; however, at the time of this analysis, 12 strokes have been reported with 2 occurring after 1 year follow-up.

### Device-Related Thrombus

Through the end of the 1-year follow-up window, 7 patients had a DRT with 4 discovered during scheduled follow-up TEE visits (1 at 45 days in a patient who discontinued DOAC early and 3 at 12 months), 1 noted during a workup for a planned pulmonary vein isolation procedure and 2 observed as a result of a suspected embolic event. Of the 2 who experienced an embolic event, one patient presented with acute stroke 132 days after implant with a dissection flap in the carotid artery, died the next day, and autopsy findings revealed a thrombus adherent to the device. The second patient presented with sepsis and was diagnosed with critical limb ischemia at 175 days after implant, and

**Table 3. LAA Closure (Core Laboratory Assessment)**

Peri-device flow	Implant	45 days	12 mo
Jet size $\leq 5$ mm	100.0% (376/376) [99.0%, 100.0%]	100.0% (389/389) [99.1%, 100.0%]	100.0% (344/344) [98.9%, 100.0%]
Jet size $> 0$ and $\leq 5$ mm	7.4% (28/376) [5.0%, 10.6%]	17.2% (67/389) [13.6%, 21.4%]	10.5% (36/344) [7.4%, 14.2%]
Jet size $> 5$ mm	0.0% (0/376) [0.0%, 1.0%]	0.0% (0/389) [0.0%, 0.9%]	0.0% (0/344) [0.0%, 1.1%]
Transesophageal echocardiogram deemed not evaluable for leak by Core Laboratory*	2.3% (9/385) [1.1%, 4.4%]	0.8% (3/392) [0.2%, 2.2%]	0.9% (3/347) [0.2%, 2.5%]

Data are % (n/N) [min, max].

\*Site evaluation of transesophageal echocardiograms assessed peri-device flow as  $\leq 5$  mm in all cases.

**Table 4. Major Clinical Events (Clinical Events Committee Adjudicated)**

Event	Kaplan-Meier Event Rate (n) [95% CI]	
	45 Days	12 mo
All-cause death	0.5% (2) [0.1, 2.0]	6.6% (13) [4.5, 9.7]
Cardiovascular/unknown death	0.3% (1) [0.0, 1.8]	4.4% (9) [2.7, 7.1]
All stroke	0.7% (3) [0.2, 2.3]	2.6% (10) [1.4, 4.8]
Ischemic stroke	0.7% (3) [0.2, 2.3]	2.6% (10) [1.4, 4.8]
Hemorrhagic stroke	0.0% (0) [0.0, 0.0]	0.0% (0) [0.0, 0.0]
Transient ischemic attack	0.0% (0) [0.0, 0.0]	0.3% (1) [0.0, 1.8]
Systemic embolism	0.0% (0) [0.0, 0.0]	0.3% (1) [0.0, 1.9]
Device embolization	0.0% (0) [0.0, 0.0]	0.0% (0) [0.0, 0.0]
Pericardial effusion		
Requiring open cardiac surgery	0.0% (0) [0.0, 0.0]	0.0% (0) [0.0, 0.0]
Requiring pericardiocentesis	0.7% (3) [0.2, 2.3]	1.0% (4) [0.4, 2.7]
Major bleeding (BARC 3 or 5)	3.0% (12) [1.7, 5.2]	7.9% (31) [5.6, 11.1]
BARC 3 bleeding	2.8% (11) [1.5, 4.9]	7.4% (29) [5.2, 10.5]
BARC 5 bleeding	0.3% (1) [0.0, 1.8]	0.5% (2) [0.1, 2.1]

BARC indicates Bleeding Academic Research Consortium.

TEE revealed a large mobile thrombus attached to the device. Additional detail regarding the 7 patients with DRT can be found in [Table IV in the Data Supplement](#).

## DISCUSSION

The first-generation LAA closure device has been evaluated in multiple clinical studies and has been implanted in >100 000 patients worldwide. Mechanical closure of the appendage is intended to help patients with NVAf to discontinue lifelong anticoagulant therapy for stroke prevention. Procedural safety and efficacy of the currently available device has been proven in multiple randomized trials and prospective registries with extensive follow-up,<sup>3,6,8</sup> and the incidence of major procedure-related complications has improved over time and with increasing physician experience.<sup>4,9</sup> However, improvements can be made to the present device to further reduce the incidence of pericardial effusion, device embolization, peri-device leak, and device-related thrombus. The next-generation LAA closure device was designed to address these issues and was evaluated in the PINNACLE FLX study. The principal findings were that the device met both the primary safety and efficacy end points, showing a low incidence of periprocedural safety events and a very high incidence of effective closure at 1 year (100%).

The WATCHMAN and Amplatzer Amulet Occluder are the most used LAA closure devices globally, with only the WATCHMAN being available for clinical use in the United States. To minimize the risk of the major

complications of LAA closure, pericardial effusion, device embolization, and periprocedural stroke, the next-generation LAA closure device was developed. It comprises a self-expanding nitinol frame with 18 peripheral fixation anchors (2 rows of 9) and a permeable polyester fabric covering the atrial-facing surface. Unlike the predicate device, the new device is available in 5 sizes, but covers a slightly larger range of LAA diameters, from 14 to 31.5 mm, accommodating a wider variety of anatomies. The atraumatic closed distal end was designed to reduce the risk for perforation, along with 2 rows of J-shaped fixation anchors to provide control and stability of deployment, and the ability for full and partial recapture and redeployment. The 18- rather than 10-strut design along with an open architecture configuration allows the device to conform to the LAA ostium and reduce peri-device leak. The threaded insert in the center of the proximal face is recessed, decreasing the amount of exposed metal volume to potentially improve healing and decrease device-related thrombus. Similar to the predicate device, size and placement is determined by LAA measurements using fluoroscopy and TEE guidance. Last, the length of the device is reduced, so that LAA depth is only required to be one-half that of the width of the LAA ostium, thus facilitating treatment of shallower appendages.

Pericardial effusion is the most common serious procedure-related complication. In contemporary clinical studies, the incidence of early (<7 days) pericardial effusion varies from 0.4% to 4%,<sup>10,11</sup> and in the National Cardiovascular Data Registry LAAO Registry of commercial implants within the United States, in-hospital pericardial effusion requiring surgical or percutaneous drainage occurred in 1.4%.<sup>4</sup> In the present study, there were no pericardial effusions requiring drainage in the first 7 days. Between 7 and 45 days, 3 cases required percutaneous drainage. The mechanism of these late effusions is unknown but could be attributable to micropunctures of the LAA in combination with postimplant DOAC therapy, which can lead to slow accumulation of blood in the pericardial space. Regardless, the closed atraumatic distal end of the device and newly constructed anchors may have contributed to these early favorable results.

Device embolization is one of the most serious complications associated with LAA closure. The incidence of this complication using current devices varies ≈0.2% to 2%,<sup>10,11</sup> whereas a more contemporary reporting from the National Cardiovascular Data Registry report was 0.07%.<sup>4</sup> When embolization does occur, especially with larger devices, the device may be caught in the left ventricle requiring surgical removal. It is important to note that there were no early or late embolizations of this next-generation LAA closure device in this study. The decreased height, presence of 2 rows of anchors, and the ability to fully recapture and reposition the device

allowing for optimal deployment are design changes that may have contributed to this notable finding.

Periprocedural stroke did occur in 2 (0.5%) patients, both of whom made a good recovery. The incidence of this complication was in line with the incidence reported in the literature that went from 0% to 0.9%.<sup>4,9–11</sup> Both cases appeared unrelated to the device, because, in the first case, no device was placed, and in the second case, the likely cause was attributable to severe intracranial atherosclerotic disease.

The primary efficacy end point of peri-device leak at 12 months was met, with no instances of >5 mm peri-device leak as adjudicated by the core laboratory in any patient at either the 45-day or 1-year follow-up TEE. In addition, only 17.2% and 10.5% of patients had any peri-device flow  $\leq$ 5 mm in diameter at 45-day and 12-month follow-up, respectively. It should be noted that this compares favorably with the incidence of peri-device flow observed in the PROTECT-AF trial with the predicate LAA closure device, in which 40.9% and 32.1% of patients had peri-device flow at similar time points.<sup>12</sup> In an analysis of the PROTECT AF and PREVAIL trials, no peri-device flow at 12 months was seen in 66% of cases,<sup>13</sup> whereas, in this study, no peri-device flow was seen in 90% of cases. There was modest discordance between the magnitude of site-reported peri-device flow and that determined by the echocardiography core laboratory. The conformability of the new-generation device, and the ability to use the atraumatic tip to achieve optimal positioning, as well, likely contributed to the relatively high incidence of effective closure. Although small amounts of residual flow around LAA occluder devices have not been robustly associated with ischemic stroke or device-related thrombus,<sup>12,13</sup> a relationship is mechanistically reasonable, and the high incidence of closure we observed may improve long-term clinical efficacy. Further clinical follow-up of the PINNACLE FLX cohort will provide greater insights into this possibility.

DRT occurred in 7 patients after 12 months of follow-up; however, only 2 of these patients had an embolic event. Despite the adverse events, the overall incidence of device-related thrombus compares favorably with the 3.7% of patients in whom DRT was reported in the predicate LAA closure device experience.<sup>14</sup> Furthermore, the postimplant regimen using a 6-week course of DOAC and low-dose aspirin therapy, compared with the combination of warfarin and aspirin used in the PROTECT-AF and PREVAIL clinical trials, may have also influenced the findings. The pathogenesis of DRT is still likely multifactorial, including patient-related factors, postprocedure antithrombotic therapy, and actual device characteristics. Although the improved incidence of LAA closure and decreased titanium surface area of the central insert

may have contributed to the results, firm conclusions about DRT are precluded because of the relatively small number of events, limited follow-up, and the nonrandomized nature of this comparison.

Last, unlike previous studies, the 45-day postimplant antithrombotic regimen consisted of aspirin in combination with a DOAC rather than with warfarin. The low incidence of periprocedural pericardial effusion and the absence of DRT in patients who were compliant with medication supports the use of a DOAC and low-dose aspirin as the standard postprocedural antithrombotic regimen.

## Study Limitations

Our study has several limitations. First, the study was not randomized to a control group; the procedural safety and efficacy of closure of the next-generation LAA closure device was not directly compared with that of the predicate device, and clinical event incidence with the first-generation device cannot be directly compared with a similar population treated with oral anticoagulation. Second, we report the incidence of anatomic and effective closure that are surrogates for the clinical outcomes of stroke and systemic embolism; these outcomes and others will be reported when the prespecified 2-year follow-up is complete. Third, our results should not be generalized to patients who have absolute contraindications to oral anticoagulant therapy. Last, the study sample size was not large enough to provide robust estimates of the incidence of rare events, such as device embolization.

## Conclusions

The PINNACLE FLX study results demonstrate that the next-generation LAA closure device, in combination with a 6-week postprocedural regimen of a DOAC and low-dose aspirin, is associated with a low incidence of safety events and high incidence of effective appendage closure.

## ARTICLE INFORMATION

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## Supplemental Materials

Data Supplement Tables I–IV

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