Rationale and design of a randomized study comparing the Watchman FLX device to DOACs in patients with atrial fibrillation

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Background Percutaneous left atrial appendage (LAA) closure (LAAC) was developed as a nonpharmacologic alternative to oral anticoagulants (OACs) in patients with atrial fibrillation (AF) who are at an increased risk for stroke or systemic embolism. The Watchman device permanently seals off the LAA to prevent thrombi from escaping into the circulation. Previous randomized trials have established the safety and efficacy of LAAC compared to warfarin. However, direct OACs (DOACs) have become the preferred pharmacologic strategy for stroke prevention in patients with AF, and there is limited data comparing Watchman FLX to DOACs in a broad AF patient population. CHAMPION-AF is designed to prospectively determine whether LAAC with Watchman FLX is a reasonable first-line alternative to DOACs in patients with AF who are indicated for OAC therapy.

Study Design A total of 3,000 patients with a CHA2DS2-VASc score ≥2 (men) or ≥3 (women) were randomized to Watchman FLX or DOAC in a 1:1 allocation at 142 global clinical sites. Patients in the device arm were to be treated with DOAC and aspirin, DOAC alone, or DAPT for at least 3 months postimplant followed by aspirin or P2Y12 inhibitor for 1-year. Control patients were required to take an approved DOAC for the duration of the trial. Clinical follow-up visits are scheduled at 3- and 12-months, and then annually through 5 years; LAA imaging is required at 4 months in the device group. Two primary end points will be evaluated at 3 years: (1) composite of stroke (ischemic/hemorrhagic), cardiovascular death, and systemic embolism compared for noninferiority, and (2) nonprocedural bleeding (International Society on Thrombosis and Haemostasis [ISTH] major and clinically relevant nonmajor bleeding) tested for superiority in the device arm against DOACs. The third primary noninferiority end point is the composite of ischemic stroke and systemic embolism at 5 years. Secondary end points include 3- and 5-year rates of (1) ISTH-defined major bleeding and (2) the composite of cardiovascular death, all stroke, systemic embolism, and nonprocedural ISTH bleeding.

Conclusions This study will prospectively evaluate whether LAAC with the Watchman FLX device is a reasonable alternative to DOACs in patients with AF.

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Background

Atrial fibrillation (AF) is a major chronic cardiovascular disorder, affecting 2% to 4% of the population worldwide.[1] The incidence of AF and AF-related strokes is increasing rapidly in an aging population and in those with certain comorbidities (eg, hypertension, heart failure, diabetes, coronary artery disease or chronic kidney disease).[2] AF is independently associated with a 5-fold increased risk of stroke, which consequently leads to disability and death.[1]

Oral anticoagulation therapy with warfarin, a vitamin-K antagonist, has shown to reduce the risk of both stroke and mortality in patients with AF, however is associated with increased risk of bleeding complications.[3,4] Direct oral anticoagulants (DOACs) when compared to warfarin, eliminate the need for frequent monitoring, dose adjustments, and have minimal dietary and metabolic interactions. DOACs have shown favorable results in randomized comparisons to warfarin for patients with AF and consequently have now largely replaced warfarin as a first line therapy for AF.[5-10] Despite these findings, sustained treatment with these newer agents can be challenging for patients over time because of concerns related to drug compliance, bleeding complications and affordability.

Percutaneous left atrial appendage (LAA) closure (LAAC) is a minimally invasive procedure for stroke prevention in patients with AF.[11,12] Watchman is a LAAC device that prevents embolization of thrombi by completely sealing off the LAA. FLX is a next-generation Watchman device with a closed distal end structure and an increased number of struts to potentially reduce both the risk of pericardial effusion and periprocedural device leaks, respectively. These design modifications were implemented to improve procedural safety and expand the eligible patient population to include complex LAA anatomies. In the National Cardiovascular Data Registry (NCDR) LAA occlusion registry,[13] Watchman FLX has shown significantly improved implantation success and procedural safety compared with the original device, including reduced pericardial effusions requiring intervention. LAAC with Watchman was found to be noninferior to warfarin for the prevention of stroke, systemic embolism and cardiovascular death in the randomized PROTECT-AF trial.[14] PREVAIL was a confirmatory randomized controlled trial (RCT) that also supported the safety of Watchman compared to warfarin.[15] The PINNACLE FLX study reported favorable outcomes with the next-generation Watchman FLX device in patients with AF.[11] Currently however, LAAC has a Class IIB recommendation for stroke prevention in patients with AF and remains largely confined to patients who have a clinical reason to seek an alternative to oral anticoagulants (OAC) such as prior bleeding or recurrent falls.[1] Data from randomized controlled trials comparing LAAC devices to DOACs in a broad population of patients with AF are scarce. The CHAMPION-AF study is designed to investigate whether the Watchman FLX device is a reasonable first-line alternative to DOACs in patients with nonvalvular AF who are also suitable candidates for OAC therapy.

Study design and methods

CHAMPION-AF is a prospective, multicenter trial that randomized patients with nonvalvular AF to either the Watchman FLX device or DOACs at up to 200 clinical sites globally (ClinicalTrials.gov: NCT04394546). This study is being conducted in accordance with ISO 14155 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice, the International Conference on Harmonisation, the Declaration of Helsinki, and applicable local regulations. The study initiated after approval from the institutional review board/ethics board at each center and patients provided written informed consent. CHAMPION-AF is funded and sponsored by Boston Scientific Corporation (BSC). The study is designed by the authors in collaboration with the sponsor. Additionally, the authors are responsible for the drafting and editing of this paper, and its final contents; no extramural funding will be used to support this work.

Study device description

The Watchman FLX LAAC device (BSC, Marlborough, MA) consists of (1) a self-expanding nitinol frame structure with dual-row J-shaped fixation anchors to maximize device stability and (2) a permeable polyester fabric covering the atrial facing surface of the closure device to minimize metal exposure.[11] Watchman FLX, available in 5 sizes ranging from 20 to 35 mm in diameter, is permanently implanted at or slightly distal to the ostium of the LAA to trap potential emboli before they exit the LAA.

Study population and patient selection

CHAMPION-AF randomized 3,000 patients at 142 global investigational sites in the United States, Europe, Japan, and Brazil between October 2020 and November 2022. Patients were screened according to the clinical inclusion and exclusion criteria listed in Table I. Briefly, patients of legal age capable of providing written informed consent and documented nonvalvular AF with a CHA2DS2-VASc score $\geq$2 (men) or $\geq$3 (women) were included in the trial. Key exclusion criteria were MI, stroke, or transient ischemic attack within the 30 days before enrollment and International Society on Thrombosis and Haemostasis (ISTH) major bleeding event[16] within the 30 days prior to randomization. In addition, all enrolled patients were required to undergo baseline transthoracic echocardiographic evaluation to further confirm eligibility (Table I).

Table I. CHAMPION-AF study inclusion and exclusion criteria.

Key inclusion criteria:

1. The subject is of legal age to participate in the study per the laws of their respective geography.
2. The subject has documented nonvalvular AF, defined as AF in the absence of moderate or greater mitral stenosis or a mechanical heart valve.
3. The subject has a calculated CHA_2DS_2-VASc score $\geq$2 (for men) and $\geq$3 (for women).
4. The subject is deemed to be suitable for the protocol defined pharmacologic regimens in both the test and control arms.
5. The subject (or legal representative) understands the trial requirements and provides written informed consent before participating in the trial.
6. The subject is able and willing to return for required follow-up visits and examinations.

Key exclusion criteria:

1. Subjects who are currently enrolled in another investigational study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments.
2. The subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (ie, even if the device is implanted, the subjects would not be eligible to discontinue OAC due to other medical conditions requiring chronic OAC therapy).
3. The subject is contraindicated or allergic to oral anticoagulation medication and/or aspirin.
4. The subject is indicated for chronic P2Y12 platelet inhibitor therapy.
5. The subject had or is planning to have any cardiac or noncardiac intervention or surgical procedure within 30 days prior to or 60 days after implant (including, but not limited to: cardioversion, PCI, cardiac ablation, cataract surgery, etc.).
6. The subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or transient ischemic attack (TIA) within the 30 days prior to enrollment.
7. The subject had a prior major bleeding event per ISTH definition within the 30 days prior to randomization. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event.
8. The subject has an active bleed.
9. The subject has a reversible cause of AF or transient AF.
10. The subject is absent of a LAA or the LAA is surgically ligated.
11. The subject has had a MI documented in the clinical record as either a NSTEMI or STEMI, with or without intervention, within 30 days prior to enrollment.
12. The subject has a history of atrial septal repair or has an ASD/PFO device.
13. The subject has an implanted mechanical valve prosthesis in any position.
14. The subject has a known contraindication to percutaneous catheterization procedure and/or TEE.
15. The subject has a cardiac tumor.
16. The subject has signs/symptoms of acute or chronic pericarditis.
17. The subject has an active infection.
18. There is evidence of tamponade physiology.
19. The subject has New York Heart Association Class IV congestive heart failure at the time of enrollment.
20. The subject is of childbearing potential and is, or plans to become, pregnant during the time of the study (method of assessment upon study physician's discretion).
21. The subject has a documented life expectancy of less than 3 years.

Transthoracic echocardiographic exclusion criteria:

1. The subject has LVEF <30%.
2. The subject has an existing pericardial effusion with a circumferential echo-free space >5 mm.
3. The subject has a high-risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion >15 mm or length >15 mm.
4. The subject has significant mitral valve stenosis (ie, MV area < 1.5 cm^2).

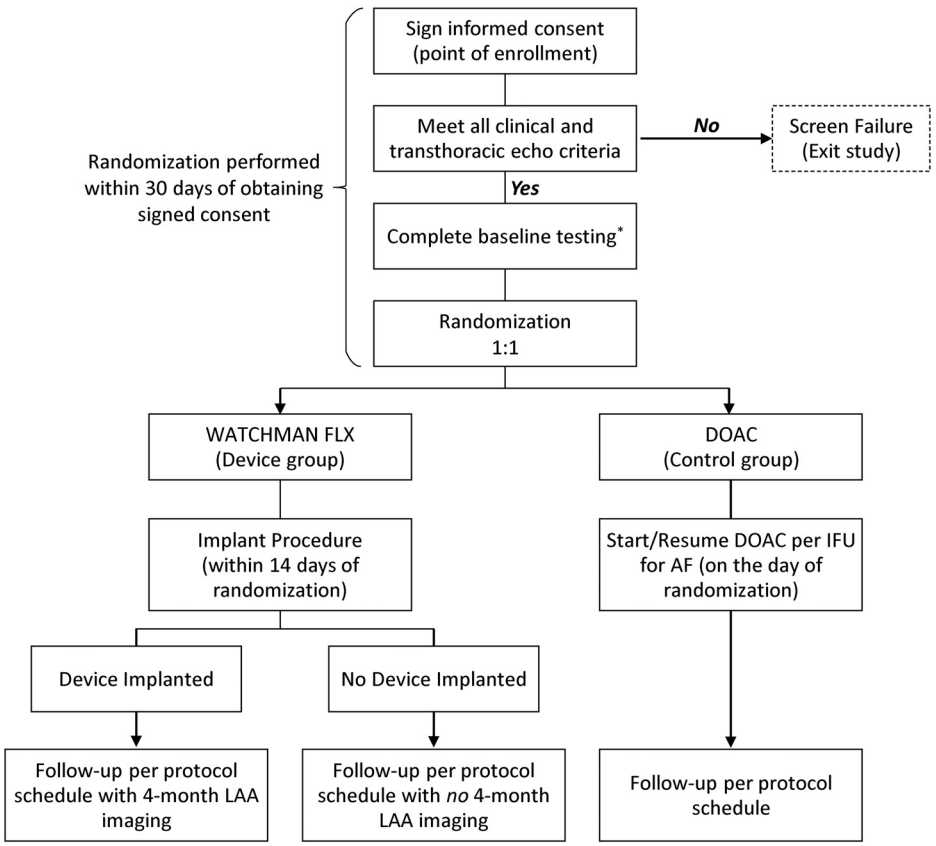
ASD, atrial septal defect; *AF*, atrial fibrillation; *ISTH*, International Society on Thrombosis and Haemostasis; *LAA*, left atrial appendage; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MV*, mitral valve; *NSTEMI*, non-ST-segment elevation myocardial infarction; *OAC*, oral anticoagulants; *PCI*, percuteneous coronary intervention; *PFO*, patent foramen ovale; *STEMI*, ST-segment elevation myocardial infarction.

Randomization and treatment protocol

Patients who satisfied the study selection criteria and complete baseline testing were randomized in a 1:1 allocation to receive treatment with either Watchman FLX (device arm) or DOAC (control arm; Figure 1). A computer-generated list of random treatment allocations was used to randomize enrolled patients within 30 days of obtaining informed consent. Patients in the Watchman FLX arm were required to undergo implantation no later than 14 days after randomization.

The implantation procedure described previously[11] was performed by study physicians trained in percutaneous and transseptal procedures who have completed the Watchman FLX physician training program using

Figure



CHAMPION AF study design. *baseline testing includes TTE, modified Rankin scale (MRS) and NIH stroke scale (NIHSS), quality of life questionnaires (SF-12/EQ-5D-5L) and Montreal cognitive assessment (MoCA). *AF*, atrial fibrillation; *IFU*, instructions for use; *LAA*, left atrial appendage.

standard of care methods. TEE imaging was recommended for all implant procedures; however, intracardiac echocardiography (ICE) was a permissible alternative if (1) preplanning using TEE or computerized tomography (CT) was completed prior to the implant procedure, and (2) the implanting physician had performed ≥25 ICE-guided Watchman and/or Watchman FLX procedures. Watchman FLX implantation was not to be performed if intracardiac thrombus, complex atheroma with mobile plaque of the descending aorta and/or aortic arch, high-risk patent foramen ovale, LAA sludge or dense spontaneous echo contrast was observed on the TEE/ICE or fluoroscopy.

Both device and control groups have clinical follow-up visits scheduled for 3 months, 12 months, and then annually through 5 years. Four-month LAA imaging (TEE or CT) was required for the device group only (Figure 1). TEE/CT imaging data will be reviewed by experienced LAAC echocardiographers who will also independently adjudicate the presence of device-related thrombus (DRT) and peri-device leak.

Study medication

The postimplant drug regimen includes DOAC and aspirin, DOAC alone, or dual antiplatelet therapy (DAPT; 75 mg clopidogrel and 75-100 mg aspirin recommended). Apixaban and rivaroxaban are recommended DOACS that can be used at the indicated AF dosing. Patients are required to discontinue the prescribed medication at the 3-month follow-up visit if technical success is achieved during implant (leak ≤ 5 mm). If technical success is not achieved (leak > 5 mm), patients take DOAC and aspirin until a leak ≤5 mm is demonstrated on subsequent LAA imaging. OAC therapy will be at the discretion of the treating physician for other indications provided that any peri-device flow demonstrated by LAA imaging was ≤5 mm. Patients are recommended to continue either aspirin or P2Y12 inhibitor (if tolerated better than

aspirin) through at least 12 months postimplant. If DRT is detected during LAA imaging at 4 months, the patient will be recommended to restart anticoagulation therapy with aspirin.

Following randomization, control patients will be required to continue or commence an approved DOAC for the duration of the trial as per the instructions for use and recommended guidelines for AF stroke prevention.

Study end points

CHAMPION-AF will test the following: (1) primary endpoint #1: composite of stroke (including ischemic and/or hemorrhagic), cardiovascular death (including hemorrhagic and/or unexplained death), and systemic embolism at 3 years; (2) primary endpoint #2: nonprocedural bleeding at 3 years based on the ISTH definitions for major bleeding[16] and clinically relevant nonmajor bleeding[17]; (3) primary end point #3: composite of ischemic stroke and systemic embolism at 5 years.

Stroke is defined as a rapid onset of a focal- or global-neurologic deficit with neurologic signs/symptoms consistent with stroke, or neurologic deficit resulting in death. The diagnosis of stroke, categorized as ischemic or hemorrhagic, will be confirmed by a neurologist or neurosurgical specialist, neuroimaging procedure or lumbar puncture. Systemic embolism is defined as an acute systemic vascular insufficiency or occlusion of an artery supplying the extremities or organs not involving the central nervous system accompanied with clinical, imaging, surgical/autopsy evidence of arterial occlusion (in the absence of other likely mechanisms). ISTH major[16] and clinically relevant nonmajor bleeding[17] events occurring more than 3 days after implantation of Watchman FLX will be deemed nonprocedural; all bleeding events in the control arm will be considered nonprocedural. ISTH major bleeding[16] is defined as having a symptomatic presentation and fatal bleeding and/or bleeding in a critical area or organ and/or bleeding that causes a fall in hemoglobin level (20 g $L^{-}1$ or more) or leading to transfusion of $\geq$2 units of whole blood or red cells. ISTH clinically relevant nonmajor bleeding[17] is defined as any sign or symptom of hemorrhage that requires either medical intervention or hospitalization/increased level of care, which does not fit the criteria for ISTH major bleeding.

Secondary endpoints included 3- and 5-year rates of (1) ISTH defined major bleeding[16] and (2) the composite of cardiovascular death, all stroke, systemic embolism, and nonprocedural bleeding (ISTH defined major bleeding[16] and clinically relevant nonmajor bleeding.[17]) Additional endpoints will include individual components of the composite endpoints, all deaths,[18] procedural and nonprocedural major and clinically relevant nonmajor bleeding, procedure-related major complications, and the rate of patient adherence to DOACs (ie, number of patients who are on DOAC $\geq$80% of the time). Procedure-related complications are defined as the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: (1) all-cause death, (2) ischemic stroke, (3) systemic embolism, or (4) device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, arteriovenous fistula repair, or any other major endovascular repair. Percutaneous drainage of pericardial effusions is not considered a procedure-related complication. Montreal Cognitive Assessment will be assessed at baseline and 36 months. The EQ-5D-5L and SF-12 quality of life questionnaires are administered at the baseline visit, at 3 months, 1-year, and 3-year follow-up visits.

A data monitoring committee will review safety events and a clinical events committee will adjudicate stroke, systemic embolism, pericardial effusion requiring intervention, deaths and ISTH major bleeding and clinically relevant nonmajor bleeding for all patients beginning at the point of randomization.

Statistical methods

The study is designed to investigate whether LAAC with the Watchman FLX device is a reasonable alternative to DOACs in patients with AF and will be considered a success if primary endpoints 1 and 2 are met. Statistical analyses of the primary endpoints summarized in Table II will be performed on an intent-to-treat basis, with each patient examined as being part of their randomized arm regardless of the treatment received. All primary and secondary endpoints will be calculated after the last patient randomized has been followed for 3 or 5 years and completed their respective follow-up.

The first primary endpoint of stroke, cardiovascular death and systemic embolism at 3 years is powered for noninferiority (NI). The expected 3-year cumulative incidence rate is estimated to be 12% in the device and control groups, based on historical event rates from previous Watchman[12,19,20] and DOAC[5-8] studies, respectively. NI will be proven if the 1-sided 97.5% upper confidence bound for the difference between the device and control groups is less than the predefined margin (δ) of 4.8% (40% relative to corresponding expected rate). Assuming a 3-year cumulative rate of 12% in both arms and a 1-sided test significance level (α) of 2.5%, a total of 3,000 patients provide 90% power to demonstrate NI with a δ of 4.8% after adjusting for cumulative attrition rate in both arms (12.5%).

The second primary endpoint of nonprocedural bleeding at 3 years will test for superiority of the Watchman FLX device to DOAC. The expected Kaplan Meier rate of nonprocedural bleeding at 3 years is estimated to be 27% in the device arm (based on previous Watchman stud-

Table II. Statistical analysis of primary end points.

		Primary endpoint #1*	Primary endpoint #2†	Primary endpoint #3‡
Model		Noninferiority comparison—Kaplan Meier event rate difference	Superiority comparison—2-sided log-rank test	Noninferiority comparison—Kaplan Meier event rate difference
Assessment period		36-month follow-up visit	36-month follow-up visit	60-month follow-up visit
Hypothesis		H_0: $P_1(t) \geq P_0(t) + \delta$ H_a: $P_1(t) < P_0(t) + \delta$	H_0: $P_1(t) = P_0(t)$ H_1: $P_1(t) \neq P_0(t)$	H_0: $P_1(t) \geq P_0(t) + \delta$ H_a: $P_1(t) < P_0(t) + \delta$
		$P_1(t)$ = Kaplan Meier estimates for the device group $P_0(t)$ = Kaplan Meier estimates for the control group		
Expected rate	Control	12%	33%	7.5%
	Device	12%	27%	7.5%
Noninferiority margin (δ)		4.8%	NA	4%
Test significance level		2.5%	5%	2.5%
Power		90%	93%	90%
Cumulative attrition rate		12.5% in both groups	20% in both groups	33% in both groups
Subjects required		3,000	3,000	3,000

The expected cumulative event rates in the device and control arms based on historical event rates from previous Watchman[12,19,20] and DOAC[5-8] studies, respectively
Primary endpoints 1 and 3 will be tested for superiority if the noninferiority hypothesis is met

*Primary endpoint #1 defined as Kaplan Meier rate of stroke (including ischemic and/or hemorrhagic), cardiovascular death (including hemorrhagic and/or unexplained death) and systemic embolism at 36-months.

†Primary endpoint #2 defined as the Kaplan Meier rate of nonprocedural bleeding (ISTH major bleeding and clinically relevant nonmajor bleeding) at 36 months.

‡Primary endpoint #3 defined as Kaplan Meier rate of ischemic stroke and systemic embolism at 60 months.

ies[12,19,20]) and 33% in the control arm (based on the major/clinically relevant nonmajor bleeding rates reported in DOAC trials[5-8]). With a 2-sided α of 5%, 2,400 evaluable patients provide 93% power to meet superiority. To further account for up to 20% expected rate of attrition, a total of 3,000 patients will be randomized.

The study was also powered to assess the third primary endpoint of ischemic stroke and systemic embolism at 5 years. Based on the historical event rates from previous Watchman studies,[12,19,20] the expected cumulative incidence of ischemic stroke and systemic embolism at 5 years in the device group was 7.5%. The expected event rate of 7.5% in the control arm was derived from previous DOAC trials[5-8] (6.0%) but increased due to the anticipation of a somewhat higher risk patient population being enrolled in the CHAMPION-AF trial. To account for variability in the event rates over 5 years of follow-up with possibly fewer high-risk patients, the δ was calculated to be 4% (53% relative to corresponding expected rate). Treatment with Watchman FLX will be considered noninferior to DOAC if the 1-sided 97.5% upper confidence bound for the difference in rates is less than δ. An estimated 3,000 patients would provide 90% power to demonstrate NI with a δ of 4%, 1-sided α of 2.5% and the cumulative attrition rate of 33% in both the device and control arms.

The power and sample size calculations for the secondary endpoints are displayed in Table III. A hierarchical testing structure will be used to ensure that each hypothesis (H) test is performed sequentially at the family-wise level to maintain overall α spending and that no additional multiplicity adjustment is needed.[21] Hypothesis testing will follow a fixed sequence procedure: H1 (primary end point #1 at 3 years, NI) and H2 (primary endpoint #2 at 3 years, superiority) → H3 (secondary endpoint #1 at 3 years, NI) → H4 (secondary endpoint #2 at 3 years, NI) → H5 (primary endpoint #3 at 5 years, NI) → H6 (secondary endpoint #1 at 5 years, superiority) → H7 (secondary endpoint #2 at 5 years, superiority), and stop at Hi (i = 1,2,…7) if it fails to reject the null hypothesis. Each endpoint in the hierarchy will be considered significant only if the P-value for that and all prior endpoints show statistical significance.

Statistical analyses will be performed using SAS version 9.2 or later (SAS Institute, Inc, Cary, NC). Continuous variables will be summarized as mean ± standard deviation and compared between treatment groups using one-way analysis of variance or the nonparametric Kruskal-Wallis test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using Pearson's χ^2 or Fisher exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores. The power and sample size were calculated assuming 2-proportion difference for NI or log-rank test methodology for superiority using EAST 6.5 software (Cytel,

Table III. Statistical analysis of secondary end points.

		Secondary endpoint #1*		Secondary endpoint #2†	
Model		Noninferiority comparison—Kaplan Meier event rate difference	Superiority comparison if noninferiority is met	Noninferiority comparison—Kaplan Meier event rate difference	Superiority comparison if noninferiority is met
Assessment period		36 mo	60 mo	36 mo	60 mo
Hypothesis		$H_0: S_1(t) \geq S_0(t) + \delta$ $H_a: S_1(t) < S_0(t) + \delta$	$H_0: S_1(t) = S_0(t)$ $H_1: S_1(t) \neq S_0(t)$	$H_0: S_1(t) \geq S_0(t) + \delta$ $H_a: S_1(t) < S_0(t) + \delta$	$H_0: S_1(t) = S_0(t)$ $H_1: S_1(t) \neq S_0(t)$
		$S_1(t)$ = Kaplan Meier estimates for the device group $S_0(t)$ = Kaplan Meier estimates for the control group			
Expected rate	Control	12%	18%	24%	37%
	Device	12%	13.3%	24%†	31%
Noninferiority margin (δ)		4.8%	NA	9.6%	NA
Test significance level		2.5%	2.5%	2.5%	2.5%
Power		95%	90%	99%	91%
Cumulative attrition rate		15% in both groups	33% in both groups	12.5% in both groups	20.5% in both groups
Subjects required		3,000	3,000	3,000	3,000

The δ was chosen to be 40% relative to the corresponding expected rate
The expected cumulative event rates in the device and control arms based on historical event rates from previous Watchman[12,19,20] and DOAC[5-8] studies, respectively
* Secondary endpoint #1 defined as Kaplan Meier estimates for cumulative incidence of all ISTH major bleeding.
† Secondary endpoint #2 defined as the Kaplan Meier estimates for cumulative incidence of CV death, all stroke, systemic embolism, and nonprocedural bleeding (ISTH major bleeding and clinically relevant nonmajor bleeding).

Waltham, MA). Kaplan-Meier method will be used to report time-to-event analysis. Exploratory analyses for competing risk of mortality may be performed as appropriate. The variance estimate will be calculated using Greenwood's formula. Log-rank test will be used to compare survival curves.

Discussion

The CHAMPION AF study is designed to evaluate Watchman FLX LAAC device as a safe and effective alternative to DOACs in a broad population of patients with AF. The trial data will be used to support an expanded label indication for the Watchman FLX device and potentially expand the breath of patients who may benefit from LAAC as a first-line therapy. Watchman, an FDA-approved LAAC device, has been implanted internationally in >200,000 patients and has shown promising clinical results across numerous trials.[11,12,19,20] Despite this, LAA occlusion remains at a Class IIB indication for stroke prevention in patients with AF and contraindications for long-term OAC therapy.[1]

The risks of bleeding and related complications in patients with AF requiring anticoagulation have been well-described. Warfarin has shown to be effective in preventing stroke however, it has a narrow therapeutic range and is often not well tolerated.[22] Given these limitations, DOACs were developed that have shown a reduced risk of intracranial hemorrhage and major bleeding, to warfarin.[5-8] Considering the vast abundance of favorable data, DOACs are given preference over warfarin under the current guidelines. The net clinical benefit of DOACs may however be offset by decreased patient compliance or contraindications in certain patient population (eg, kidney dysfunction/advanced chronic kidney disease) and potential interaction with other drugs.[23]

The new-generation Watchman FLX device differs from its predecessor in various aspects. First, change in the shape of the distal end from open to closed provides deployment stability and control, and is less traumatic. Second, addition of more dual-row anchors and struts promotes device stabilization, better anchoring and sealing of the LAA, and increased conformability; the device can be fully recaptured, repositioned, and redeployed, thereby reducing the number of devices used per case. Third, the low device height permits improved handling in shallow LAA anatomies. Fourth, changes in the threaded insert minimize metal exposure outside of the permeable polyester implant fabric, potentially reducing DRT. Finally, a wider sizing matrix and shorter length enables treatment of a larger patient population with different LAA anatomies. In the PINNACLE FLX study,[11] LAAC with Watchman FLX was associated with a high incidence of effective appendage closure (100%) and implant procedure success (98.8%). The ALSTER-FLX reg-

istry[24] also showed all Watchman FLX implantations to be successful ($N = 164$) with a favorable device safety profile. There were no cases of pericardial effusions or device embolization in both studies.[11,24] The rates of device success in the NCDR[13] were significantly higher with FLX versus the predicate Watchman 2.5 (97.4% versus 96.6%; $P < .001$), as were implantation success (97.8% versus 96.8%; $P < .001$) and procedural success (96.1% versus 94.6%; $P < .001$). Pericardial effusion and device embolization were significantly lower with the new generation device than Watchman 2.5 (0.42% versus 1.23%; $P < .0001$ and 0.02% versus 0.06%; $P = .03$, respectively).[13]

There are limited trial data available on the efficacy of LAAC compared to DOACs in a broad population of patients with AF. In the PRAGUE-17 trial[25,26] that randomized high-risk AF patients (CHA_2DS_2VASc 4.7 ± 1.5), LAAC (Watchman/Watchman FLX/Amulet) was found to be noninferior to DOACs for the composite endpoint of stroke, cardiovascular death, major or nonmajor clinically relevant bleeding, procedure- or device-related complications, systemic embolism, or transient ischemic attack at a median follow-up of 19.9 months and 3.5 years. The incidence of nonprocedural clinically relevant bleeding at 4 years was significantly lower with LAAC versus DOACs (3.4% versus 5.9%; $P = .039$). In a propensity-score matched comparative study of 2 separate registries,[27] AF patients treated with the Amulet LAAC device demonstrated a significantly lower risk of the composite end point (mortality, ischemic stroke, or major bleeding) at 2 years compared with DOACs. These differences were mainly driven by significantly reduced risk of major bleeding and all-cause mortality in patients with LAAC. Similar results were reported in the APPLY propensity-matched observational study,[28] where the incidence of the primary composite endpoint of stroke and cardiovascular death at the mean follow-up of 2.7 years was significantly lower in the LAAC group (AMPLATZER Cardiac Plug/Amulet) compared to DOACs. The rates of cardiovascular death and all-cause mortality were both lower with the LAAC device than DOACs. The primary safety endpoint of major procedural adverse events and major bleeding was similar between groups. Additional randomized trials are needed to evaluate the durability of these observations.

CHAMPION-AF will test 3 primary endpoints at different timepoints. The first primary endpoint of all cause stroke, systemic embolism and cardiovascular death at 3 years has been chosen in previous clinical trials comparing LAAC to warfarin. This trial compares a device-based therapy to medical therapy for prevention of stroke. DOACs can prevent ischemic stroke, but at the expense of a small increase in hemorrhagic stroke. A device-based therapy may be more effective in lowering the incidence of hemorrhagic stroke while offering protection against thromboembolism. This endpoint is intended to demonstrate that net benefit is similar with both approaches. The second primary endpoint of nonprocedural bleeding at 3 years is crucial for this study as it will evaluate whether device-based therapy is superior to DOACS in lowering the long-term risk of bleeding. These first 2 endpoints are likely most critical for evaluating the therapy from a patient's point of view. Finally, the third endpoint will assess the longer-term (5 years) benefits of device-based therapy compared to blood thinners in the prevention of ischemic stroke and systemic embolism. Long-term anticoagulation therapy though effective, may not be a permanent solution considering the high proportion of patients who will be noncompliant to medications due to genuine clinical or financial reasons, whereas device-based therapy offers a permanent solution. This endpoint is therefore evaluated at 5 years, and the hypothesis is that for all the above reasons, a device-based therapy should be noninferior to DOACs in longer term prevention of ischemic stroke or systemic embolization. Collectively, these 3 endpoints together with the secondary endpoints will help establish the safety and efficacy of LAAC in comparison to long-term intake of blood thinners.

Conclusions

There are limited clinical trial data on outcomes with LAAC compared to DOACs. Moreover, the studies comparing these therapies are nonrandomized and underpowered to detect differences in clinical events. CHAMPION-AF is the first large RCT comparing Watchman FLX to contemporary DOACs in a broad AF population, and not just in patients with a history of prior bleeding or other reasons to seek an alternative to OAC. Enrollment into this study ended in November 2022 and data for the first 2 primary end points are anticipated in 2026.

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