


BMJ Open Double-blind, placebo-controlled randomised clinical trial to evaluate the effect of ASPIRIN discontinuation after left atrial appendage occlusion in atrial fibrillation: protocol of the ASPIRIN LAAO trial

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ABSTRACT

Introduction It is the common clinical practice to prescribe indefinite aspirin for patients with non-valvular atrial fibrillation (NVAF) post left atrial appendage occlusion (LAAO). However, aspirin as a primary prevention strategy for cardiovascular diseases has recently been challenged due to increased risk of bleeding. Therefore, aspirin discontinuation after LAAO in atrial fibrillation (ASPIRIN LAAO) trial is designed to assess the uncertainty about the risks and benefits of discontinuing aspirin therapy at 6 months postimplantation with a Watchman LAAO device in NVAF patients.

Methods and analysis The ASPIRIN LAAO study is a prospective, multicentre, randomised, double-blinded, placebo-controlled non-inferiority trial. Patients implanted with a Watchman device within 6 months prior to enrollment and without pre-existing conditions requiring long-term aspirin therapy according to current guidelines are eligible for participating the trial. Subjects will be randomised in a 1:1 allocation ratio to either the Aspirin group (aspirin 100 mg/day) or the control group (placebo) at 6 months postimplantation. A total of 1120 subjects will be enrolled from 12 investigational sites in China. The primary composite endpoint is stroke, systemic embolism, cardiovascular/unexplained death, major bleeding, acute coronary syndrome and coronary or periphery artery disease requiring revascularisation at 24 months. Follow-up visits are scheduled at 6 and 12 months and then every 12 months until 24 months after the last patient recruitment.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of Xinhua Hospital, Shanghai, China (reference number XHEC-C-2018-065-5). The protocol is also submitted and approved by the institutional Ethics Committee at each participating centre. Results are expected in 2024 and will be disseminated through peer-reviewed journals and presentations at national and international conferences.

Trial registration number NCT03821883.

INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is associated with a fourfold to fivefold increase in stroke rates and cardioembolic events leading to increased mortality.^{1 2} The use of

Strengths and limitations of this study

- First randomised, placebo controlled trial to optimise the long-term antithrombotic regimen after left atrial appendage occlusion.
- Adequately powered and will inform the appropriate and judicious use of aspirin in atrial fibrillation patients with left atrial appendage occluder.
- This study only includes Chinese patients with Watchman device, which limits its generalisability to other types of devices and population.

oral anticoagulants (OAC), either warfarin or novel OAC, to prevent thromboembolism in patients with NVAF has a class I recommendation in guidelines, unless a truly low risk of stroke is evident.^{3–5} However, gaps exist between the real world situations and guideline recommendations,^{6 7} especially in China.⁸ A considerable number of NVAF patients are not suitable or have increased concern on taking long-term OAC due to previous bleeding experience or at high risks of bleeding. Besides absolute or relative contraindications to anticoagulation, poor compliance and personal preference also contribute to the low guideline adherence worldwide.^{7 9 10} The undertreatment and underdosing of OAC remain as a reason related with increased risks of stroke and mortality in NVAF patients.^{6 7 10}

As 90% of stroke-causing thrombi in patients with NVAF originate in the left atrial appendage (LAA),^{11 12} the LAA occlusion (LAAO) develops a mechanical barrier to block emboli from leaving the LAA by sealing its orifice. As a 'local' therapy, the advantage of LAAO over OAC might be revealed in

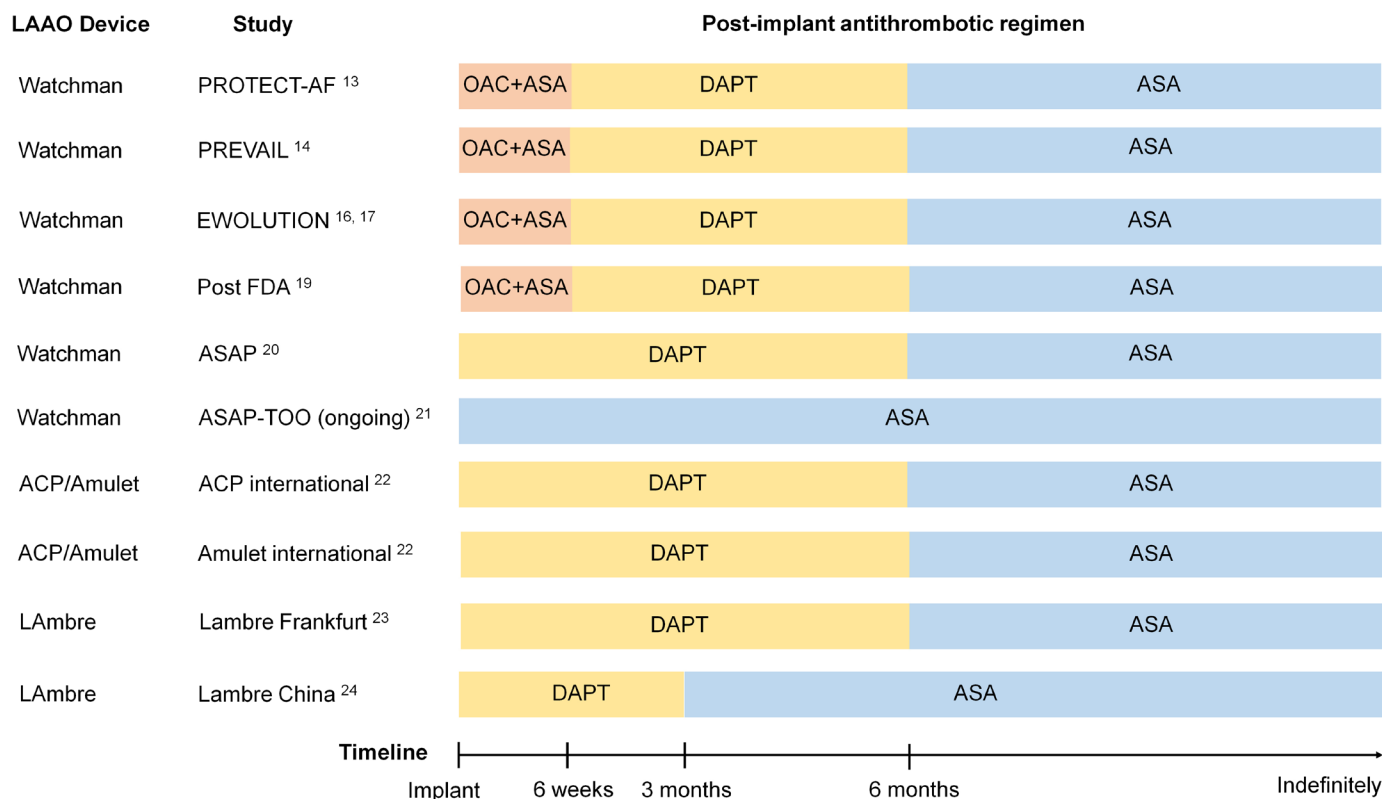


Figure 1 Antithrombotic regimen after LAAO. ACP, Amplatzer Cardiac Plug; ASA, aspirin; DAPT, dual antiplatelet therapy; LAAO, left atrial appendage occlusion; OAC, oral anticoagulant.

patients who are at high risks of both stroke and bleeding and are contraindicated to systemic anticoagulation. Therefore, LAAO is emerging as the most useful approach for stroke prevention in NVAF patients, who are not suitable for or unwilling to receive long-term OAC. Among multiple LAAO devices, the Watchman device (Boston Scientific, Marlborough, Massachusetts, USA) was shown to be non-inferior to warfarin or direct OAC on reducing outcome events in randomised controlled trials.^{13–15} The safety and effectiveness of Watchman devices in real-world clinical practice has been further confirmed by the EWOLUTION (Registry on WATCHMAN Outcomes in Real-Life Utilization), POST-FDA (Post-Approval by the US Food and Drug Administration) and the most recent NCDR (National Cardiovascular Data Registry) LAAO registries,^{16–19} both exhibiting acceptable periprocedural complications and consistently low rates of stroke and bleeding during the follow-up.

However, even patients with successful LAAO device implantation are not completely free from antithrombotic (anticoagulation and/or antiplatelet) treatment, in order to allow sufficient endothelialisation and prevent thrombus formation on the surface of the device. As summarised in [figure 1](#), the postimplant antithrombotic regimens are complex, however, empirical, and consensus around the optimal regimen has not been achieved. In the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVEIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long

Term Warfarin Therapy) trials, patients received warfarin with target international normalised ratio (INR) 2–3 plus aspirin (81 mg/day) for the initial 45 days postprocedure. In subjects who showed complete sealing and no device related thrombus (DRT) at 45-day follow-up, OAC was discontinued and dual antiplatelet therapy, consisting of clopidogrel (75 mg) and aspirin (81 mg), was prescribed until 6 months postprocedure. After 6 months, patients were prescribed aspirin (325 mg) indefinitely.^{13 14} In real-world practice, postimplant antithrombotic regimens vary during the initial 1–6 months postprocedure, including direct, sequential or combination therapy of warfarin/novel OAC and antiplatelet drugs.^{13 14 16–18 20}

Regardless of various drug regimen in the first 6 months, patients are generally administered lifelong aspirin thereafter.^{13 14 16–18 20 21} Similarly, for patients implanted with other LAAO devices, including Amplatzer Cardiac Plug (ACP)/Amulet²² and LAmbré,^{23 24} indefinite aspirin is generally administered postimplant. Of note, the long-term aspirin therapy after LAAO implantation is only empirical, and was not tested in randomised trials.

Aspirin does not benefit NVAF patients, which has been demonstrated by a meta-analysis that aspirin is not superior to a control treatment or a placebo in the prevention of stroke, systemic embolism or mortality.²⁵ Specifically, in NVAF patients implanted with Watchman device, non-procedure related major bleeding and haemorrhagic stroke were also noticed on aspirin during the long-term follow-up.²⁶ The real-world EWOLUTION registry has suggested comparable outcomes at 2 years between

no long-term therapy and long-term antiplatelet or anticoagulation therapy in NVAF patients with Watchman device.²⁷ Similarly, a prospective registry of Amulet LAAO devices also revealed similar clinical outcomes between long-term aspirin and no antithrombotic therapy groups at 3-year follow-up.²⁸ As those studies raised questions on the rational and necessity of lifelong aspirin post LAAO in NVAF patients, the impacts of the postimplant aspirin therapy on cardiovascular risks need to be re-examined by randomised trials.

Here, we speculate whether long-term low-dose aspirin really provides a benefit to NVAF patients who have been implanted with an LAAO device, as non-procedure-related major bleedings were noticed in LAAO arm when on aspirin in previous trials.²⁶ Aspirin discontinuation at 6 months after LAAO (ASPIRIN LAAO) trial (NCT03821883) is therefore launched, aiming to address this issue in the scientific context. In the current trial, we only focus on the Watchman device due to the following reasons. First, among multiple LAAO devices, Watchman is the only device to be studied in randomised trials to date.^{13–15} Second, Watchman device is the most implanted LAAO device in China and worldwide. Third, focusing on one device might avoid potential discrepancy among different devices. In addition, we focus on patients without previous stroke or coronary artery diseases which may require long-term aspirin for secondary prevention. In that case, we are not in violation of the current guideline and only aim to clarify the grey area.

METHODS AND ANALYSIS

Patient selection

Patients with paroxysmal, persistent, long-standing persistent or permanent NVAF, between 18 and 90 years of age, are eligible for this study. Inclusion criteria are as follows (box 1): (1) Diagnosis of NVAF; (2) Patients who have implanted with a Watchman LAAO-occluder 6 months prior to enrolment. The implantation of Watchman device was done with full informed consent. Patients should have paroxysmal or persistent NVAF with ECG evidence, with contraindications or unwillingness to receive long-term OAC or HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly) score ≥ 3 and with CHA₂DS₂-VASc (congestive heart failure, hypertension, 65 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female) score ≥ 2 . The clinical exclusion criteria for the current trial (box 1) include patients taking aspirin for secondary prevention for established vascular diseases (such as coronary artery or carotid diseases), prior strokes and systemic embolisms, or having conditions contraindicated for aspirin therapy (such as active peptic ulcer, thrombocytopenia or anaemia). Patients with uncontrolled malignancy, abnormal liver, renal or coagulation function, or terminal illness with life

Box 1 Patient selection

Inclusion criteria

- Age between 18 and 90 years.
- Paroxysmal, persistent, long-standing persistent or permanent non-valvular AF.
- Have already had a Watchman LAAO device implanted 6 months ago.

Exclusion criteria

Clinical exclusion criteria

- Long-term aspirin therapy required
 - Including coronary artery disease, symptomatic carotid disease, prior myocardial infarction, strokes or systemic embolism.
- Contraindicated for aspirin therapy
 - Including active peptic ulcer, thrombocytopenia or anaemia.
- Uncontrolled malignant tumour.
- Abnormal liver, renal or coagulation function.
- Pregnant or pregnancy is planned during the course of the investigation.
- Terminal illness with life expectancy <1 year.
- Enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug.

TEE exclusion criteria*

- Peridevice leak >5 mm.
- Device-related thrombus.
- Other intracardiac thrombus.

*TEE performed between 6 weeks and 6 months after LAAO implantation. If repeated TEE were performed within this period, the evaluation will be determined by last TEE.

AF, atrial fibrillation; IDE, investigational device exemption; IND, investigational new drug; LAAO, left atrial appendage occlusion; TEE, transesophageal echocardiography.

expectancy less than 1 year are also excluded. The transesophageal echocardiography (TEE) exclusion criteria include peridevice residual leak >5 mm, or any DRT or other intracardiac thrombi. TEE will be performed to further evaluate the echocardiographic exclusion criteria. Of note, TEE performed between 6 weeks and 6 months postimplant are acceptable as baseline TEE evaluation. If the patients have had multiple TEEs within this period, the evaluation is determined by the last examination.

Study design

The ASPIRIN LAAO trial is a prospective, multicentre, randomised, double-blinded, placebo-controlled non-inferiority study. A total of 12 academic hospitals from mainland China will participate in the trial. NVAF patients who implanted Watchman device will be identified during the routinely 6-month postimplant follow-up visit. If informed consent is obtained, screening will be performed and patients who meets the inclusion criteria and does not meet any of the exclusion criteria will be enrolled. Randomisation will be subsequently performed which is prepared by the biostatistician. The eligible participants will be randomised in a 1:1 ratio to either the Aspirin group or the control (placebo) group. The randomisation code will be computer generated with a block size of 4, and the randomisation will be stratified by sites. Both patients and treating physicians will be blinded to

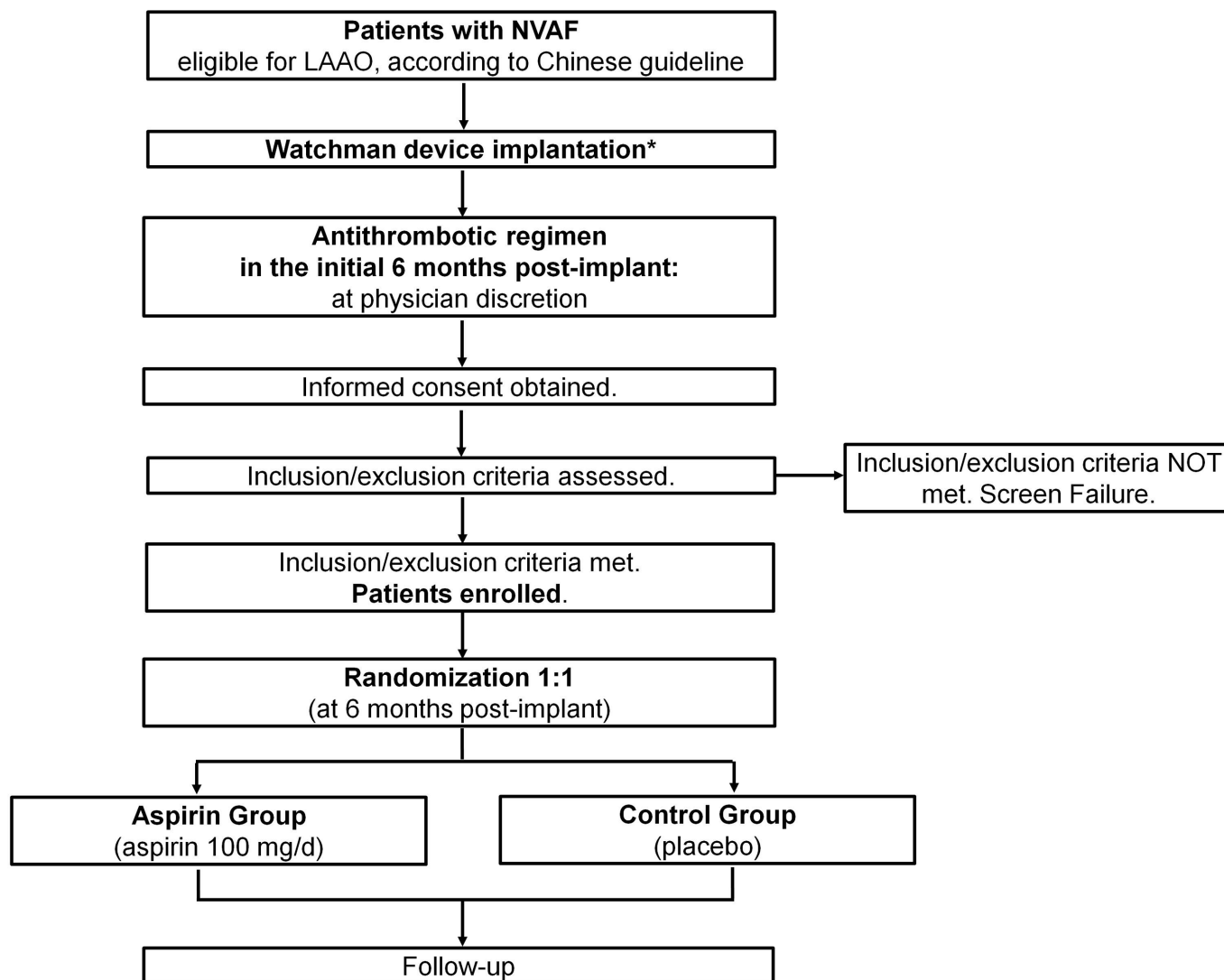


Figure 2 Patient enrolment scheme. *Concomitant catheter ablation of atrial fibrillation might be performed in the same procedure of LAAO. LAAO, left atrial appendage occlusion; NVAF, non-valvular atrial fibrillation.

the allocated therapy. Study patients assigned to Aspirin group will receive enteric coated aspirin (100 mg/day, by Yung Shin Pharm, Jiangsu, China). The control group receives placebo (by Yung Shin Pharm, Jiangsu, China). The recruited patients will start to receive randomised drugs from the day after the allocation day. Subjects of both groups will have follow-up visits by the investigators at AF Centre of each participating institution at 6 and 12 months and then every 12 months until 24 months after the last patient recruitment. Additionally, investigators will enhance telephone follow-up every 2 months to guarantee medication regimen according to the protocol. The enrolment begins in June 2020 and the anticipated completion will be in December 2024. The patient enrolment schemes are shown in figure 2.

The protocol and informed consent (see online supplemental file) are approved by each investigator's institutional review board before patient recruitments. Prior to enrolment, informed consent will be obtained from patients. Patients who have fulfilled all the inclusion

criteria will also undergo baseline characteristics evaluation, including intraprocedural parameters and antithrombotic regimen in the initial 6 months post-implant.

Endpoints

The primary endpoint is a composite consisting of stroke, systemic embolism, cardiovascular or unexplainable death, acute coronary syndrome, coronary artery disease or periphery vascular disease requiring revascularisation and major bleeding. The secondary endpoints are all-cause death, DRT, minor bleeding and rehospitalisation due to heart failure. The outcome definitions, as shown in table 1, are adhered to the Munich consensus which document on definitions, endpoints and data collection requirements for clinical studies of LAAO.²⁹

Sample size justification

The statistical objective is to determine if the control group is non-inferior to the aspirin group with respect to the event rate for the composite endpoints. The reasons

Table 1 Outcome definitions

Outcomes of the primary composite endpoints	Definition
Stroke ²⁹	Acute episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury due to haemorrhage or infarction.
Systemic embolism ²⁹	Acute vascular occlusion or insufficiency of any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely conditions, such as trauma, atherosclerosis or instrumentation.
Cardiovascular or unexplainable death ²⁹	<ul style="list-style-type: none"> ▶ Death from cardiac causes: myocardial infarction, heart failure and endocarditis. ▶ Death from non-coronary, non-CNS vascular conditions: pulmonary embolism, ruptured aortic aneurysm and dissecting aneurysm. ▶ Death from CNS vascular causes: haemorrhagic and ischaemic stroke. ▶ Sudden death: non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in a healthy subject. ▶ Unwitnessed death: fatal event which is not witnessed, and the victim was in good health 24 hours before the event. ▶ Death of unknown cause.
Acute coronary syndrome	<ul style="list-style-type: none"> ▶ Myocardial ischaemic states that includes unstable angina, non-ST elevated myocardial infarction or ST-elevated myocardial infarction.
Coronary artery disease or periphery vascular disease requiring revascularisation	<ul style="list-style-type: none"> ▶ Coronary artery disease, which requires 1 of the following: thrombolysis with fibrinolytic drugs, or percutaneous coronary intervention with or without stent placement, or coronary artery bypass grafting. ▶ Periphery vascular disease, which require 1 of the following: surgery, angioplasty (cryoplasty, drug-coated, cutting, and standard angioplasty balloons), stenting or atherectomy.
Major bleeding ²⁹	Bleeding meets at least 1 of the following criteria: <ul style="list-style-type: none"> ▶ A drop in the haemoglobin level of at least 30 g/L. ▶ Requiring transfusion of 2 or 3 units of whole blood/ red blood cells. ▶ Causing hospitalisation or permanent injury, or requiring surgery.
Outcomes of the secondary endpoints	Definition
All-cause death	All deaths regardless of the cause.
Device-related thrombus ²⁹	Thrombus forming on the atrial surface of the Watchman LAAO device, which is identified by TEE.
Minor bleeding	Any bleeding worthy of clinical mention which does not qualify as life threatening, disabling, or major bleeding.
Rehospitalisation due to heart failure	Readmit to hospital due to heart failure.

The outcome definitions are adhered to the Munich consensus,²⁹ which document on definitions, endpoints and data collection requirements for clinical studies of LAAO.

CNS, central nervous system; LAAO, left atrial appendage occlusion; TEE, transesophageal echocardiography.

for the non-inferiority design are as follows. First, aspirin, as one of the most widely used drugs, serves as a standard treatment. Second, if placebo is non-inferior to aspirin, discontinuation of aspirin post LAAO will be of high cost effectiveness and may improve quality of life if not on medication. Also, testing the non-inferiority hypothesis requires smaller sample size.

Event rate is defined as the expected number of events per 100 patient years of follow-up. The study event rate is the combination of event rates from both the aspirin and placebo arms. The estimated event rates for this trial were established based on the rates seen in the LAAO arm of previous Watchman studies and the aspirin arm of previous aspirin trials.^{13 14 16–18 20 30–33} In the EWOLUTION study, the rates of stroke, major bleeding and

cardiovascular death were 1.3%, 2.7% and 2.25%, respectively.¹⁷ In the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, the rates of myocardial infarction and vascular diseases requiring revascularisation were approximately 0.9%.³² Therefore, we conservatively estimate a combined rate for the primary endpoint of 7 events per 100 patient-years. A risk ratio criterion (control group over aspirin group) of 1.5 will be used to establish non-inferiority with a power of 0.8. Therefore, 191 events are required to be observed based on one-sided alpha of 0.025. The subject recruitment is assumed to be over a 2-year period and all subjects will be followed up until 2 years after the last recruitment. Given these assumptions, the sample size of the ASPIRIN LAAO trial is calculated as 1120 subjects, considering a 10% attrition rate. The

attrition rate is estimated according to our follow-up data of a previous registry regarding Watchman device implantation (ClinicalTrials.gov: NCT03788941). Achieving adequate participant enrollment to reach target sample size should be feasible within the 2-year recruitment period due to the large operation volume of the participating centres. To further facilitate the recruitment of patients, advertisement of this study will be exhibited by posters in the wards and outpatient clinics.

Data management

Data will be collected by the investigators from each participating institution and be uploaded and stored on the secure Research Electronic Data Capture to protect confidentiality before, during, and after the trial. The database will not be unblinded until protocol violations have been identified, data collection has been declared as complete and the medical and scientific review has been completed. The final dataset is encrypted and stored in an online database accessible only to main researchers and administrators.

Data analysis

All comparisons of the primary endpoints between treatments will be on an intention-to-treat (ITT) basis, with each patient analysed as being part of their group regardless of the actual treatment received. The ITT population will also be used for the primary analysis of all secondary endpoints. The primary composite endpoint and each component of the primary endpoint (stroke, systemic embolism, cardiovascular or unexplained death, acute coronary syndrome, coronary artery disease or periphery vascular disease requiring revascularisation and major bleeding) will be summarised as a rate per 100 patient-years of follow-up. The event rates will be analysed using the same method as the composite endpoint. The analysis will include 95% CIs with these analyses. Secondary endpoints will be presented as proportions with 95% CIs.

The per-protocol (PP) analysis will also be conducted for both primary and secondary endpoints, as PP analysis may be of lower efficacy but provide more reliable data. The PP population includes patients receive at least 80% of planned trial medication. For patients who do not complete the study or do not have an outcome event, their time-to-event measure will be censored at the last contact date. In addition, Net Clinical Benefit (NCB) analysis will also be performed post hoc. We define the NCB of aspirin as the sum of the differences between the annualised rates of death event, stroke, systemic embolism, acute coronary syndrome, coronary artery disease or periphery vascular disease requiring revascularisation and major bleeding occurring after the randomisation and the respective rates on placebo, weighting each component by a factor reflecting the severity of functional impact relative to death event (unity).

Descriptive data will be collected at baseline (6 months post-implant) and at follow-up. The information of device-related and intraprocedural properties, as well

as postimplant antithrombotic regimen at the initial 6 months will also be reviewed. For continuous variables, the mean, SD and 95% CIs will be reported. Differences between groups, including means, proportions and ratios, will be reported by 95% credible intervals. The Poisson, logistic and Cox regression models will be used for rates in patient years, binary response variables and time-to-event analysis, respectively.

Study organisation

The study Steering Committee is responsible for managing the scientific aspects of the study and formed by principal investigators of each participating institution and representatives from the Sponsor and from the Clinical Research Organisation (CRO). The study Steering Committee interacts with the Sponsor and the CRO on study progress and related issues. Of note, as an investigator sponsored research programme, the manufacturer (Boston Scientific) of the LAAO device does not participate in the design, conduct, data collection and statistical analysis of the study. The manufacturer only provides funding, technical and coordination support to this study. An independent Clinical Events Committee (CEC) is responsible for adjudicating events that are reported during this clinical trial. The CEC consists of three independent members, including two cardiologists and one neurologist. The CEC is blinded to the patient's treatment arm for the adverse events they are adjudicating. In addition, an independent data monitoring committee (DMC) has been established, including two cardiologists and one biostatistician. The DMC holds meetings periodically to review study data. DMC may recommend stopping the study early if the observed event rate is deemed to be unacceptable, and may also recommend the protocol be revised if deemed necessary to maintain the safety and welfare of the subjects involved. DMC also has the right to unblinding the patient and the investigator when the patient has serious adverse events suspected to be related to aspirin or placebo.

Patient and public involvement

Patients or the public are not directly involved in the design or conduct of this study, and are not invited to contribute to the writing or editing of this document. Patients are recruited in the study based on their eligibility and agreement to participate (signed informed consent form). All participants are asked if they want to be informed about the results of the trial when signing the informed consent. If required, they will receive a summary of the results.

ETHICS AND DISSEMINATION

ASPIRIN LAAO has ethics approval from the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (reference number XHEC-C-2018-065-5, Version 5, 05/28/2020) and other participating centres (see online supplemental

file). This study will be conducted in accordance with the Declaration of Helsinki and with the National Health and Medical Research Council Guidelines on Human Experimentation. Clinical trial insurance is purchased to provide compensation in the event of physical damage to the participants through the trial as well as in the events of health impairment and death. Results are expected in 2024 and will be published in a peer-reviewed medical journal, as well as presented at both national and international conferences.

Collaborators ASPIRIN LAAO trial investigators: Jian-An Wang, from the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Bin Yang, from the Dongfang Hospital, Tongji University School of Medicine, Shanghai, China; An-Li Tang, from the First Affiliated Hospital, Zhongshan University, Guangzhou, China; Hao Hu, from the Second Affiliated Hospital, Lanzhou University, Lanzhou, China; Si-Ming Tao, from the Second People's Hospital of Yunnan Province, Kunming, China; Qi Lu, from the Affiliated Hospital of Nantong University, Nantong, China; Yansong Li, Songjiang District Central Hospital, Shanghai, China; Zongjun Liu, Putuo District Central Hospital, Shanghai, China; Zhaohui Qiu, Tongren Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Xiaochen Wang, from the Second Affiliated Hospital, Anhui Medical University, Hefei, China; Chun Gui, from the First Affiliated Hospital, Guangxi Medical University, Nanning, China.

Contributors Y-GL initiated the study design and is the principal investigator. MC wrote the first manuscript draft and subsequent revisions. QW, JS, P-PZ, WL, B-FM, T-ZC and XT provided input on the study design, statistical analysis and daily research management. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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