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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.

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.

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 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

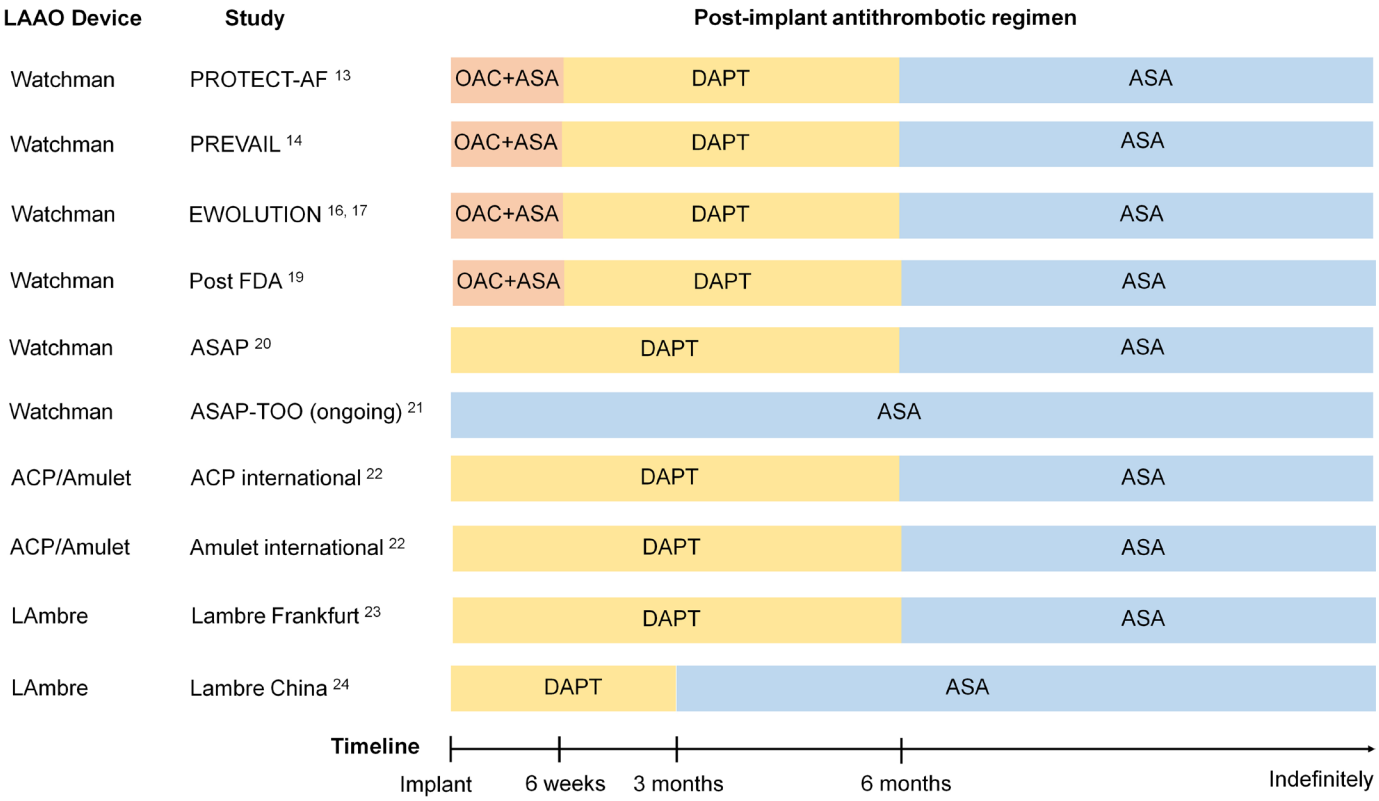

Figure 1 Antithrombotic regimen after LAAO. ACP, Amplazter Cardiac Plug; ASA, aspirin; DAPT, dual antiplatelet therapy; LAAO, left atrial appendage occlusion; OAC, oral anticoagulant.

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 Amplazter Cardiac Plug (ACP)/Amulet[22] and LAmbre,[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.

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.

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 LAA-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 CHA_2DS_2-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 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

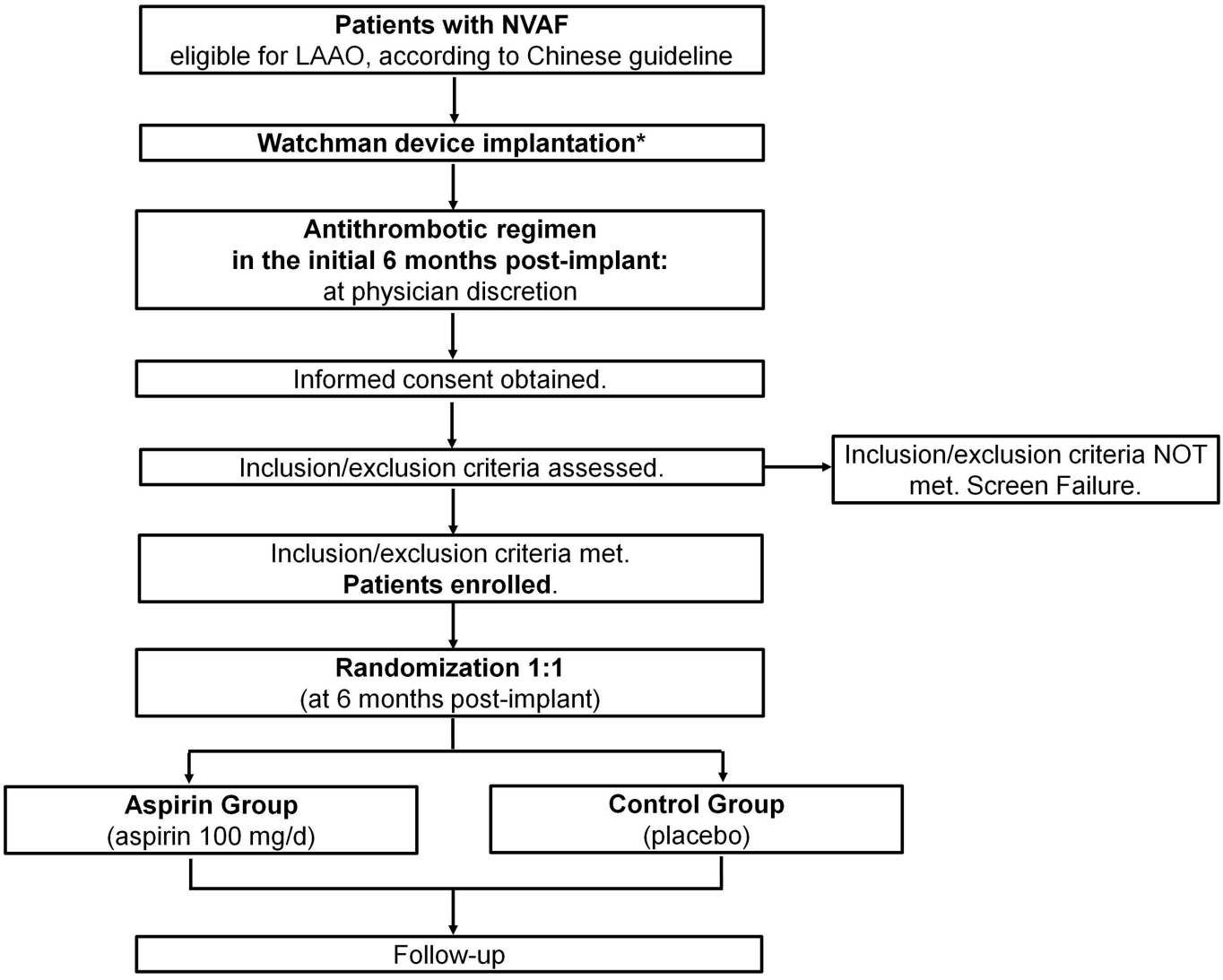

Figure 2 Patient enrolment scheme. *Concomitant catheter ablation of atrial fibrillation might be performed in the same procedure of LAAO. LAAO, left atrial appendage occlusion; NVAF, non-valvular atrial fibrillation.

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]	► 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: fetal event which is not witnessed, and the victim was in good health 24 hours before the event. ► Death of unknown cause.
Acute coronary syndrome	► 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	► 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: ► 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.

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Patient Consent Form

筛选号：□□□□□□

房颤患者左心耳封堵术后

停用阿司匹林的安全性研究

知 情 同 意 书

（第5版， 2020年05月14日）

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知情同意书·告知页

尊敬的_____先生/女士：

我们真诚地邀请您参加“房颤患者左心耳封堵术后停用阿司匹林的安全性研究”。本研究由上海交通大学医学院附属新华医院心血管内科进行。在您同意参加本项研究之前，请您仔细阅读这份知情同意书，它将提供给您本研究背景、目的、方法、试验过程中给您带来的益处和可能产生的风险或者不变以及您的权益保护等内容。本知情同意书提供给您的信息可以帮助您决定是否参加此项研究。如有任何疑问可以向该项目的研究者咨询，以确保您充分理解有关的内容。如果您同意参加本研究，请您签署知情同意书，并且保存一份双方签字的知情同意书。本研究方案已通过新华医院医学伦理委员会批准。

1、为什么要参加这项研究?

本研究背景：心房颤动简称房颤，是最常见快速性持续性心律失常，房颤总的发病率为 0.4%-1%，随着年龄增长房颤的发生率不断增加，75 岁以上人群可达 10%。房颤时心房率达 500-600 次/分，心室率可以达到 100-180 次/分，而且绝对不齐，心房失去有效的收缩功能，严重影响心功能。我国大规模调查研究显示房颤患病率为 0.77%，男性房颤患病率（0.9%）高于女性（0.7%），80 岁以上房颤患病率达 7.5%。此外房颤患病率的增长还与冠心病、高血压病和心力衰竭等疾病的增长密切相关，未来 50 年房颤将成为最流行的心血管疾病之一。

房颤治疗目的包括：（1）恢复窦性心律：是房颤治疗的最佳结果。只有恢复窦性心律（正常心律），才能达到完全治疗房颤的目的；所以对于任何房颤病人均应该尝试恢复窦性心律的治疗方法。（2）控制快速心室率：对于不能恢复窦性心律的房颤病人，可以应用药物减慢较快的心室率。（3）防止血栓形成和中风：在房颤时如果不能恢复窦性心律，或危险因素较多，CHA2DS2-VASc 评分较高可以应用抗凝药物预防血栓形成和中风的发生。

虽然目前抗心律失常药物和抗凝药物依然是房颤治疗的重要方法，但各种毒副作用很大程度限制了它们的临床使用。新近发展的左心耳封堵术，采用封堵器封堵住左心耳，研究表明其可降低 90%卒中风险，与经典的抗凝药物华法林相比可进一步降低脑卒中风险,且同时可明显降低大出血风险，引起学界的认可和广泛关注。我中心目前常规开展左心耳封堵术、房颤射频消融术及左心耳封堵+房颤射频消融术“一站式”治疗房颤，以期最大程度提高房颤治疗的效果和安全性，为患者带来更多获益。

根据目前国际惯例，患者使用 WATCHMAN 封堵器行左心耳封堵术时，常规抗栓治疗策略为术后前 45 天服用华法林及阿司匹林，之后维持双联抗血小板治疗（DAPT）至术后 6 个月，最后使用阿司匹林进行终身抗凝治疗。若患者禁忌使用华法林，封堵器置入后，前 6 个月可使用氯吡格雷联合阿司匹林进行双联抗血小板，替代口服抗凝药，6 个月后终身服用阿司匹林。

长期以来，阿司匹林一直被用于卒中、冠心病等血管疾病的一级、二级预防。然而， 2018 年 ARRIVE、ASCEND、ASPREE 三项重要随机对照研究提示：长期服用阿司匹林进行一级预防不但没有降低心、脑血管事件风险，反而显著增加出血风险。阿司匹林在左心耳封堵术后长期应用的疗效及安全性尚未明确。对于能否/何时停用抗小板药物，目前国际上尚无相关研究报道。

本研究的目的：观察左心耳封堵术或左心耳封堵+射频消融术后 6 月开始停用阿司匹林的安全性，以期在房颤患者左心耳封堵术后尽早停用阿司匹林，降低出血风险，提高患者生活质量。

2、哪些人可以参加这项研究?

（1）入选标准：

1）非瓣膜性房颤，6 个月前曾接受过左心耳封堵术，包括左心耳封堵+射频消融术一站式
2）18- 90 周岁（含 18 和 90 周岁）
3）提供愿意参加研究、顺从随访试验及评估程序的知情同意书；

（2）排除标准：

1) 合并冠心病、脑卒中等疾病需长期服用阿司匹林进行二级预防
2) 存在急性病变，如心梗后急性期（3 个月内），心衰急性发作或新发脑梗后 3 个月内；
3) 预期寿命少于 1 年；
4) 年龄>90 周岁
5) 具有活动性消化道溃疡或其他出血性疾病等阿司匹林使用禁忌症
6) 癌症未控制患者；
7) 明显肝肾功能、凝血功能异常；
8) 术后 6 月内经食道心脏超声提示器械相关血栓或具有残余漏>5mm
9) 女性怀孕期、哺乳期、正计划怀孕者，或育龄妇女但未采取可靠避孕方法者。

3、多少人参加这项研究?

本研究为多中心临床试验，预计总共 1120 人将参与本项研究，阿司匹林组和安慰剂组各 560 人。其中本中心预计入选 500 人。

4、研究是怎样进行的?

本研究为前瞻性、多中心、随机、双盲、安慰剂对照的临床试验，一组于左心耳封堵术或左心耳封堵+射频消融术术后 6 月开始使用阿司匹林 2 年，另一组：左心耳封堵术或左心耳封堵+射频消融术术后 6 月继续使用安慰剂 2 年。

随机是指研究人员与受试者双方都不知道哪一名参与研究的受试者会分配到两组中的哪一组，采用电脑中的随机程序，类似“抽签”或“抛硬币”的方法进行分组。受试者分配到任何一组的机会都是均等的，受试者从电脑中获取数值为 0 或 1，根据获得的数字进行分组，其中 0 代表阿司匹林组，于左心耳封堵术后第 6 月继续使用阿司匹林（100mg）2 年， 1 代表安慰剂组，于左心耳封堵术后 6 月开始使用安慰剂 2 年。您有 50%的几率进入任意一组。

具体研究步骤为：对有意向参与本研究且符合入排标准的患者，在左心耳封堵术后 6 月签署知情同意书并且符合入组标准的患者纳入研究；基线评估包括：心电图/Holter、超声心动图、食道超声、心脏 CT、疾病史、药物史。

左心耳封堵术或左心耳封堵+房颤消融术后 6 月开始随机化，之后的第 6 月、12 个月，以及以后每 12 个月随访 1 次。

随访时主要监测卒中、系统性栓塞、大出血、心血管/不明原因死亡、急性冠脉综合征或冠心病需血运重建、外周血管疾病需血运重建等情况。每次随访需按照方案进行检查，并记录用药情况、主要临床事件和生活质量评分。 随访过程中，如有心悸等不适症状应及时就诊行 ECG 检查和 Holter。如有头晕、肢体活动障碍、感觉障碍及其他怀疑脑梗症状，需完善头颅 CT 或 MRI 检查。

5、参加本研究可能的风险与不良反应

本研究开始于左心耳封堵术后 6 月。因此左心耳封堵术围术期相关的风险与本研究无关。随机化分组后，一组使用阿司匹林治疗，另一组使用安慰剂。对继续服用阿司匹林的患者。您可能出现与阿司匹林相

关的副作用和不良反应，包括出血、哮喘、胃肠道不适等。如果您有任何不适，或者病情发生新的变化，或任何意外情况，不管是否与药物有关系，均应及时通知研究医生，研究医生将对此作出判断和医疗处理。对停用阿司匹林的患者，停用阿司匹林可能增加脑梗塞、系统性栓塞、心梗、外周血管梗塞、封堵器相关血栓的风险。如果您有任何不适，或者病情发生新的变化，或任何意外情况，不管是否与药物有关系，均应及时通知研究医生，研究医生将对此作出判断和医疗处理。其他风险：还可能存在一些目前无法预知的风险、不适，药物相互作用或不良反应。我们将对您进行生活质量评估，问卷中某些问题可能会让您感到不舒服，您可以拒绝回答。

6、参加本研究有什么获益吗?

参加本试验，研究医生将会为您建立术后 2 年的健康随访档案，对您术后的健康状况提供一定的指导建议。此外您的参加将对我们进一步优化房颤介入治疗策略，提高房颤的治疗成功率，降低脑卒中、大出血发生有较大帮助，有益于人类最终攻克心房颤动这一疾病。

7、如果不参加此项研究，有没有其他备选治疗方案?

目前针对您的健康情况，常规的治疗方法为继续口服阿司匹林 100mg，每天一次。如果您决定不参加这项研究，您将会得到其他的标准化的治疗，即口服阿司匹林 100mg，每天一次。您的研究医生也会乐意解释用于治疗您的疾病的其他疗法的可能的好处和风险。

8、是否一定要参加并完成本项研究?

您是否参加这个研究完全是自愿的。如果您不愿意，可以拒绝参加，这对您目前或未来的卫生医疗不会有任何负面影响。即使您同意参加之后，您也可以在任何时间改变主意，告诉研究者退出研究，这同样不会影响您获得正常的医疗服务。当您决定不再参加本研究时，希望您及时告知您的研究医生，研究医生可就您的健康状况提供建议和指导。

一旦有任何可能会影响您决定是否继续参与本研究的信息，我们会及时告知您。研究机构也可能在研究期间终止本研究。如果发生本研究提前终止的情况，我们将及时通知您，您的研究医生会根据您的健康状况为您下一步的治疗计划提供建议。

对于中途退出的受试者，出于安全性考虑，我们有末次随访计划，您有权拒绝。若您退出后，发现新的与您健康和权益相关的信息时，我们可能会再次与您联系。

原则上，在您退出之后，研究者将严密保存您的相关信息直至最终销毁，期间不会继续使用或透露这些信息。但在以下极少数情况下，研究者将继续使用或透露您的相关信息，即使您已经退出研究或研究已经结束。这些情况包括:

－除去您的信息将影响研究结果的科学性或对数据安全的评价;

－为研究、教学或其他活动提供一些有限的信息（这些信息不会包括您的姓名、身份证号码、或者其他能识别您身份的个人信息）;

－当学校和政府监管部门需要监督研究时，他们会要求查看所有的研究信息，其中也会包括您当时参与研究的相关信息。

9、参加此项研究的费用

本研究的阿司匹林和安慰剂费用均为免费提供。本研究的其他检查、药品费用均不在免费范围之内。如果您同时合并其他疾病所需的治疗和检查，以及因治疗无效而改用其他治疗的费用和交通费用也不在免费的范围之内。

10、参加该项研究受试者是否获得报酬?

参加本研究没有报酬。

11、发生研究相关伤害的处理

如果您在研究期间发生了任何伤害，请及时告知研究者，您可以在您所在的研究医院获得积极治疗。如果您在研究期间发生了不良事件，该不良事件是否由本研究方案所需的诊断检查有关，应由研究者作出判断。确因本研究方案所需诊断检查及治疗引起不良事件并对造成伤害的可以依据医疗鉴定结果给予相应赔偿。如您没有遵从本知情同意书上的要求，或未按研究医生根据本临床试验方案给您的要求，研究机构将不会承担您的医疗费用。

12、受试者的个人信息会得以保密吗?

如果您决定参加本项研究，您参加研究及在研究中的个人资料均属保密。可以识别您身份的信息将不会透露给研究小组以外的成员，除非获得您的许可。所有的研究成员和研究申办者都被要求对您的身份保密。您的档案将保存在有锁的档案柜中，仅供研究人员查阅。为确保研究按照规定进行，必要时，政府管理部门或伦理委员会的成员按规定可以在研究单位查阅您的个人资料。这项研究结果发表时，将不会披露您个人的任何资料。

13、如果有问题或困难，该与谁联系?

您可以随时了解与本研究有关的信息资料和研究进展，如果您有与本研究有关的问题，或您在研究过程中发生了任何不适与损伤，请可以联系您的研究医生：陈牧 电话：13585757166。如果在研究过程中您有相关权益方面的问题，可以联系新华医院医学伦理委员会，联系电话：021-25076143。

知情同意书·签字页

受试者知情同意声明

我已经阅读了这份知情同意书，并充分理解所有内容。

我有机会提问而且所有问题均已得到解答。

我理解参加本项研究是自愿的。

我可以选择不参加本项研究，我的任何医疗待遇与权益不会因此而受到影响。

如果我需要其它治疗，或者我没有遵守研究计划，或者发生了与研究相关的

损伤或者有任何其它原因，研究医师可以终止我继续参与本项研究。

我将收到一份签过字的“知情同意书”副本。

受试者姓名：_____ 法定代理人签名：

受试者签名：_____ 与受试者关系：

受试者电话：_____ 法定代理人电话：

日期：____年__月__日 日期：____年__月__日

（注：如果受试者无行为能力时则需法定代理人签名）

研究者告知声明

我已经向该受试者或其法定代理人详细介绍了该研究的目的、方法、程序及研究的风险和获益等；给与他/她足够的时间阅读知情同意书、与他人讨论，并回答了他/她提出的所有问题；我已经告知该受试者当遇到问题时的联系方式；我已告知该受试者或其法定代理人他/她在研究期间的任何时候无需任何理由退出本研究。

研究者姓名：

研究者签名：

研究者电话：

日期：____年__月__日

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