Left atrial appendage occlusion for patients with valvular diseases: a prospective study design

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Abstract

Background: As increasing evidence showed the efficacy of percutaneous left atrial appendage (LAA) occlusion in reducing the stroke risks in patients with non-valvular atrial fibrillation(AF), we design this study to quantify the effect of surgical LAA occlusion (SLAAO) for patients with valvular diseases and with or without AF. Methods: The current study will be implemented in two parts: Part 1 (AF study) is a prospective longitudinal study with a plan to consecutively register 2032 patients diagnosed with valvular diseases and AF and receiving cardiovascular surgeries. SLAAO will be performed at the individual surgeon's preference. We centrally conducted a one-year follow-up on stroke, systemic arterial embolism, and all-cause mortality. Part 2 (non AF study) is a single-blinded, multicenter, randomized controlled trial with the purpose to evaluate the efficacy of SLAAO to reduce one-year embolism events in patients with valvular diseases, without AF, and receiving cardiovascular surgeries. 2118 patients will be randomized 1:1 to the intervention or control arm using a central randomization system. Results: The primary outcome is a composition of newly occurred ischemic stroke/transient ischemic attack (TIA) with positive neuroimaging or systemic arterial embolism, and cardiovascular mortality during one-year follow-up. Conclusion: The trial is designed to evaluate the efficacy of SLAAO to reduce embolism events one year after mitral or aortic surgeries, and this paper presents the prospective study protocol. It provides details of patient randomization, follow-up, methods of analysis of the material, and publication plan.

INTRODUCTION

With the global population aging trend, valvular heart diseases have been increasing, affecting more than 10% individuals over 75 years.[1-3] The risk of perioperative stroke in these patients remains high and confers six times greater risk of all-cause death and 12.7 times greater risk of stroke-specific death.[4-7] Previous studies have shown that perioperative strokes are mainly composed of ischemic strokes, which are often the embolism results.[8]

Atrial fibrillation (AF) manifests in 40.3% of patients presenting for mitral valve surgery and 11.3% for aortic valve surgery and is recognized as a significant cause of perioperative stroke.[9, 10] The left atrial appendage (LAA) is the major source of emboli in patients with AF, accounting for 57% of non-rheumatic and 91% of rheumatic atrial fibrillation-related strokes.[11, 12]

There is increasing evidence showing the efficacy of percutaneous LAA occlusion in reducing the stroke risks in patients with non-valvular AF.[13-17] However, these data could not be readily generalized to surgical LAA occlusion (SLAAO) for patients with valvular AF.[15, 18, 19]

More recently, three large cohort studies published focused on the evaluation of SLAAO during cardiac surgeries,[20-22]which convey essential information for further studies:

First, the association between SLAAO and stroke reduction seems to be confined to patients with AF history.[20-22] Second, for patients in the absence of baseline AF, SLAAO may not provide any benefit and may be associated with increased AF in the early postoperative period and two years after surgery.[20]Third, although SLAAO in all-comers has been proven to be ineffective, the risk profile of patients without AF was not well defined in the above studies.[20]

To address the evidence gap, we planned to launch the study with a prospective study design. The aims of the current research are to (1) evaluate, in patients receiving mitral or aortic valve surgeries and with baseline AF, the efficacy of SLAAO to reduce long-term stroke in a prospective longitudinal study; (2) test the hypothesis that, in patients receiving mitral or aortic valve surgeries and without a history of AF and with a CHA_2DS_2-VASc score[?]2, opportunistic SLAAO can prevent long-term stroke after cardiac surgery in a prospective, open-label, multicenter, randomized controlled trial.

METHODS

Three cardiovascular surgery centers in Beijing will participate the LAA off study. A steering committee has been set up to supervise the study's conduct and the management of the data.

The current study will be implemented in two parts (Table 1):

Part 1 (AF study) is a prospective longitudinal study with a plan to consecutively register patients diagnosed with valvular diseases and AF and receiving cardiovascular surgeries. We centrally conducted a one-year follow-up on stroke, systemic arterial embolism, and all-cause mortality.

Part 2 (non AF study) is a single-blinded, multicenter, randomized controlled trial with the purpose to evaluate the efficacy of SLAAO to reduce one-year embolism events in patients with valvular diseases, without AF, and receiving cardiovascular surgeries.

Inclusion/exclusion criteria

For AF study

The inclusion criteria include 1. Over 18 years of age; 2. At least undergoing mitral valve or aortic valve surgeries; 3. With a documented history of atrial fibrillation or atrial flutter.

The exclusion criteria include 1. Undergoing heart transplantation, or complex congenital heart surgery, or ventricular assist device implantation; 2. Redo cardiovascular surgeries.

For non AF study

The inclusion criteria include 1. Over 18 years of age; 2. At least undergoing mitral valve or aortic valve surgeries; 3. successful excision of the LAA, defined as absence of doppler flow across the closure line and residue LAA stump<1 cm; 4. Without baseline atrial fibrillation and atrial flutter; 5. With CHA2DS2-VASc score [?] 2.

The exclusion criteria include 1. Undergoing heart transplantation, or complex congenital heart surgery, or ventricular assist device implantation; 2. Redo cardiovascular surgeries; 3. Conditions requiring anticoagulation therapy after surgeries for more than three months; 4. Left atrium diameter over 6 cm; 5. Presence of thrombus in the left atrium or LAA; 6. With a history of stroke/cerebrovascular accident within one month before surgeries.

SLAAO procedure and evaluation

For AF study

Three types of SLAAO are allowed as a part of cardiovascular surgeries: 1. Closure of the LAA ostium from inside the left atrium: the ostium of the LAA will be closed with two layers of polypropylene running

suture from inside the left atrium; 2. Closure of the LAA ostium from outside the left atrium: the ostium of the LAA will be closed with ligation or two layers of polypropylene running suture from outside the left atrium; 3. Suture excision of the LAA: the LAA will be amputated and its opening is sutured in two layers of polypropylene suture from the outside of the heart.

Intraoperative trans-esophagus echocardiography (TEE) will be routinely performed.

For non AF study

Only the LAA suture excision is allowed. Residue LAA stump over 1 cm by intraoperative TEE is defined as SLAAO failure, and the case will be excluded from the randomization.

Blinding and randomization

For non AF study, the steering committee is responsible for recruiting patients to the trial and supervising the research process but had no access to the randomization procedure. Extraction of the outcome measures will be performed primarily by research staff not directly involved in the study. The data analysts will be blinded to the randomization.

Patients will be randomized 1:1 to the intervention or control arm using a central randomization system. The randomization plan will be established by research staff not directly involved in the study.

RESULTS

For AF study

The primary outcome is a composition of newly occurred ischemic stroke/transient ischemic attack (TIA) with positive neuroimaging or systemic arterial embolism (ICD-9 codes 434.x or 444.x [thromboembolic stroke or systemic embolism] or 435.x [transient ischemic attack]), and cardiovascular mortality during one-year follow-up.

Secondary outcomes include: cardiovascular mortality, newly occurred ischemic stroke, newly occurred transient ischemic attack, newly occurred hemorrhagic stroke (ICD-9 codes 430-432), and bleeding events of BARC type III, IV, and V.[23] AF-related health utilization, measured by the occurrence of outpatient visits and hospitalizations with a diagnosis of AF, will also be recorded.

For non AF study

The primary outcome is a composition of newly occurred ischemic stroke/transient ischemic attack and cardiovascular mortality during one-year follow-up.

Secondary outcomes include postoperative AF (defined as newly diagnosed AF within 30 postoperative days [ICD-9 427.31; ICD-10 I48.0, I48.1, I48.2, I48.91]), cardiovascular mortality, newly occurred ischemic stroke, newly occurred transient ischemic attack, newly occurred hemorrhagic stroke (ICD-9 codes 430-432), bleeding events of BARC type III, IV, and V, and AF-associated health utilization.

Sample size calculation

The estimation of the primary outcome in the control group is based on reasonable assumptions about the patient risk and the possible types of antithrombotic therapy during follow-up (Table 2 and Figure 1).

For AF study

The primary outcome in AF group is estimated to be 7.6 per 100 person-year in non SLAAO group. Assuming 80% power and two-sided type I error of 0.05, we need to enroll 1016 patients in each group to detect a 40% relative risk reduction in the primary outcome in SLAAO group, accounting for 5% of patients' loss during the one-year follow-up.

The scheme for estimation of the primary outcome for AF study is as follows (Table 2 and Figure 1):

Based on previous large registries,[24] the proportion of patients receiving mechanical valve replacement is estimated to be 63.2%. We assume that all these patients take warfarin and adhere to standard warfarin medication during one year follow-up.

As for those receiving bioprosthesis or valve repair, four medication conditions are assumed: taking warfarin, aspirin, new anticoagulant, or no anticoagulant therapy. According to a extensive insurance database, we have reasonable estimates of the proportions of the four medication conditions in Chinese patients with AF.[25]

Based on the recent large trials, we estimate the newly occurred ischemic stroke/TIA in the control group taking warfarin will be 1.7 per 100 person year;[26] taking aspirin will be 3.7 per 100 person year;[27] taking new anticoagulants (dabigatran and the Factor 10a) will be 1.5 per 100 person year;[26, 28]without any anticoagulant therapy will be 5.1 per 100 person year.[27, 28]

The ischemic stroke/TIA event rate in the control arm is estimated at 2.6 per 100 person-year. Because the postoperative mortality is 4.3-9.2 per 100 person-year based on studies from a large US administrative database and the cohort from the Society of Thoracic Surgeons Adult Cardiac Surgery Database,[21, 22] we assume that cardiovascular mortality will be 5.0 per 100 person-year.

Thus, the overall event rate's final estimates will be 7.6 per 100 person-year in the control arm without SLAAO.

For non AF study

Assuming 1059 patients in each group, we would detect a relative reduction rate of at least 40%, with a power of 80% and two-sided type I error of 0.05, in the primary outcomes with an estimated control event rate of 6.8 per 100 person-year.

The scheme for estimation of the primary outcome for AF study is as follows (Table 2 and Figure 1):

As aforementioned, we could easily estimate the annual stroke/TIA event rate in patients receiving mechanical valve replacement who will take warfarin for life long time.

As for those receiving bioprosthesis or valve repair, we first categorize the patients into three proportions: CHA2DS2-VASc score=2, CHA2DS2-VASc score=3, CHA2DS2-VASc score[?]4. We have estimates about the three proportions from a recent large registry study.[29] We also have estimates about the occurrence rate of postoperative AF (POAF) in the three categories.[30, 31]

For patients receiving bioprosthesis/valve repair and not developing POAF, we have good estimates of the stroke/TIA in each category.[29]

For patients receiving bioprosthesis/valve repair and developing POAF, we assume four medication conditions and have a reliable estimate of the four proportions: taking warfarin, aspirin, new anticoagulant, or no anticoagulant therapy.[25] We also have estimates of the ischemic stroke/TIA event rate in the four medication conditions described in "For AF study (the prospective longitudinal study)" section.[26-28]

Thus, the ischemic stroke/TIA event rate in the control arm is estimated at 1.8 per 100 person year. We assume that cardiovascular mortality will be 5.0 per 100 person-year. Then we get the final estimates of the overall event rate of 6.8 per 100 person-year in the control arm without SLAAO.

Case report form (CRF) abstraction, follow-up, and data process.

Research staff from each site will scan all the patients' medical charts in either the prospective longitudinal study or the randomized controlled trial, then transmitted the scanned copy to the coordinating center through the mail on encrypted, password-protected flash drives. The CRF will be quality-controlled, and the medical records will be de-identified by hiding all personal information in the records.

The CRFs include the patients' baseline information (age, gender, and cardiac/non-cardiac history, et al.), invasive/non-invasive testing (ECG, echocardiography, chest X-ray, CT scans, angiography, et al.), labo-

ratory results, in-hospital medications and surgical interventions, in-hospital complications, and discharge medications (Table 3). Trained abstractors will abstract this information under the supervision of trained quality control personnel. 10% of these records will be randomly selected for review by project managers to ensure adherence to the research protocol.

The detailed protocol for the follow-up was described elsewhere.[32] Briefly, patients discharged alive are interviewed at the time point of discharge, postoperative 30 days, three months, six months, and one year. Face to face interview is the most preferred approach, but the telephone interview is also acceptable. The data will be stored at the coordinating center and protected in an encrypted and password-protected database.

Ethics approval

The Ethics Committee in Fuwai hospital approved this study. Patients will give informed consent to the study. An information leaflet will be provided to participating patients to introduce the SLAAO procedure.

COMMENT

Recently, three cohort studies with many patients of a broad spectrum of conditions were published to explore the association between SLAAO and long-term risk of stroke.[20-22] Those studies may have better generalizability than that of previous studies but are subject to confounding and not quite granular due to the retrospective nature.

There is one ongoing trial (Left Atrial Appendage Occlusion Study III, LAAOS III trial, NCT01561651) which plans to enroll 4,700 patients. Nevertheless, this trial is focused on patients with a history of AF or atrial flutter undergoing coronary artery bypass graft (CABG) and will not include those without AF and those undergoing valve surgeries.

As far as we know, the current research is among the first to evaluate the efficacy of SLAAO. A significant output of the current research will be answering whether LAAO reduces long-term embolism events in patients with and without AF receiving valve surgeries.

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Table 1 The summary of the main points of the OPINION study.

	Part 1 (AF study)
Study type	Prospective longitudinal study
Study design	Cohort study
Target disease	Valvular diseases and AF
Inclusion criteria	1. Over 18 years of age; 2. At least undergoing mitral valve or aortic valve surgeries; 3. W
Exclusion criteria	1. Undergoing heart transplantation, or complex congenital heart surgery, or ventricular a
Sample size:	2032
Intervention	Left atrial appendage occlusion
Measure time point of outcome	One-year
The primary outcome	A composition of newly occurred ischemic stroke/transient ischemic attack, and cardiovas
Secondary outcomes	Cardiovascular mortality, newly occurred ischemic stroke, newly occurred transient ischem

Table 2 estimates of proportions and event rates

	Proportions (%) or event rates (per 100 person year)	Additional remarks
PROPORTION ESTIMATES	**PROPORTION ESTIMATES**	**PROPORTION ESTIMATES**

Surgery types (for stroke/TIA estimation in both AF study and non AF study) Mechanical valve replacement	Surgery types (for stroke/TIA estimation in both AF study and non AF study) 63.2	Surgery types (for stroke/TIA estimation in both AF study and non AF study) Based on a large registry from US comparing mechanical and biological prosthesis (n=45,639);[24] proportion of valve repair is estimated based on our own data (unpublished).
Bioprosthesis or valve repair	36.8	
Anticoagulant conditions among patients with a history of AF (for stroke/TIA estimation in both AF study and non AF study) No anticoagulant therapies	Anticoagulant conditions among patients with a history of AF (for stroke/TIA estimation in both AF study and non AF study) 43.9	Anticoagulant conditions among patients with a history of AF (for stroke/TIA estimation in both AF study and non AF study) Based on the medical insurance database in Yunnan Province, China; 1,237 out of 471,446 participants diagnosed with AF, thus creating 4,859 person-years of experience.[25]
Warfarin	8.0	
Aspirin	46.1	
New anticoagulant agents	2.0	
Distribution of CHA_2DS_2-VASc scores among patients without baseline AF (for stroke/TIA estimation in non AF study) 2	Distribution of CHA_2DS_2-VASc scores among patients without baseline AF (for stroke/TIA estimation in non AF study) 33.4	Distribution of CHA_2DS_2-VASc scores among patients without baseline AF (for stroke/TIA estimation in non AF study) By using Outcomes Assessment in Coronary Heart disease (APPROACH) prospective registry involving 20,970 patients with primary diagnosis of ACS and without baseline AF.[29]
3	27.9	
[?]4	38.7	
EVENT RATE ESTIMATES Stroke/TIA rates among the four types of anticoagulant conditions (for stroke/TIA estimation in both AF study and non AF study)	**EVENT RATE ESTIMATES** Stroke/TIA rates among the four types of anticoagulant conditions (for stroke/TIA estimation in both AF study and non AF study)	**EVENT RATE ESTIMATES** Stroke/TIA rates among the four types of anticoagulant conditions (for stroke/TIA estimation in both AF study and non AF study)

No anticoagulant therapies	5.1	Based on large randomized controlled trials: Warfarin: RELY,[26] n=6,022; Aspirin: ACTIVE A,[27] n=3,782; New anticoagulants: AVERROES,[26, 28] n=2,808; RELY, n=6,015; No therapies: ACTIVE A and AVERROES.
Warfarin	1.7	
Aspirin	3.7	
New anticoagulant agents	1.5	
Stroke/TIA rates among the three CHA_2DS_2-VASc score categories (for stroke/TIA estimation in non AF study)	Stroke/TIA rates among the three CHA_2DS_2-VASc score categories (for stroke/TIA estimation in non AF study)	Stroke/TIA rates among the three CHA_2DS_2-VASc score categories (for stroke/TIA estimation in non AF study)
2	0.4	By using Outcomes Assessment in Coronary Heart disease (APPROACH) prospective registry involving 20,970 patients with primary diagnosis of ACS and without baseline AF.[29]
3	0.9	
[?]4	1.5	
Development of POAF at each CHA_2DS_2-VASc score category (for stroke/TIA estimation in non AF study)	Development of POAF at each CHA_2DS_2-VASc score category (for stroke/TIA estimation in non AF study)	Development of POAF at each CHA_2DS_2-VASc score category (for stroke/TIA estimation in non AF study)
CHA_2DS_2-VASc score=2 Yes No	19.0 81.0	Based on two institutional data involving 277 patients and 518 patients in the absence of previous AF receiving cardiac surgeries.[30, 31]
CHA_2DS_2-VASc score=3 Yes No	70.0 30.0	
CHA_2DS_2-VASc score[?]4 Yes No	48.5 51.5	
Cardiovascular mortality (for both AF study and non AF study)	5.0	According to three large registries with a sample size of 75, 782, 10,524, and 9,792, respectively.[21, 22]

AF=atrial fibrillation; ACS=acute coronary syndrome; POAF=postoperative atrial fibrillation; TIA= transient ischemic attack

Table 3 OPNION data elements

VARIABLES
CLINICAL CHARACTERISTICS Medical history/risk factors Clinical characteristics Pre-operation care Diagnostic t
ECHOCARDIOGRAPHY Size of left atrium Size of left atrial appendage Left atrial thrombus Size of right atrium EF

LAB TESTS Blood routine test Blood biochemical test Urine routine test Chest X-ray CT scan Electrocardiogram Angio
PATIENT INTERVIEWS Education Work status Marital/living status Household income Postoperative medication
OUTCOMES Ischemic stroke/TIA Cardiovascular mortality Hemorrhagic stroke Bleeding events Newly occurred AF AF-

EF= Left ejection fraction; LVEDD= Left ventricular end diastolic diameter; LVESD= Left ventricular end systolic diameter; CT=Computed tomography; TIA= transient ischemic attack; AF=atrial fibrillation

Figure 1A The estimation of the primary outcome for AF study.

Figure 1B The estimation of the primary outcome for none AF study.