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Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding: a non-randomized controlled clinical study

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Abstract

Introduction： Non-valvular atrial fibrillation (NVAF) is a high-risk factor for ischemic stroke. The 2010 ESC Atrial Fibrillation Management guidelines recommend oral anticoagulants (OAC) to prevent stroke in men with CHA2DS2-VASc scores ≥ 2 and women ≥ 3. However, in patients with a high risk of stroke and a high risk of bleeding (HAS-BLED ≥ 3), OAC had a higher risk of bleeding. Left atrial appendage closure has been shown to be non-inferior to OAC as a means of preventing stroke in several studies. As a minimally invasive intervention to prevent stroke, transthoracic left atrial appendage clipping (TS-LAAC) has a high successful closure rate, but there is a lack of literature reports directly comparing with OAC. Our research compares TS-LAAC with new oral anticoagulants (NOAC), and provides an appropriate program for stroke prevention in specific population.

Methods and Analysis: This is a single-center, prospective, non-randomized, controlled study, conducted from April 2022 to April 2025. The study included 186 patients with confirmed NVAF, 93 of whom completed thoracoscopic left atrial appendage clipping, and the control group treated with NOAC. The primary outcome was the incidence of stroke and systemic embolism, as well as the composite endpoint events (stroke, systemic embolism, myocardial infarction, bleeding, cardiovascular death, etc.). Secondary outcomes were ischemic stroke, hemorrhagic stroke, any bleeding events, death from cardiovascular causes, death from all causes, residual root rate in the surgery group, device-related thrombosis in the surgery group, changes in blood pressure, and cardiac chambers size changes, etc. Each subject completed at least one year of follow-up.

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Ethics and dissemination： The study has been approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China (approval number: KY2022-013-02). The results from this study will be disseminated through manuscript publications and national/international conferences.

Trial registration number: Chinese Clinical Trial Registry (ChiCTR2200058109).

Introduction

Background and rationale

As a common arrhythmia, the most serious complication of atrial fibrillation is thrombosis caused by hemodynamic changes, and further thrombus shedding, which leads to ischemic stroke. Non-valvular atrial fibrillation has become one of the main causes of ischemic stroke. (1, 2) Cerebral embolism accounts for 13-26% of ischemic strokes, and the proportion increases with age. (3-5) 2016ESC Atrial Fibrillation Management guidelines (6) point out that the risk of thromboembolic events is significantly increased when the CHA2DS2 score is ≥ 2 in males and ≥ 3 in females. Long-term anticoagulant therapy is recommended (Ⅰ , A).(6) The risk of ischemic stroke can be significantly reduced with appropriate oral anticoagulation in patients with atrial fibrillation who do not wish to undergo surgery. (7) However, as a vitamin K-dependent antagonist, warfarin has a narrow safety margin for anticoagulation, with a fivefold increased bleeding risk compared with non-anticoagulated patients. (8) Although the use of new oral anticoagulants for antithrombotic therapy is effective and significantly reduces the overall risk of bleeding compared with warfarin, (9) there is still an increase in adverse events such as thrombosis and bleeding due to missed doses and inadequate anticoagulation management. (10-13) We have observed in large randomized controlled trials (RCT) ,such as ARISTOLE (14), ROCKET-AF (15), and RE-LY (16) that the annual incidence of major bleeding events among subjects receiving new oral anticoagulants or warfarin ranged from 2.13% to 3.6%, and the cumulative incidence of annual bleeding events (including major and minor bleeding events) ranged from 14.4% to 25.6%. In addition, the discontinuation rate of subjects was as high as 16.6%-25.3% due to bleeding or fear of bleeding risk. When the HAS-BLED score is higher than the CHADS2 score of the patient, that is, the risk of bleeding is greater than the potential benefit of anticoagulation, (17) oral anticoagulants no longer benefit such patients. In addition, even if new oral anticoagulants are taken in patients with previous stroke, the risk of stroke recurrence is still high, up to 9.3%, and the incidence of recent bleeding events, including hemorrhagic transformation, is approximately 7.8%, or even up to half.(18) Therefore, we need to find a safer and more effective alternative.

Ninety percent of thrombi in nonvalvular atrial fibrillation originate from the left atrial appendage. (19-21) The isolation of the left atrial appendage, theoretically, can significantly reduce the occurrence of stroke caused by thrombosis of the left atrial appendage from an anatomical point of view. Left atrial appendage closure (LAAC) as a stroke prevention measure, compared with oral anticoagulation therapy, has been shown to be no better than warfarin in the risk-benefit prevention of stroke, systemic embolism and cardiovascular death through numerous

clinical trials. (22-25) In a recent RCT study PRAGUE-17, left atrial appendage closure surgery was noninferior to newer oral anticoagulants.(26) The 2016 European Society of Cardiology recommends closing the LAA to prevent thromboembolic events, level II evidence level b recommendation. (6) However, due to the direct contact between the metal mesh of the left atrial appendage occlusion and the blood, antithrombotic therapy should not be stopped until it is completely endothelialized to avoid instrument-related thrombosis. Patients implanted with left atrial appendage occlusion are advised to receive aspirin combined with warfarin for at least 45 days and continue antiplatelet therapy with aspirin and clopidogrel for 6 months after confirming that there is no thrombus by TEE examination and then maintain single antiplatelet therapy for a long time. (27) Therefore, this strategy does not apply to patients with anticoagulant taboos or patients with a high risk of bleeding. Studies have found that transcatheter LAA occlusion has been shown to have residual leaks in 32% of patients, and transesophageal ultrasonography in half of the patients revealed LAA thrombus in 22%. (28, 29) In addition, the incidence of thrombus associated with the use of an endocardial closure device was as high as 7.2%.(30) Surgical closure of the left atrial appendage also plays an important role in stroke prevention. (31) Due to the lack of exogenous foreign bodies in epicardial clamps, the risk of device-related thrombosis is lower in theory. Conor Toale systematically reviewed the PubMed, EMBASE and Cochrane library databases. (32) 902 patients (97.8%) achieved complete closure of the left atrial appendage (LAA). The success rates of placement under video-assisted thoracoscopy and open surgery were 95.3% and 99.2%, respectively, and no residual leakage was reported. Surgical left atrial appendage closure has exerted its advantages in preventing stroke through data from the clinical randomized controlled trial LAAOS-LAAOSIII. (33-35) However, the comparison with other surgical procedures may disrupt the balance of comparison with oral anticoagulants alone. At present, there is a new type of left atrial appendage closure surgery, and the use of video-assisted or total thoracoscopic surgery for left atrial appendage closure, (36-39) can be used as a separate operation to prevent stroke. The results of multiple studies have demonstrated high rates of complete closure and low rates of cerebrovascular events during follow-up.(40-42)

However, there is no direct head-to-head study of oral anticoagulation and surgical LAA closure. We designed a non-randomized controlled trial comparing thoracoscopic left atrial appendage closure surgery versus concurrent oral novel anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation at high bleeding risk and high stroke risk to increase evidence for thoracoscopy left atrial appendage closure surgery as a means of stroke prevention.

Methods and analysis

1. Study design

This study is a planned 3-year clinical trial of stroke prevention in atrial fibrillation, comparing the effect of thoracoscopic left atrial appendage closure surgery with oral anticoagulants in stroke prevention. This is a non-

randomized controlled feasibility study. The patients were divided into the intervention group and the control group according to their willingness to accept the intervention measures of thoracoscopic left atrial appendage closure surgery. In the intervention group, the left atrial appendage was clipped with a thoracoscopic left atrial appendage closure device; the control group adjusted anticoagulation therapy according to the current CHA2DS2-VASC and HAS-BLED conditions. The purpose was to verify the safety and efficacy of thoracoscopic left atrial appendage clipping surgery, or its noninferiority. The trial was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (ethics number: KY2022-013-02) in 2022-3-02 and registered as first edition with the China Clinical Trial Center (ChiCTR2200058109) in 2022-3-30. Recruited from April 1, 2022 to April 1, 2025 in Neurology and Cardiac Center wards and outpatient clinics. The study flow chart is shown in figure1.

2. Study setting

Data collection will be performed in the Cardiovascular Center and Neurology Department of Beijing Tiantan Hospital, Capital Medical University, Fengtai District, Beijing. The choice of location assignment was not random, but was based on data such as the incidence of cardioembolic stroke in patients who had previously visited our hospital.

3. Eligibility criteria

Inclusion criteria:

Adults over 18 years old, diagnosed with non-valvular atrial fibrillation; CHA2DS2-VASc≥3, HAS-BLED≥3; if there is a history of stroke, consider cardiac stroke or (STAF score ≥ 5 points or LADS score ≥ 4 points), and there is no acute cerebral infarction or bleeding; signed informed consent.

Exclusion criteria:

Malignant tumor, life expectancy less than 1 year; intracardiac thrombus; clear imaging signs such as severe carotid atherosclerosis, intracranial vascular stenosis, and criminal blood vessels; presence of patent foramen ovale; other cardiac surgery with thoracotomy; presence of movable aortic plaques (including ascending aorta, aortic arch, and descending aortic thoracic segment); patients with no willingness to follow-up or who cannot cooperate with completion of follow-up; pregnant or lactating women; those in the surgical intervention group with poor lung function and unable to tolerate surgery can be transferred to the control group; those in the surgical intervention group with pericardial or thoracic adhesions caused by the history of lung surgery or cardiac surgery can be transferred to the control group.

4. Discontinuation criteria:

The patient had serious adverse reactions to surgery or anticoagulant drugs.

5. Interventions

1) Surgical intervention group (thoracoscopic left atrial appendage clipping)

All patients underwent selective right-sided one-lung ventilation with double-lumen endotracheal intubation under general anesthesia. Intraoperative transesophageal echocardiography (TEE) was performed and guided intraoperative left atrial appendage clipping. The patient was placed in the right lateral decubitus position with the left forearm raised in line with the shoulder to expose the axillary region. Surgery was performed through 3 incisions in the chest wall. The camera port (5 mm) is located in the 6th intercostal space of the midaxillary line, and the remaining 2 working ports (5 mm and 5 mm) are located in the 4th intercostal space of the midaxillary line in front of the axilla and the 5th intercostal space in the posterior axillary line in the rear of the axilla, respectively. The pericardium opens parallel to 2 cm to the right of the phrenic nerve. The pericardium is suspended by a prolene wire and fixed to the skin to fully expose the left atrial appendage. The E-clip, the left atrial appendage clipping system of Beijing Med-Zenith, was used to close the base of the left atrial appendage in parallel through the 3 cm opening of the 6th intercostal space in the posterior axillary line. Transesophageal echocardiography confirmed no residual root or residual leakage. After hemostasis and nerve block around the incision, the operation was completed.

Complications during hospitalization (whether severe bleeding, need for reoperation, myocardial infarction, etc.) were observed after surgery, and the complete state of postoperative clipping was reassessed after surgery. According to the clipping state, ① incomplete clipping: if there is a residual fistula or the residual root is larger than 1 cm, anticoagulation therapy should be continued; ② if the clip is complete, anticoagulant drugs should be stopped.

2) Control group (novel oral anticoagulant anticoagulation group)

All patients in the control group were treated with standard doses of new oral anticoagulants (dabigatran 150/110 mg bid or rivaroxaban 20/15 mg Qd, etc.), with appropriate adjustments. If severe bleeding or intolerance occurs during drug administration, discontinue anticoagulant or standard-dose antiplatelet therapy (aspirin 100 mg orally once a day; or clopidogrel 75 mg orally once a day).

6. Imaging examination and laboratory examination, physical examination, questionnaire survey

1) ECG or 24-hour Holter ECG examination:

Atrial fibrillation rhythm needs to be identified before enrollment, through ECG or 24-hour Holter ECG or long-term ECG (any type, including initial atrial fibrillation, paroxysmal atrial fibrillation, persistent atrial fibrillation, permanent atrial fibrillation, etc.); static electrocardiograms were scheduled at the third, sixth, and 12th months

after enrollment and during the follow-up.

2) Cardiac Doppler ultrasonography:

Cardiac Doppler ultrasonography was perfoemed before enrollment to determine whether there was thrombosis in the cardiac cavity and whether there was serious valvular disease; Cardiac function (cardiac ejection fraction EF), cardiac chamber size (atrial size (maximum systolic diameter), left ventricular end-diastolic volume or internal diameter) and intracardiac thrombosis were evaluated at the time of admission, after operation, and at the third, sixth and 12th months of follow-up.

3) Computed Tomography Angiography(CTA) :

Before enrollment, atrial CTA was performed to determine whether there was thrombus in the cardiac cavity, the shape and size of the left atrial appendage, and the size of the left atrium. Aortic CTA was used to determine whether there was severe atherosclerosis and plaque in the aorta and cranial and cerebral vessels above the aortic arch before enrollment. Through CTA examination, the operation group was evaluated for the presence of residual root, residual fistula, intra-atrial thrombosis, and displacement of the clamp at the postoperative and 3-month follow-up nodes.

4) Chest Computed Tomography :

Before enrollment, determine whether there is pleural adhesion and whether there is aortic plaque

5) Pulmonary function tests :

Before the operation group was enrolled, the lung volume measurement and pulmonary ventilation function needed to be measured. Vital capacity (VC)>50% predicted value, forced expiratory volume in 1 second (FEV1)>50% predicted value, residual capacity/total lung capacity ratio (RV/TLC)>50% predicted value, pulmonary diffusing capacity of carbon monoxide (DLco)>50% of expected value. Ventilation reserve capacity, ventilation reserve %= (maximal voluntary ventilation (MVV)-minute ventilation (VE))/ MVV*100%>70%.

6) Transesophageal echocardiography(TEE) :

Before enrollment, the presence of atrial appendage thrombus and the presence of patent foramen ovale were evaluated.

7) Brain Computed Tomography :

Brain CT was used to determine whether there were imaging signs of stroke, and brain CT was used to determine the presence of ischemic foci and/or hemorrhagic foci during the 3-month, 6-month and 12-month follow-ups.

8) Laboratory Examination：

Electrolytes, BNP, coagulation function, renin inflammatory response indexes, myocardial enzyme indexes, etc. at the time of enrollment and during the follow-up period.

9) Physical Examination：

At the time of enrollment and during the follow-up, physical activity examination, muscle strength, muscle tone, nerve reflex, language expression, etc. were used to evaluate whether there were any neurological symptoms of stroke.

10) Questionnaire：

Before entering the group, we collected CHA2DS2-VASc, HAS-BLED, NIHSS, STAF and LADS scores. These tables are shown in Appendix 1.

7. Follow-up

The subjects in the group were followed up every 3 months, 6 months and 12 months after they were discharged from the hospital or began to receive treatment. Stroke-related events were evaluated in the examination or questionnaire completed by the hospital or outpatient clinic at that time. We will establish a network consultation platform to guide patients in medication and symptom consultation. During the follow-up period, subjects can no longer receive clinical trials of other cardiovascular drugs.

8. Clinical evaluation and analysis

Primary outcome measure：①The incidence of stroke and systemic embolism in the two groups；②The composite endpoint event rate included stroke, systemic embolism, myocardial infarction, major bleeding (intracranial hemorrhage or gastrointestinal hemorrhage), and death from cardiovascular causes.

Analysis：In patients with non-valvular atrial fibrillation, the ultimate goal of either LAA closure surgery or oral anticoagulant therapy is to prevent cardioembolism from causing stroke or systemic embolism. The advantage of LAA closure surgery is to highlight the reduction of 90% of the source of thrombus formation in the LAA, thereby reducing the risk of bleeding from long-term oral anticoagulants. Since cardiac surgery often causes myocardial damage in the perioperative period, the incidence of myocardial infarction and cardiac death can be monitored at the same time on this basis, and the occurrence of overall cardiac and cerebral events can be known to reflect its safety. According to the clinical manifestations of patients combined with CT or MR, the occurrence of stroke events was determined, and the type of stroke (ischemic or hemorrhagic) was determined. Then, the specific follow-up time was recorded as the end point. Each case is recorded as 1, (whether it is

ischemic or hemorrhagic stroke, including TIA). There is a total of n cases, divided by the overall base of the single group to obtain the stroke incidence rate; at the same time, the follow-up time of each case is calculated to complete the time-to-event rate calculation.

Secondary outcome measures : ① Ischemic stroke event ; ② systemic embolism event ; ③ major bleeding event (gastrointestinal hemorrhage or intracranial hemorrhage) ;④ bleeding event ;⑤ cardiovascular cause death ;⑥ all cause of death ;⑦ residual root rate in operation group ;⑧ instrument related thrombosis in operation group;⑨ blood pressure changes ;and ⑩ changes in cardiac cavity size.

Analysis：Because the incidence of individual event diagnosis is low and a large amount of data is needed, ischemic stroke events, non-cerebrovascular embolism events, major bleeding events, summation of major and small bleeding events, cardiovascular death and all-cause death are taken as secondary outcome indicators. Although it is a secondary outcome indicator, it is still the focus of this study. In this study, it was found that which kind of event has a higher incidence will become one of the issues discussed in this study, in order to guide specific clinical treatment. In addition, the effectiveness and safety of thoracoscopic left atrial appendage closure surgery is explained by the rate of residual roots and the occurrence of instrument-related thrombus events.

In addition, in a prospective, non-randomized study (43) , it was found that when there was no significant difference in baseline SBP between the epicardial group and the endocardial group, the systolic blood pressure in the epicardial left atrial appendage closure group was significantly lower than that in the endocardial left atrial appendage closure group at three months and 1 year. Here, we re-explored and verified indicators such as changes in blood pressure and cardiac cavity size in our secondary outcome indicators. The trial outcome is shown in table1

Table 1 Trial outcome in protocol

	Ts-LAAC (n=93)			NOAC(n=93)				
	No. of patient with event	No. of events	Event rate	No. of patient with event	No. of events	Event rate	HR(95%CI)	P value
Primary endpoint								
Any Stroke and systemic								

Composite endpoint
Second endpoint
Ischemic stroke
Systemic embolism
Major bleeding event
MI
Cardiac Death
Death from any cause
Blood pressure(mmHg)
LVEDD (mm)

Ts-LAAC = thoracoscopic left atrial appendage clipping, NOAC = Novel oral anticoagulants , MI=Myocardial infarction, LVEDD=Left ventricular end diastolic volume , Event rate is defined as no. of events per 100 patient-years.

9. Sample size and research plan

There are few studies on the direct comparison between thoracoscopic left atrial appendage closure surgery and anticoagulation therapy, especially in patients with high risk of stroke and high risk of bleeding. According to the noninferior efficacy study of left atrial appendage closure surgery and new oral anticoagulants in PRAGUE-17 's randomized clinical trial(44), it is estimated that the incidence of annual compound end point events is 13% in new oral anticoagulants and 10% in left atrial appendage closure surgery. Based on the literature data of transepicardial clipping of the left atrial appendage under one-group thoracoscopy (42), it is considered that in non-valvular atrial fibrillation, the stroke event can be controlled within 1.5%, and the expected maximum is no more than 6%. Therefore, the target value of this test is 1.5%, and the noninferior boundary value is δ = 5%. In the case that the statistical significance level is unilateral test α = 0.025 and the test efficiency is not less than 80% (1-β), according to the abovementioned data parameters, statistical assumptions and sample estimation formula, PASS15.0 is used for sample estimation: the calculated sample size needs at least 93 cases in each group, with a total of 186 cases.

10. Data collection

1) Baseline information

The collection of baseline information included demographic data, including age, sex, weight, etc.; past history: smoking, drinking, respiratory diseases, cardiovascular diseases, endocrine diseases, neurological diseases, past surgical history, family history, past use of drugs (antihypertensive drugs, anticoagulants, antiarrhythmic drugs, etc.). Physical examination: heart rate, murmur, blood pressure, muscle strength. Questionnaire survey: CHA2DS2-VASc score, CHA2DS2-VASc score, NIHSS score, STAF or LADS score, etc. Laboratory examination: biochemical and inflammatory factors, coagulation factors, myocardial enzymes, BNP, renin, angiotensin, etc. The craniocerebral signs of CT, the size of the atrium and the index of cardiac function were examined by ultrasound.

2) Data recording of interventions

Operation group: Operation time, perioperative complications, drainage volume, perioperative stroke, bleeding, events of death, repeated laboratory examinations, ultrasound and CT examinations were recorded. Oral drug control group: The type, frequency and dose of drugs used were recorded.

3) Data records during follow-up

The intervention group and the control group were followed up by telephone or network, outpatient clinic, recorded the clinical symptoms at 3, 6, and 12 months of follow-up, and informed the subjects to complete repeated laboratory and imaging examinations. If there is an outcome indicator, it will be recorded in time. The time points of data collection are shown in table2.

Table2 Overview of study measurements and time points for data collection

Time point	Screening	Intervention period					Follow up		
	or before intervention	Surgical procedure/OAC	DAY0	DAY1	DAY2	DAY3	DISCHARGE/DAY4	MONTH3	MONTH6	MONTH12
Eligibility	X									
Informed consent	X									
Participant demographics	X									
Surgical history	X									

Antiplatelet drug use	X	X	X	X	X	X	X	X	X	X
Anticoagulant drug use	X	X	X	X	X	X	X	X	X	X
The use of hypertension drugs	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X	X	X	X	X	X	X	X	X	X
CHA2DS2-VASc score	X									
Has-bled score	X						X	X	X	X
NIHSS score	X	X	X	X	X	X	X	X	X	X
STAF/LADS score	X									
Major bleeding	X	X	X	X	X	X	X	X	X	X
Non-massive hemorrhage	X	X	X	X	X	X	X	X	X	X
Stroke assessment	X	X	X	X	X	X	X	X	X	X
Heart failure	X	X	X	X	X	X	X	X	X	X
Myocardial infarction	X	X	X	X	X	X	X	X	X	X
Peripheral vascular disease	X	X	X	X	X	X	X	X	X	X
Cerebrovascular disease CT	X						X	X	X	X
Neurological symptom assessment	X	X	X	X	X	X	X	X	X	X

Arterial CTA	X							X	X	X
Atrial CTA	X						X	X	X	
Echocardiography(TTE/TEE)	X	X					X	X	X	X
Ejection fraction	X						X	X	X	X
Cardiac cavity size	X						X	X	X	X
Thrombus evaluation	X						X	X	X	X
Myocardial enzyme	X	X	X	X	X	X	X	X	X	X
Electrolyte	X	X	X	X	X	X	X	X	X	X
Renin level	X	X	X	X	X	X	X	X	X	X
Brain natriuretic peptide	X	X	X	X	X	X	X	X	X	X
Heart rate	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X
Adverse events or deaths		X	X	X	X	X	X	X	X	X

OAC= Oral Anticoagulant, CT= Computed Tomography, CTA=Computed Tomography Angiography, TTE=Transthoracic echocardiography, TEE =transesophageal echocardiography

Data collection for baseline and follow-up measures was assigned to different members of the research team. Follow-up outcome indicators at each stage were followed up by different study team members and entered into paper and electronic databases by the study team members who submitted them to data processing. Follow-up executive members will not have access to the electronic database.

11. Data management

Each data controller will be given an account number stored in an electronic database. Research Electronic

Data Capture is a secure web-based software platform. The China Trial Management Public Platform will be used to store all data. All data are stored using anonymized codes. The code with the paper data is kept in a lockable warehouse that can only be accessed by researchers involved in the project. Data will be kept for at least 5 years after the study is completed.

12. Statistical methods

All data can be recorded in the worksheet of Microsoft Excel. All data analysis was performed by using appropriate statistical software, such as IBM SPSS statistics for Windows, version 25 (IBM Corp., Armonk, NY) software or R statistical software (rfoundation for statistical computing, Vienna, Austria) or stata14.0 software (statacorp LP, College Station, TX). All data are represented by appropriate features such as the mean, standard deviation, median, mean and percentage. We will use the intention-to-treat approach for all analyses in the general population. Categorical variables and continuous variables were analyzed using independent t tests and chi-square tests, respectively. We will calculate HRs, 95% confidence intervals, and P_values for time-to-event analyses using a Cox proportional hazards model with risk factors as covariates. A P value is less than 0.05 was considered statistically significant. When the proportion of missing data is less than 5% or greater than 40%, it will not be processed. When 10-20% of the data are missing, the method of multiple imputation is implemented with SAS software.

13. Interim analyses

In the mid-term of the clinical trial, the data of the research team will be counted for the main outcome indicators of the two groups, and the safety and efficacy of the closure of the left atrial appendage under thoracoscopy will be evaluated, as well as whether there is a significant difference between the resolution indicators of the control group and the control group. When the clinical trial indicated that ① the safety of thoracoscopic left atrial appendage closure surgery was poor, ② there were more serious adverse events in the two groups, and ③ the data between the two groups showed that there was a significant difference. If one of the above situations occurs, the trial will be terminated early according to the decision of the ethics committee.

Ethics

1. Informed consent

Participants who are interested and meet the exclusion/ inclusion criteria will be provided with written and verbal information about the study. Informed consent was provided by specialized researchers. All participants are given the opportunity to discuss participation with family members or other responsible persons close to the participant. Consent is continually monitored during the research by asking participants if they want to continue

at the start and end of each session. The specific content of the informed consent form is in Appendix 2.

2. Protocol amendments

Protocol amendments Any protocol amendments will be submitted to the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University for approval. The primary investigator will update the trial registry after amendments have been approved.

3. Harms

The possibility of harm is low. Closure of the left atrial appendage in patients at high risk of stroke and high bleeding risk reduces the chance of LAA thrombosis and reduces the chance of stroke and bleeding from anticoagulant drugs. Since its introduction in 2007 in the first in-person prospective device trial (NCT00567515), epicardial LAA closure has been shown to be an effective tool for safe and durable LAA occlusion in cardiac surgery patients.(45) Ailawadi et al. (37)reported favorable short-term safety and durability results in a prospective, non-randomized, multicenter study. In addition, 3-year follow-up data were provided in a trial cohort that documented 100% persistent and complete LAA clipping by CT imaging.(38) In nonsurgical patients with atrial fibrillation, the risk of ischemic stroke can be significantly reduced by appropriate oral anticoagulants .(7) In the FDAMAUDE database, there are unique reports of adverse events using the lariat device, (46)but there are no reports of adverse events caused by thoracoscopic closure of the left atrial appendage with the epicardial left atrial appendage clip device. However, there are still cardiac rupture or coronary involvement events, depending on the surgeon's judgment. If participants do experience any side effects or adverse reactions, researchers will monitor them, or rescue them, until symptoms subside. The sponsor, Beijing Tiantan Hospital, Capital Medical University, will bear the cost of treatment and give you corresponding financial compensation in accordance with relevant national regulations.

4. Auditing

During the clinical trial process, any modification to all trial protocols should be reported to the ethics committee and implemented after approval. Any events that occur during the trial that may affect patient safety or the continuation of clinical trials, especially changes in safety, should be reported to the ethics committee. Updates to the investigator's operating manual should be submitted to the ethics committee. A progress report of the clinical trial and a summary of the clinical results after the clinical trial should be submitted to the ethics committee annually.

5. Confidentiality

The original medical records will be kept in the hospital. Electronic data will be stored in the clinical trial public management platform, and personal data will be stored in random numbers. Investigators, research

authority personnel, ethics committees, monitors, auditors, and drug regulatory authority inspectors may consult the subjects' original medical records to verify the clinical trial process and data. The above-mentioned personnel are responsible for the confidentiality of patients' personal information, and violations of disclosure will be punished. The confidentiality of any subject-related identification records will not be used publicly. If clinical trial results are released, identifying information will remain confidential. We will make every effort to protect the privacy of personal medical information to the extent permitted by law.

6. Patient and public involvement

Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial; however, they will not be involved in the recruitment and conduct of the study. Besides, the burden of the intervention will be assessed by patients themselves. After signing an informed consent by the participants, they will be assessed for eligibility and data collection will begin. Dissemination of the general results (no personal data) will be made on demand.

Discussion

The most conventional treatment for non-valvular atrial fibrillation is anticoagulation, which is an I, A recommendation. However, in patients at high bleeding risk, the rate of side effects such as bleeding compromises stroke prevention. Left atrial appendage closure (LAAC) is a stroke prevention measure and systemic oral anticoagulation in the prevention of stroke, systemic embolism and cardiovascular death in patients with non-valvular atrial fibrillation (NVAF), according to a large number of clinical trials. , has been shown to be noninferior to warfarin.(22, 26) Because stent exposure is in direct contact with blood, even with combined anticoagulation and antiplatelet therapy, the incidence of device-related thrombosis associated with endocardial devices can range from 3% to 7.2%.(47-50)Transepicardial closure of the left atrial appendage theoretically has a lower risk of device-related thrombosis due to the lack of an intravascular foreign body, and anticoagulants can be discontinued. Caliskan et al(31) advocated discontinuation of warfarin or novel anticoagulant therapy 3 months after treatment for LAA clipping. (51)Kurfirst et al(39) again advocated continuation of anticoagulation for 3 months after surgery; if the patient was in sinus rhythm, anticoagulation should be discontinued at this time. Continued blood flow to the LAA has been shown to increase the risk of stroke in patients undergoing surgical closure of the LAA. The current consensus is that a left atrial appendage stump <10 mm is routinely used as the criterion for success.(52) Once intraoperative transesophageal ultrasound confirms the stable position of the clipping device, and the postoperative residual root is less than 1 cm and/or there is no residual fistula, or the presence of a matte surface due to exposed trabeculae, it can be

stopped immediately (53) Anticoagulant drugs.(53) Given the potentially catastrophic nature of cerebrovascular events, a robustly designed study is needed to support discontinuation of OAC after transepicardial closure of the left atrial appendage. It is not currently possible to make strong recommendations to support discontinuation of OAC after surgery.(54) However, for patients with high bleeding risk, it is clinically meaningful to stop anticoagulant drugs after complete closure of the left atrial appendage through epicardial closure, especially for minimally invasive surgery under thoracoscopy, which is more conducive to acceptance. Therefore, the setting of this article is necessary on the basis of high-risk stroke and bleeding risk.

An additional finding was that in a prospective, non-randomized study , patients with epicardial closure of the left atrial appendage compared with endocardial occlusion had a significant decrease in systolic blood pressure at 3 months and 1 year.(43) Although the exact mechanism of this reduction in systemic blood pressure is unclear, the most powerful explanation is the persistent downregulation of the renin-angiotensin-aldosterone system (RAAS) and its interaction with epicardial left atrial appendage clipping, sympathetic nervous system and natriuretic peptide .(55) In addition, Lakkireddy et al(55) found that after transepicardial LAA closure, epinephrine, norepinephrine and aldosterone were significantly downregulated immediately 3 months after surgery. ANP and BNP levels increased significantly at 24 hours and returned to baseline after 3 months. Even adiponectin, free fatty acid, and glucose metabolism are affected by LAA closure surgery. The exact mechanisms of these phenomena are poorly understood. Changes in natriuretic peptides and the autonomic nervous system innervating the left atrial appendage led to the effects of downregulation of the renin-angiotensin-aldosterone system.(56-58)

Left atrial appendage surgery plays a prominent role in patients with contraindications to anticoagulation, reducing the chance of hemorrhage and stroke. At the same time, changes in endocrine and blood pressure during treatment make left atrial appendage clipping surgery an advantageous surgery, especially the more acceptable thoracoscopic left atrial appendage closure. Further clinical evidence is still needed to verify that it is more suitable for subjects with high stroke and high bleeding risk.

It is necessary to design a randomized controlled trial to theoretically randomize patients with nonvalvular atrial fibrillation to thoracoscopic left atrial appendage closure surgery versus oral novel anticoagulants alone to reduce selection bias. However, in the process of clinical practice, there is no such environment in which randomization is performed without the knowledge of patients. Instead, patients choose to receive surgery or oral anticoagulant therapy according to their own wishes. Alternatively, patients are more inclined to surgery because of the confusion caused by multiple bleeding events in the past. In addition, patients who choose to receive oral anticoagulants without surgery are still a large group, although patients have been informed of the

risk of bleeding.

Strengths and limitations of this study

Our study design proposes a direct comparison between thoracoscopic left atrial appendage closure surgery and anticoagulant drugs, which is one of the few controlled studies to date, and provides data evidence for a new option for stroke prevention. The study is a non-randomized trial due to the real-world nature of the study.

Dissemination

The results from this study will be disseminated through manuscript publications and national/international conferences. All study investigators will be eligible for authorship depending on contributions to the manuscripts, the use of professional writers is not intended.

Declaration of interests

None declared.

Contributors

Cong Ye and Dong Xu: conception of the work. Cong Ye drafted the manuscript. Xuedong Han, Yiming Chen, Hao Ma, Fei Liu, Yang Liu, Yu Yang, Qingfeng Hu, Qing Yao, and Wenting Xie critically revised the work critically for important intellectual content and have read and approved the manuscript. Members of the team will randomly serve as follow-up staff and data statisticians and data monitors at each stage.

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Figure 1

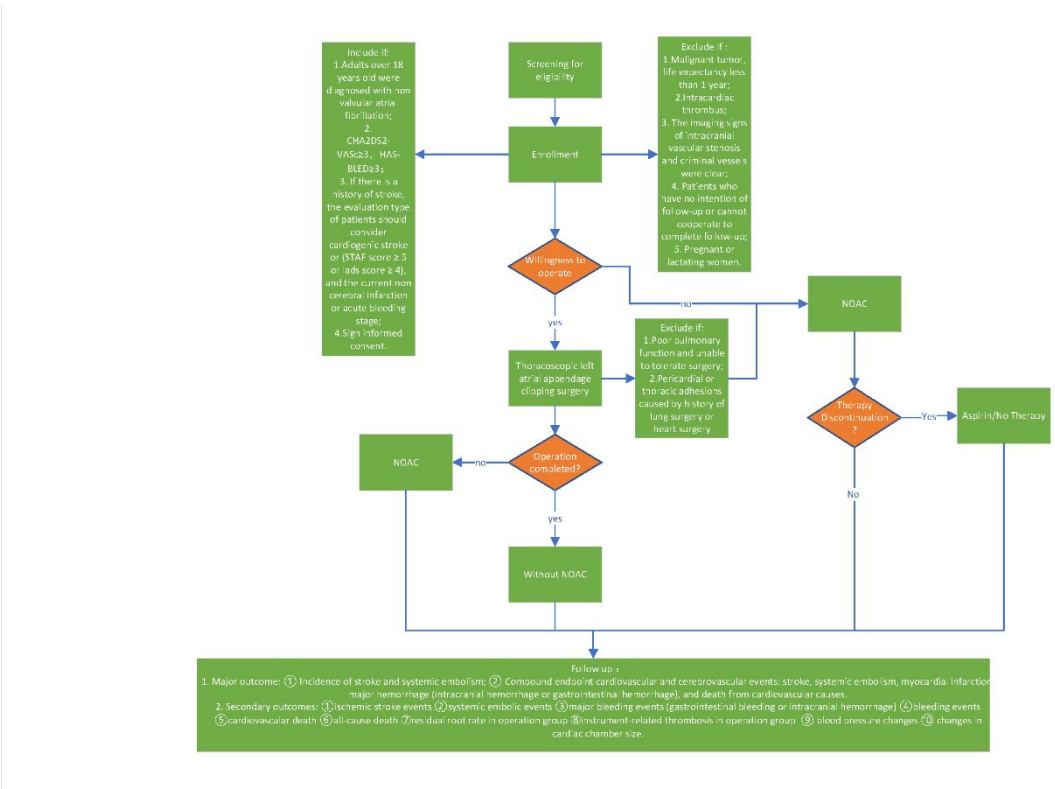

Figure 1 Study flow chart with inclusion and exclusion criteria, as well as outcome measures

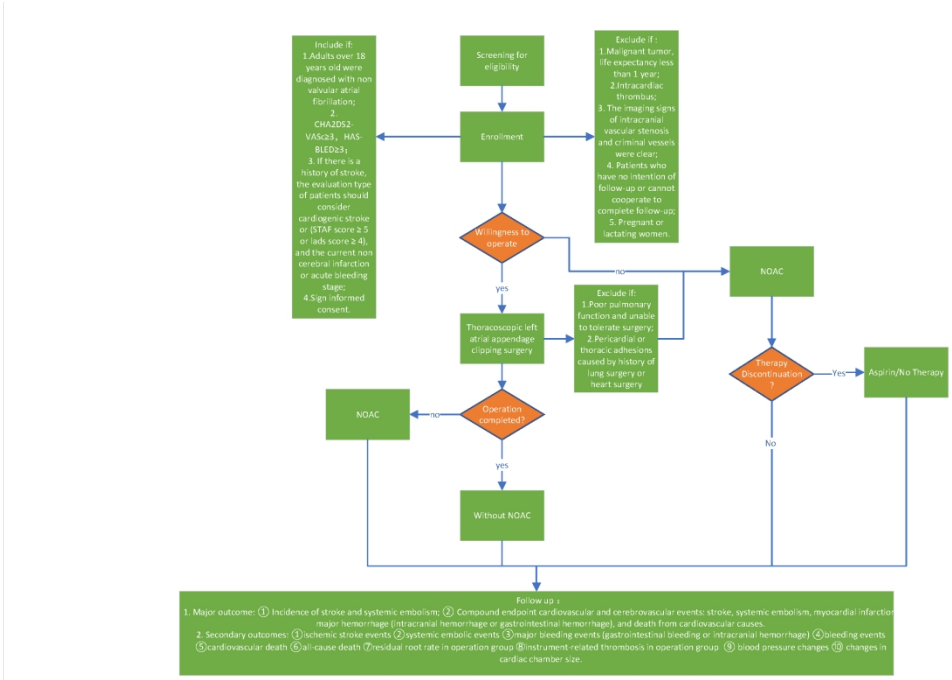

Figure 1 Study flow chart with inclusion and exclusion criteria, as well as outcome measures

297x210mm (200 x 200 DPI)

CHA2DS2-VASc score

Hazard Factor	Points	Score
Congestive heart failure / Left Ventricular Ejection Fraction (LVEF)≤40%	1	
Hypertension	1	
Age ≥ 75 years old	2	
Diabetes mellitus	1	
Stroke or Transient Ischemia Attack (TIA) or Embolism	2	
Vascular disease (prior myocardial infarction, Peripheral arteriosclerosis, or aortic plaque)	1	
Age 65-74 years old	1	
Sex category（Female）	1	
Total score	9	

The highest score is 9. When the CHA2DS2-VASc score is ≥ 2, oral anticoagulant therapy is recommended; when the score is 1, oral anticoagulant or no antithrombotic therapy is acceptable; if there are no risk factors, the patients with 0 score do not need antithrombotic therapy.

HAS-BLED score

Hazard Factor	Points	Score
Hypertension (H)	1	
Abnormal renal and liver function (A)	1 point each	
Stroke (S)	1	
Bleeding (B)	1	
Labile INRs (L)	1	
Elderly ,Age > 65 years old (E)	1	
Drugs (Combined use of antiplatelet or non-steroidal anti-inflammatory drugs) or alcohol (D)	1 point each	
The annual risk of major bleeding in patients with atrial fibrillation increased significantly with increasing total score. At present, it is clinically believed that a HAS-BLED score ≥ 3 points indicates a high risk of bleeding, but this is not a contraindication to anticoagulation therapy. Attention should be paid to correcting the controllable factors that increase the risk of bleeding, anticoagulation and close monitoring and enhanced follow-up.		

STAF score

Element	Points	Score
Age, y		
> 62	2	
≤62	0	
Baseline NIHSS score		
≥8	1	
< 8	0	
Left atrial dilatation (inner diameter over 35mm)		
Yes	2	
No	0	
Vascular etiology		
Yes	0	
No	3	

1. Vascular etiology, Defined by the absence of symptomatic extra- or intracranial stenosis ≥50%, symptomatic arterial dissection, clinico-radiological lacunar syndrome.

2. This scale is used to distinguish cardiac cerebral embolism from arterial cerebral embolism. Total score is 0-8. If the total score is ≥5 points, it is 90% probability to consider cardiogenic stroke; If the score is less than 5, the diagnosis is inclined to arteriogenic stroke.

LADS score

Element	Points	Score
Left atrial diameter (mm)		
< 35	0	
35~44	1	
≥45	2	
Age, y		
< 60	0	
60~79	1	
≥80	2	
Diagnosis		
TIA	0	
Stroke	1	
Smoking		
Yes	0	
No	1	
Total score	6	
When the LADS score ≥ 4, the diagnosis was inclined to cardiogenic stroke. The higher the total score, the greater the likelihood of cardiac stroke.		

Informed consent

Name of the research scheme：Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding

Applicant: Beijing Tiantan Hospital, Capital Medical University

CRO：None

Version number：V1.4

Version date：2022–02-21

Informed consent

Dear patients,

You have been diagnosed with atrial fibrillation. After careful discussion by experts of Cardiovascular Surgery and Neurology of Beijing Tiantan Hospital, Capital Medical University, one of the treatment options of oral anticoagulant or transcatheter left atrial appendage occlusion or thoracoscopic left atrial appendage clipping surgery can be chosen to prevent cardiogenic stroke.

We will invite you to participate in a study of stroke prevention in patients with non-valvular atrial fibrillation who are at high risk of stroke and bleeding during thoracoscopic epicardial left atrial appendage clipping. This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University and complies with the principles of the Helsinki Declaration and medical ethics. Participation in this study is voluntary.

Please read this article as carefully as possible before you decide whether to participate in this study. Part of the content covered in this article is determined by the requirements of laws and regulations, and to protect the rights and interests of patients participating in the study, it has been examined and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. It can help you understand the content of the study and why it is conducted, the procedure and duration of the study, and the benefits and discomfort that may be brought to you after participating in the study. If you are inclined to participate in this study, you can also discuss it with your relatives and friends or ask your doctor for an explanation to help you make a decision.

1. Why conducts this research?

As a common arrhythmia, the most serious complication of atrial fibrillation is the occurrence of ischemic stroke caused by thrombosis

and shedding after its hemodynamic changes. Nonvalvular atrial fibrillation is a risk factor for ischemic stroke. The 2016 ESC management guidelines for atrial fibrillation pointed out that when the CHA2DS2-VASc score is ≥2 in men and ≥3 in women, the risk of thromboembolic events is significantly increased, and long-term anticoagulation therapy is recommended (I, A). The safety margin for warfarin is narrow, with a fivefold increased risk of bleeding with warfarin compared to patients who were not anticoagulated. Even with the use of novel oral anticoagulant therapy to reduce the risk of bleeding, there are still adverse events such as thrombosis and bleeding, due to missed doses or improper anticoagulation. In many randomized controlled trials, including subjects receiving new oral anticoagulants or warfarin, the annual incidence of major bleeding events ranged from 2.13% to 3.6%, and the cumulative incidence of annual bleeding events ranged from 14.4% to 25.6%. The discontinuation rate of subjects was as high as 16.6%-25.3% due to bleeding or fear of bleeding. When the risk of bleeding outweighs the potential benefit of oral anticoagulation if the HAS-BLED score is higher than the patient's CHADS2 score, then oral anticoagulation is no longer beneficial for such patients. Therefore, a safe and effective alternative method is urgently needed. Transepicardial left atrial appendage clipping surgery permanently isolates it from the left atrial blood circulation, and its occlusion rate is close to 100%, which is an advantageous method of left atrial appendage closure. In the empirical treatment of left atrial appendage clipping surgery at home and abroad, because of intracardiac implantation without foreign bodies, the complications of instrumental embolism were reduced, and the suggestion to stop anticoagulant drugs was put forward. This new treatment modality reduces the incidence of stroke in patients at high risk of embolism and bleeding and is more beneficial to patients' quality of life. However, more clinical evidence is needed to support this study.

2. How many people will participate in the study?

At least 186 people will participate in this study.

3. Who was selected for the study?

You can participate in this study if you meet the following conditions: Adults over 18 years old, diagnosed with non-valvular atrial fibrillation; CHA2DS2-VASc≥3, HAS-BLED≥3; if there is a history of stroke, consider cardiac stroke, and there is no acute cerebral infarction or bleeding. Whether you can participate in the study needs to be examined by your doctor and finally decided.

4. Who is not suitable to participate in the study?

It is not appropriate for you to participate in this study if you meet any of the following criteria: malignant tumor, life expectancy less than 1 year; intracardiac thrombus; clear imaging signs such as severe carotid atherosclerosis, intracranial vascular stenosis, and criminal blood vessels; presence of patent foramen ovale; other cardiac surgery with thoracotomy; presence of movable aortic plaques (including ascending aorta, aortic arch, and descending aortic thoracic segment); patients with no willingness to follow-up or who cannot cooperate with completion of follow-up; pregnant or lactating women.If you have the above situation, the doctor will also let you know.

5. How long will this study last?

This study will last for 3 years. Follow-up will collect information about your clinical prognosis after treatment. The follow-up period was at least 1 year. You can opt out of the study at any time without losing any of the benefits you should have earned, but it is not recommended. If you decide to quit during the study, we suggest that you consult with your doctor first. In view of your security issues, it is possible to conduct a check before exiting.

6. How was the study conducted?

If you would like to participate in this study, your doctor will review your medical history, ask about past and current treatments and medications, and undergo the following tests to further confirm your suitability for participation in this study:

• Physical examination and medical history inquiry

• Bleeding risk and embolism risk assessment

• Laboratory tests, imaging tests (CT/CTA/MR/MRA, etc.)

• Electrocardiogram for recording electrophysiological activity of the heart

After completing the relevant examinations, it is necessary to conduct a sufficient safety assessment for the individual patient's situation by a neurologist and a cardiac surgeon.

The patients were grouped according to their willingness to undergo surgery. If you enter the left atrial appendage clipping surgery group, we will complete the preoperative examination and post thoracoscopy left atrial appendage clipping surgery, and stop the use of anticoagulant drugs after the operation according to the completeness of the clipping. If you are in the nonsurgical group, we treated you with a new oral anticoagulant and adjusted subsequent medication based on follow-up review results. Throughout the research process, we will collect your health status through a series of monitoring methods and checks to ensure your safety. During the study, your treatment will not be affected or delayed because of the study. After being discharged from the hospital, the patients were followed up by telephone and online.

7. What are my obligations to participate in research?

During the study period, you need to do the following things:

1）Have the obligation to truthfully provide the medical history and "previous participation in clinical trials";

2）take the medicine in strict accordance with the doctor's orders；

3）You need to go back to the hospital for at least 3 clinical visits during the study. (CT, ultrasound, and laboratory tests were performed at the 3rd, 6th, and 12th months of follow-up, respectively).

4）The patient follow-up diary card is filled out by you or your relative. Record the patient's diary card within one week before each visit, and bring the diary card to your research doctor for review during each visit.

5）During the study period, without the permission of the clinician, other anticoagulant drugs may not be added without permission, and the clinician may be consulted as appropriate.

8. What are the costs involved in participating in the research?

（1） Expenses you will be responsible for include:

The examination and treatment expenses for clinical needs during hospitalization are not included in the free range.

（2） Expenses that you are not responsible for include the following:

You need to complete the established follow-up content at 3, 6 and 12 months after joining the study. This study will provide you with free relevant examinations in our hospital (left atrial CTA, craniocerebral CT, cardiac ultrasound).

In addition, to compensate for the inconvenience that may be caused by your participation in this study, you will also pay a certain amount of 200 yuan each time for the transportation expenses incurred by you to participate in the study.

9. What are the benefits of participating in the research for my disease treatment?

The information obtained from this study will help to assess your current condition and follow-up treatment monitoring to develop better treatment strategies. This will help you and other patients with the same disease. If necessary, you can apply to obtain the head CT of this study and the results of laboratory tests to help you further understand your condition.

10. Do I have other treatment options?

In addition to transepicardial left atrial appendage clipping, one can still choose oral anticoagulant therapy, including warfarin and new oral anticoagulants, or transcatheter left atrial appendage occlusion as a means of stroke prevention. This project is a registration study, and whether you participate in this study will not affect your treatment plan.

11. What are the possible risks of participating in research?

As a means of preventing stroke, thoracoscopic left atrial appendage clipping surgery has the characteristics of less trauma, quick recovery, safety and effectiveness. General anesthesia is required during the operation, and there may be complications related to anesthesia, such as respiratory and circulatory system depression or even suspension due to various reasons, arrhythmia, myocardial infarction, pulmonary embolism, adverse drug reactions and cerebrovascular complications (cerebral hemorrhage, cerebral infarction). The operation requires one-lung ventilation, and postoperative complications such as local atelectasis may occur. Pericardiotomy syndrome may be present during the surgical procedure to open the pericardium. However, as an experienced surgical team, it can be prevented and treated in time. If the above situation occurs during the operation, we will immediately notify your family members and start an emergency treatment plan to give timely treatment.

During the research period, you need to be asked by the doctor on time, and perform some physical and chemical examinations and questionnaires, which may cause trouble or inconvenience to you. If your health does suffer from study-related damage as a result of your participation in this study, please notify the study physician immediately and they will be responsible for appropriate treatment for you. The sponsor, Beijing Tiantan Hospital Affiliated to Capital Medical University, will bear the cost of treatment and give you corresponding financial compensation in accordance with relevant

national regulations. Even if you have signed this informed consent form, you still retain all your legal rights.

12. Can I voluntarily choose to participate in and withdraw from the study?

Participation in this study was entirely voluntary. You may refuse to participate in this study, or withdraw from this study at any time during the study. This decision will not affect the doctor's treatment of you, nor will their medical treatment and rights be affected.

Your doctor or investigator may discontinue your continued participation in this study during the course of the study in your best interest.

If you withdraw from this study for any reason, you may also be ordered to undergo laboratory tests and physical examinations, which are beneficial to your health, if deemed clinically necessary by your doctor.

13. What happens if there is new information related to the research content?

Occasionally new information about the research content is available. If there is any new relevant information that may affect your willingness to continue participating in this study, we will promptly notify you and discuss with you whether it is appropriate to continue participating in this study.

14. How will participating in this study affect my life?

You may find follow-up and review visits inconvenient and require special arrangements. Additionally, some tests can make you feel uncomfortable. You can ask your study doctor if you have any questions about the tests and procedures in the study.

You cannot participate in any other clinical studies of drugs or medical devices during the entire study period.

15. Is my personal information confidential?

Your medical records will be kept in the hospital. Investigators, research authority personnel, ethics committees, monitors, and drug regulatory authority inspectors can consult the subjects' original

medical records to verify the clinical trial process and data. The above-mentioned personnel are responsible for keeping your personal information confidential, and violations will be punished for disclosure. Any confidential matters relating to your identification records will not be used publicly. If clinical trial results are released, your identifying information will remain confidential. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. Your name will not be reflected in any reports.

16. How can I get more information?

You can ask any questions about this research at any time. Your doctor in charge will explain and answer all your relevant questions before enrollment and during the study.

17. Related consultation

If you have any questions related to this study, please contact Dong Xu on landline 59975105 or mobile 13910868737.

If you have any questions related to your own rights, or if you would like to report your dissatisfaction and concerns during your participation in this research, please contact the Office of the National Clinical Trials Institute of Beijing Tiantan Hospital, Tel: 010-59975178, or the Ethics Committee Office of Tiantan Hospital, contact Tel: 010-59975692. Email: ttyyirb@163.com.

Subject Consent Statement

I agree to participate in a clinical study of stroke prevention by thoracoscopic left atrial appendage clipping in patients with nonvalvular atrial fibrillation at high stroke risk and high bleeding risk.

Signing here means:

1. I have read this informed consent form and the researcher has explained the study to me.
2. I have discussed and asked relevant questions about this study, and they have been answered to my satisfaction.
3. I understand that I will be able to obtain compensation from the sponsor in the event of research-related damages.
4. I have plenty of time to make a decision.
5. I voluntarily agree to participate in the clinical research presented in this article.
6. I have been informed of the researcher I should consult during the study.

As described in this informed consent form, I consent to hospital supervision, researchers and other relevant personnel having access to my medical and personal information.

Subject's signature: _____ Date: _____

Name in block letters: _____ Contact number: _____

Signature of legal representative (if any): _____Date: _____

The name of the legal representative in block letters: _____

Contact number: _____

Legal representative and patient relationship: _____

Fair Witness Statement:

I was present throughout the informed process, and the contents of the informed consent form and other written materials were accurately explained to the subjects or legal representatives. The subjects or legal representatives fully understood the meaning of the content, and they agreed to participate in the test.

Signature of an impartial witness (if any): _____Date: _____

The name of the impartial witness in block letters: _____

Contact number: _____

Signature of researcher: _____ Date: _____

Name of researcher in block letters: _____

Contact number: _____

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

	Reporting Item		Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 1	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 1	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4,97	
Protocol version	#3	Date and version identifier	4,97	

Funding	#4	Sources and types of financial, material, and other support	16,413	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16,408	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16,414	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16,414	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16,412	N/A
Introduction			1, 28	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,29	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,75	
Objectives	#7	Specific objectives or hypotheses	3,81	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3,87	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4,100	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,105	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,121	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4,119	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5,146	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,136-145	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,196	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,99	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8,234	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4,98	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	Non randomized trial
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	Non randomized trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	Unblinded
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	Unblinded
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A	Unblinded
Methods: Data collection, management, and analysis				

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,247	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,270	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11,272	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,278	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,285	

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,288	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A	The team of this study has independent data managers ;Data monitoring is managed through China Trial Management Public Platform
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,290	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12,309	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13,325	
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3,95	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12,305	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,299	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	NOT applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13,332	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15,406	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13,334	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13,323	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15,402	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15,404	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15,404	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix2, 1	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	Not applicable

It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-

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Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding: study protocol for a non-randomized controlled clinical trial

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Title page

Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding: study protocol for a non-randomized controlled clinical trial

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Abstract

Introduction： Non-valvular atrial fibrillation (NVAF) is a high-risk factor for ischemic stroke. The 2010 ESC Atrial Fibrillation Management guidelines recommend oral anticoagulants (OAC) to prevent stroke in men with CHA2DS2-VASc scores ≥ 2 and women ≥ 3. However, in patients with a high risk of stroke and a high risk of bleeding (HAS-BLED ≥ 3), OAC had a higher risk of bleeding. Left atrial appendage closure is non-inferior to OAC as a means of preventing stroke in several studies. As a minimally invasive intervention to prevent stroke, transthoracic left atrial appendage clipping (TS-LAAC) has a high successful closure rate, but there is a lack of literature reports directly comparing with OAC. Our research compares TS-LAAC with new oral anticoagulants (NOAC) and provides an appropriate program for stroke prevention in a specific population.

Methods and Analysis: This is a non-randomized controlled trial study protocol, and we will conduct this study from April 2022 to April 2025. The study included 186 patients with confirmed NVAF, 93 of whom completed thoracoscopic left atrial appendage clipping, and the control group treated with NOAC. The primary outcome was the incidence of stroke and systemic embolism, as well as the composite endpoint events (stroke, systemic embolism, myocardial infarction, bleeding, cardiovascular death, etc.). Secondary outcomes were ischemic stroke, hemorrhagic stroke, any bleeding events, death from cardiovascular causes, death from all causes, residual root rate in the surgery group, device-related thrombosis in the surgery group, changes in blood pressure, and cardiac chambers size changes, etc. Each subject completed at least one year of follow-up.

Ethics and dissemination： The study has been approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China (approval number: KY2022-013-02). The results from this study will be disseminated through manuscript publications and national/international conferences.

Trial registration number: ChiCTR2200058109.

Strengths and limitations of this study

1. a rare study of direct comparison between thoracoscopic left atrial appendage closure surgery and anticoagulant drugs.

2. Some outcome measures could provide data support for future study designs.

3. Use of new but robust surgical techniques.

4. No randomization of treatment allocation.

5. Relatively small sample sizes and single-Centre study.

Introduction

Background and rationale

As a common arrhythmia, the most serious complication of atrial fibrillation is thrombosis caused by hemodynamic changes, and further thrombus shedding, which leads to ischemic stroke. Non-valvular atrial fibrillation has become one of the main causes of ischemic stroke. (1, 2) Cerebral embolism accounts for 13-26% of ischemic strokes, and the proportion increases with age. (3-5) 2016ESC Atrial Fibrillation Management guideline points out that the risk of thromboembolic events is significantly increased when the CHA2DS2 score is ≥ 2 in males and ≥ 3 in females. Long-term anticoagulant therapy is recommended (Ⅰ , A). (6) The risk of ischemic stroke can be significantly reduced with appropriate oral anticoagulation in patients with atrial fibrillation who do not wish to undergo surgery. (7) However, as a vitamin K-dependent antagonist, warfarin has a narrow safety margin for anticoagulation, with a fivefold increased bleeding risk compared with non-anticoagulated patients. (8) Although the use of new oral anticoagulants for antithrombotic therapy is effective and significantly reduces the overall risk of bleeding compared with warfarin(9), there is still an increase in adverse events such as thrombosis and bleeding due to missed doses and inadequate anticoagulation management. (10-13) We have observed in large randomized controlled trials (RCT), such as ARISTOLE (14), ROCKET-AF (15), and RE-LY (16) that the annual incidence of major bleeding events among subjects receiving new oral anticoagulants or warfarin ranged from 2.13% to 3.6%, and the cumulative incidence of annual bleeding events (including major and minor bleeding events) ranged from 14.4% to 25.6%. In addition, the discontinuation rate of subjects was as high as 16.6%-25.3% due to bleeding or fear of bleeding risk. When the HAS-BLED score is higher than the CHADS2 score of the patient, that is, the risk of bleeding is greater than the potential benefit of anticoagulation (17), oral anticoagulants no longer benefit such patients. In addition, even if new oral anticoagulants are taken in patients with previous stroke, the risk of stroke recurrence is still high, up to 9.3%, and the incidence of recent bleeding events, including hemorrhagic transformation, is approximately 7.8%, or even up to half. (18) Therefore, we need to find a safer and more effective alternative.

Ninety percent of thrombi in nonvalvular atrial fibrillation originate from the left atrial appendage. (19-21)The isolation of the left atrial appendage, theoretically, can significantly reduce the occurrence of stroke caused by thrombosis of the left atrial appendage from an anatomical point of view. Left atrial appendage closure (LAAC) as a stroke prevention measure, compared with oral anticoagulation therapy, is no non-inferior than warfarin in the risk-benefit prevention of stroke, systemic embolism and cardiovascular death through numerous clinical trials. (22-25) In a recent RCT study PRAGUE-17, left atrial appendage closure surgery was noninferior to newer oral anticoagulants. (26) The 2016 European Society of Cardiology recommends closing the LAA to prevent thromboembolic events, level II evidence level b recommendation. (6) However, due to the direct contact between the metal mesh of the left atrial appendage occlusion and the blood, antithrombotic therapy should not be stopped until it is completely endothelialized to avoid instrument-related thrombosis. Patients implanted with left atrial appendage occlusion are advised to receive aspirin combined with warfarin for at least 45 days and continue antiplatelet therapy with aspirin and clopidogrel for 6 months after confirming that there is no thrombus by TEE

examination and then maintain single antiplatelet therapy for a long time. (27) Therefore, this strategy does not apply to patients with anticoagulant taboos or patients with a high risk of bleeding. Studies have found that transcatheter LAA occlusion has been shown to have residual leaks in 32% of patients, and transesophageal ultrasonography in half of the patients revealed LAA thrombus in 22%. (28, 29) In addition, the incidence of thrombus associated with the use of an endocardial closure device was as high as 7.2%.(30) Surgical closure of the left atrial appendage also plays an important role in stroke prevention. (31) Due to the lack of exogenous foreign bodies in epicardial clamps, the risk of device-related thrombosis is lower in theory. Conor Toale systematically reviewed the PubMed, EMBASE and Cochrane library databases. (32) 902 patients (97.8%) achieved complete closure of the left atrial appendage (LAA). The success rates of placement under video-assisted thoracoscopy and open surgery were 95.3% and 99.2%, respectively, and no residual leakage was reported. Surgical left atrial appendage closure has exerted its advantages in preventing stroke through data from the clinical randomized controlled trial LAAOS-LAAOSIII. (33-35) However, the comparison with other surgical procedures may disrupt the balance of comparison with oral anticoagulants alone. At present, there is a new type of left atrial appendage closure surgery, and the use of video-assisted or total thoracoscopic surgery for left atrial appendage closure, (36-39) can be used as a separate operation to prevent stroke. The results of multiple studies have demonstrated high rates of complete closure and low rates of cerebrovascular events during follow-up. (40-42)

However, there is no direct head-to-head study of oral anticoagulation and surgical LAA closure. We designed a non-randomized controlled trial comparing thoracoscopic left atrial appendage closure surgery versus concurrent oral novel anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation at high bleeding risk and high stroke risk to increase evidence for thoracoscopy left atrial appendage closure surgery as a means of stroke prevention.

Methods and analysis

1. Study design

This study is a planned 3-year clinical trial of stroke prevention in atrial fibrillation, comparing the effect of thoracoscopic left atrial appendage closure surgery with oral anticoagulants in stroke prevention. This is a non-randomized controlled clinical trial study. The patients were divided into the intervention group and the control group according to their willingness to accept the intervention measures of thoracoscopic left atrial appendage closure surgery. In the intervention group, the left atrial appendage was clipped with a thoracoscopic left atrial appendage closure device; the control group adjusted anticoagulation therapy according to the current CHA2DS2-VASC and HAS-BLED conditions. The purpose was to verify the safety and efficacy of thoracoscopic left atrial appendage clipping surgery or its noninferiority. The trial was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (ethics number: KY2022-013-02) on 2022-3-

02 and registered as the first edition with the China Clinical Trial Center (ChiCTR2200058109) on 2022-3-30. Recruited from April 1, 2022, to April 1, 2025 in Neurology and Cardiac Center wards and outpatient clinics. The study flow chart is shown in figure1.

2. Study setting

Data collection will be performed in the Cardiovascular Center and Neurology Department of Beijing Tiantan Hospital, Capital Medical University, Fengtai District, Beijing. The choice of location assignment was not random but was based on data such as the incidence of cardioembolic stroke in patients who had previously visited our hospital.

3. Eligibility criteria

Inclusion criteria:

Adults over 18 years old, diagnosed with non-valvular atrial fibrillation; CHA2DS2-VASc≥3, HAS-BLED≥3; if there is a history of stroke, consider cardiac stroke or (STAF score ≥ 5 points or LADS score ≥ 4 points), and there is no acute cerebral infarction or bleeding; signed informed consent.

Exclusion criteria:

Malignant tumor, life expectancy less than 1 year; intracardiac thrombus; clear imaging signs such as severe carotid atherosclerosis, intracranial vascular stenosis, and criminal blood vessels; presence of patent foramen ovale; other cardiac surgery with thoracotomy; presence of movable aortic plaques (including ascending aorta, aortic arch, and descending aortic thoracic segment); patients with no willingness to follow-up or who cannot cooperate with completion of follow-up; pregnant or lactating women; those in the surgical intervention group with poor lung function and unable to tolerate surgery can be transferred to the control group; those in the surgical intervention group with pericardial or thoracic adhesions caused by the history of lung surgery or cardiac surgery can be transferred to the control group.

4. Discontinuation criteria:

The patient had serious adverse reactions to surgery or anticoagulant drugs.

5. Interventions

1) Surgical intervention group (thoracoscopic left atrial appendage clipping)

All patients underwent selective right-sided one-lung ventilation with double-lumen endotracheal intubation under general anesthesia. Intraoperative transesophageal echocardiography (TEE) was performed and guided intraoperative left atrial appendage clipping. The patient was placed in the right lateral decubitus position with the left forearm raised in line with the shoulder to expose the axillary region. Surgery was performed through 3 incisions in the chest wall. The camera port (5 mm) is located in the 6th intercostal space of the midaxillary line,

and the remaining 2 working ports (5 mm and 5 mm) are located in the 4th intercostal space of the midaxillary line in front of the axilla and the 5th intercostal space in the posterior axillary line in the rear of the axilla, respectively. The pericardium opens parallel to 2 cm to the right of the phrenic nerve. The pericardium is suspended by a prolene wire and fixed to the skin to fully expose the left atrial appendage. The E-clip, the left atrial appendage clipping system of Beijing Med-Zenith, was used to close the base of the left atrial appendage in parallel through the 3 cm opening of the 6th intercostal space in the posterior axillary line. Transesophageal echocardiography confirmed no residual root or residual leakage. After hemostasis and nerve block around the incision, the operation was completed.

Complications during hospitalization (whether severe bleeding, need for reoperation, myocardial infarction, etc.) were observed after surgery, and the complete state of postoperative clipping was reassessed after surgery. According to the clipping state, ① incomplete clipping: if there is a residual fistula or the residual root is larger than 1 cm, anticoagulation therapy should be continued; ② if the clip is complete, anticoagulant drugs should be stopped.

2) Control group (novel oral anticoagulant anticoagulation group)

All patients in the control group were treated with standard doses of new oral anticoagulants (dabigatran 150/110 mg bid or rivaroxaban 20/15 mg Qd, etc.), with appropriate adjustments. If severe bleeding or intolerance occurs during drug administration, discontinue anticoagulant or standard-dose antiplatelet therapy (aspirin 100 mg orally once a day; or clopidogrel 75 mg orally once a day).

6. Imaging examination and laboratory examination, physical examination, questionnaire survey

1) ECG or 24-hour Holter ECG examination:

Atrial fibrillation rhythm needs to be identified before enrollment, through ECG or 24-hour Holter ECG or long-term ECG (any type, including initial atrial fibrillation, paroxysmal atrial fibrillation, persistent atrial fibrillation, permanent atrial fibrillation, etc.); static electrocardiograms were scheduled at the third, sixth, and 12th months after enrollment and during the follow-up.

2) Cardiac Doppler ultrasonography:

Cardiac Doppler ultrasonography was performed before enrollment to determine whether there was thrombosis in the cardiac cavity and whether there was a serious valvular disease; Cardiac function (cardiac ejection fraction EF), cardiac chamber size (atrial size (maximum systolic diameter), left ventricular end-diastolic volume or internal diameter) and intracardiac thrombosis were evaluated at the time of admission, after operation, and at the third, sixth and 12th months of follow-up.

3) Computed Tomography Angiography(CTA) :

Before enrollment, atrial CTA was performed to determine whether there was thrombus in the cardiac cavity, the shape and size of the left atrial appendage, and the size of the left atrium. Aortic CTA was used to determine whether there was severe atherosclerosis and plaque in the aorta and cranial and cerebral vessels above the aortic arch before enrollment. Through CTA examination, the operation group was evaluated for the presence of residual root, residual fistula, intra-atrial thrombosis, and displacement of the clamp at the postoperative and 3-month follow-up nodes.

4) Chest Computed Tomography :

Before enrollment, determine whether there is pleural adhesion and whether there is aortic plaque

5) Pulmonary function tests :

Before the operation group was enrolled, the lung volume measurement and pulmonary ventilation function needed to be measured. Vital capacity (VC)>50% predicted value, forced expiratory volume in 1 second (FEV1)>50% predicted value, residual capacity/total lung capacity ratio (RV/TLC)>50% predicted value, pulmonary diffusing capacity of carbon monoxide (DLco)>50% of expected value. Ventilation reserve capacity, ventilation reserve %= (maximal voluntary ventilation (MVV)-minute ventilation (VE))/ MVV*100%>70%.

6) Transesophageal echocardiography(TEE) :

Before enrollment, the presence of atrial appendage thrombus and the presence of patent foramen ovale were evaluated.

7) Brain Computed Tomography :

Brain CT was used to determine whether there were imaging signs of stroke, and brain CT was used to determine the presence of ischemic foci and/or hemorrhagic foci during the 3-month, 6-month and 12-month follow-ups.

8) Laboratory Examination :

Electrolytes, BNP, coagulation function, renin inflammatory response indexes, myocardial enzyme indexes, etc. at the time of enrollment and during the follow-up period.

9) Physical Examination :

At the time of enrollment and during the follow-up, physical activity examination, muscle strength, muscle tone, nerve reflex, language expression, etc. were used to evaluate whether there were any neurological

symptoms of stroke.

10) Questionnaire :

Before entering the group, we collected CHA2DS2-VASc, HAS-BLED, NIHSS, STAF and LADS scores. These tables are shown in Appendix 1.

7. Follow-up

The subjects in the group were followed up every 3 months, 6 months and 12 months after they were discharged from the hospital or began to receive treatment. Stroke-related events were evaluated in the examination or questionnaire completed by the hospital or outpatient clinic at that time. We will establish a network consultation platform to guide patients in medication and symptom consultation. During the follow-up period, subjects can no longer receive clinical trials of other cardiovascular drugs.

8. Clinical evaluation and analysis

Primary outcome measure : ①The incidence of stroke and systemic embolism in the two groups ; ②The composite endpoint event rate included stroke, systemic embolism, myocardial infarction, major bleeding (intracranial hemorrhage or gastrointestinal hemorrhage), and death from cardiovascular causes.

Analysis : In patients with non-valvular atrial fibrillation, the ultimate goal of either LAA closure surgery or oral anticoagulant therapy is to prevent cardioembolic from causing stroke or systemic embolism. The advantage of LAA closure surgery is to highlight the reduction of 90% of the source of thrombus formation in the LAA, thereby reducing the risk of bleeding from long-term oral anticoagulants. Since cardiac surgery often causes myocardial damage in the perioperative period, the incidence of myocardial infarction and cardiac death can be monitored at the same time on this basis, and the occurrence of overall cardiac and cerebral events can be known to reflect its safety. According to the clinical manifestations of patients combined with CT or MR, the occurrence of stroke events was determined, and the type of stroke (ischemic or hemorrhagic) was determined. Then, the specific follow-up time was recorded as the end point. Each case is recorded as 1, (whether it is ischemic or hemorrhagic stroke, including TIA). There is a total of n cases, divided by the overall base of the single group to obtain the stroke incidence rate; at the same time, the follow-up time of each case is calculated to complete the time-to-event rate calculation.

Secondary outcome measures : ① Ischemic stroke event ; ② systemic embolism event ; ③ major bleeding event (gastrointestinal hemorrhage or intracranial hemorrhage) ; ④ bleeding event ; ⑤ cardiovascular cause death; ⑥ all cause of death ⑦ residual root rate in operation group ; ⑧instrument related thrombosis in

operation group;⑨ blood pressure changes ; ⑩ changes in cardiac cavity size.

Analysis： Because the incidence of individual event diagnosis is low and a large amount of data is needed, ischemic stroke events, non-cerebrovascular embolism events, major bleeding events, summation of major and small bleeding events, cardiovascular death and all-cause death are taken as secondary outcome indicators. Although it is a secondary outcome indicator, it is still the focus of this study. In this study, it was found that which kind of event has a higher incidence will become one of the issues discussed in this study, to guide specific clinical treatment. In addition, the effectiveness and safety of thoracoscopic left atrial appendage closure surgery is explaiared by the rate of residual roots and the occurrence of instrument-related thrombus events.

In addition, in a prospective, non-randomized study (43), it was found that when there was no significant difference in baseline SBP between the epicardial group and the endocardial group, the systolic blood pressure in the epicardial left atrial appendage closure group was significantly lower than that in the endocardial left atrial appendage closure group at three months and 1 year. Here, we re-explored and verified indicators such as changes in blood pressure and cardiac cavity size in our secondary outcome indicators. The trial outcome is shown in table1

Table 1 Trial outcome in protocol

	Ts-LAAC (n=93)			NOAC(n=93)				
	No. of patient with event	No. of events	Event rate	No. of patient with event	No. of events	Event rate	HR(95%CI)	P value
Primary endpoint								
Any Stroke and systemic								
Composite endpoint								
Second endpoint								
Ischemic stroke								
Systemic embolism								
Major bleeding event								
MI								

Cardiac Death	
Death from any cause	
Blood pressure(mmHg)	
LVEDD (mm)	

Ts-LAAC = thoracoscopic left atrial appendage clipping, NOAC = Novel oral anticoagulants , MI=Myocardial infarction, LVEDD=Left ventricular end diastolic volume , Event rate is defined as no. of events per 100 patient-years.

9. Sample size and research plan

There are few studies on the direct comparison between thoracoscopic left atrial appendage closure surgery and anticoagulation therapy, especially in patients with high risk of stroke and high risk of bleeding. According to the noninferior efficacy study of left atrial appendage closure surgery and new oral anticoagulants in PRAGUE-17 's randomized clinical trial(44), it is estimated that the incidence of annual compound end point events is 13% in new oral anticoagulants and 10% in left atrial appendage closure surgery. Based on the literature data of transepicardial clipping of the left atrial appendage under one-group thoracoscopy (42), it is considered that in non-valvular atrial fibrillation, the stroke event can be controlled within 1.5%, and the expected maximum is no more than 6%. Therefore, the target value of this test is 1.5%, and the noninferior boundary value is δ = 5%. In the case that the statistical significance level is unilateral test α = 0.025 and the test efficiency is not less than 80% (1-β), according to the abovementioned data parameters, statistical assumptions and sample estimation formula, PASS15.0 is used for sample estimation: the calculated sample size needs at least 93 cases in each group, with a total of 186 cases.

10. Patient allocation

This study is a non-randomized controlled study, and patients will be grouped by their preference for anticoagulation or surgery. According to the anticoagulation data of our center, the patients in the anticoagulant drug group are much larger than those in the surgery group. Therefore, patients will be 1:1 matched with CHA2DS2-VASc scores and HAS-BLED scores, gender, and age after grouping to control for bias and calibrate baseline information.

11. Data collection

1) Baseline information

The collection of baseline information included demographic data, including age, sex, weight, etc.; past history: smoking, drinking, respiratory diseases, cardiovascular diseases, endocrine diseases, neurological

diseases, past surgical history, family history, past use of drugs (antihypertensive drugs, anticoagulants, antiarrhythmic drugs, etc.). Physical examination: heart rate, murmur, blood pressure, muscle strength. Questionnaire survey: CHA2DS2-VASc score, CHA2DS2-VASc score, NIHSS score, STAF or LADS score, etc. Laboratory examination: biochemical and inflammatory factors, coagulation factors, myocardial enzymes, BNP, renin, angiotensin, etc. The craniocerebral signs of CT, the size of the atrium and the index of cardiac function were examined by ultrasound.

2) Data recording of interventions

Operation group: Operation time, perioperative complications, drainage volume, perioperative stroke, bleeding, events of death, repeated laboratory examinations, ultrasound and CT examinations were recorded. Oral drug control group: The type, frequency and dose of drugs used were recorded.

3) Data records during follow-up

The intervention group and the control group were followed up by telephone or network, outpatient clinic, recorded the clinical symptoms at 3, 6, and 12 months of follow-up, and informed the subjects to complete repeated laboratory and imaging examinations. If there is an outcome indicator, it will be recorded in time. The time points of data collection are shown in table2.

Table2 Overview of study measurements and time points for data collection

Time point	Screening or before intervention	Intervention period					Follow up		
		Surgical procedure/OAC	DAY0	DAY1	DAY2	DAY3	DISCHARGE/DAY4	MONTH3	MONTH6	MONTH12
Eligibility	X									
Informed consent	X									
Participant demographics	X									
Surgical history	X									
Antiplatelet drug use	X	X	X	X	X	X	X	X	X	X

Anticoagulant drug use	X	X	X	X	X	X	X	X	X	X
The use of hypertension drugs	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X	X	X	X	X	X	X	X	X	X
CHA2DS2-VASc score	X									
Has-bled score	X						X	X	X	X
NIHSS score	X	X	X	X	X	X	X	X	X	X
STAF/LADS score	X									
Major bleeding	X	X	X	X	X	X	X	X	X	X
Non-massive hemorrhage	X	X	X	X	X	X	X	X	X	X
Stroke assessment	X	X	X	X	X	X	X	X	X	X
Heart failure	X	X	X	X	X	X	X	X	X	X
Myocardial infarction	X	X	X	X	X	X	X	X	X	X
Peripheral vascular disease	X	X	X	X	X	X	X	X	X	X
Cerebrovascular disease CT	X						X	X	X	X
Neurological symptom assessment	X	X	X	X	X	X	X	X	X	X
Arterial CTA	X							X	X	X

Atrial CTA	X						X	X	X	
Echocardiography(TTE/TEE)	X	X					X	X	X	X
Ejection fraction	X						X	X	X	X
Cardiac cavity size	X						X	X	X	X
Thrombus evaluation	X						X	X	X	X
Myocardial enzyme	X	X	X	X	X	X	X	X	X	X
Electrolyte	X	X	X	X	X	X	X	X	X	X
Renin level	X	X	X	X	X	X	X	X	X	X
Brain natriuretic peptide	X	X	X	X	X	X	X	X	X	X
Heart rate	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X
Adverse events or deaths		X	X	X	X	X	X	X	X	X

OAC= Oral Anticoagulant, CT= Computed Tomography, CTA=Computed Tomography Angiography, TTE=Transthoracic echocardiography, TEE =transesophageal echocardiography

Data collection for baseline and follow-up measures was assigned to different members of the research team. Follow-up outcome indicators at each stage were followed up by different study team members and entered into paper and electronic databases by the study team members who submitted them to data processing. Follow-up executive members will not have access to the electronic database.

12. Data management

Each data controller will be given an account number stored in an electronic database. Research Electronic Data Capture is a secure web-based software platform. The China Trial Management Public Platform will be

used to store all data. All data are stored using anonymized codes. The code with the paper data is kept in a lockable warehouse that can only be accessed by researchers involved in the project. Data will be kept for at least 5 years after the study is completed.

13. Statistical methods

All data can be recorded in the worksheet of Microsoft Excel. All data analysis was performed by using appropriate statistical software, such as IBM SPSS statistics for Windows, version 25 (IBM Corp., Armonk, NY) software or R statistical software (rfoundation for statistical computing, Vienna, Austria) or stata14.0 software (statacorp LP, College Station, TX). All data are represented by appropriate features such as the mean, standard deviation, median, mean and percentage. We will use the intention-to-treat approach for all analyses in the general population. Categorical variables and continuous variables were analyzed using independent t tests and chi-square tests, respectively. We will calculate HRs, 95% confidence intervals, and P_values for time-to-event analyses using a Cox proportional hazards model with risk factors as covariates. A P value is less than 0.05 was considered statistically significant. When the proportion of missing data is less than 5% or greater than 40%, it will not be processed. When 10-20% of the data are missing, the method of multiple imputation is implemented with SAS software.

14. Interim analyses

In the mid-term of the clinical trial, the data of the research team will be counted for the main outcome indicators of the two groups, and the safety and efficacy of the closure of the left atrial appendage under thoracoscopy will be evaluated, as well as whether there is a significant difference between the resolution indicators of the control group and the control group. When the clinical trial indicated that ① the safety of thoracoscopic left atrial appendage closure surgery was poor, ② there were more serious adverse events in the two groups, and ③ the data between the two groups showed that there was a significant difference. If one of the above situations occurs, the trial will be terminated early according to the decision of the ethics committee.

Ethics and Dissemination

Ethics

1. Informed consent

Participants who are interested and meet the exclusion/ inclusion criteria will be provided with written and verbal information about the study. Informed consent was provided by specialized researchers. All participants are given the opportunity to discuss participation with family members or other responsible persons close to the participant. Consent is continually monitored during the research by asking participants if they want to continue at the start and end of each session. The specific content of the informed consent form is in Appendix 2.

2. Protocol amendments

Protocol amendments Any protocol amendments will be submitted to the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University for approval. The primary investigator will update the trial registry after amendments have been approved.

3. Harms

The possibility of harm is low. Closure of the left atrial appendage in patients at high risk of stroke and high bleeding risk reduces the chance of LAA thrombosis and reduces the chance of stroke and bleeding from anticoagulant drugs. Since its introduction in 2007 in the first in-person prospective device trial (NCT00567515), epicardial LAA closure has been shown to be an effective tool for safe and durable LAA occlusion in cardiac surgery patients.(45) Ailawadi et al. (37)reported favorable short-term safety and durability results in a prospective, non-randomized, multicenter study. In addition, 3-year follow-up data were provided in a trial cohort that documented 100% persistent and complete LAA clipping by CT imaging.(38) In nonsurgical patients with atrial fibrillation, the risk of ischemic stroke can be significantly reduced by appropriate oral anticoagulants .(7) In the FDAMAUDE database, there are unique reports of adverse events using the lariat device, (46)but there are no reports of adverse events caused by thoracoscopic closure of the left atrial appendage with the epicardial left atrial appendage clip device. However, there are still cardiac rupture or coronary involvement events, depending on the surgeon's judgment. If participants do experience any side effects or adverse reactions, researchers will monitor them, or rescue them, until symptoms subside. The sponsor, Beijing Tiantan Hospital, Capital Medical University, will bear the cost of treatment and give you corresponding financial compensation in accordance with relevant national regulations.

4. Auditing

During the clinical trial process, any modification to all trial protocols should be reported to the ethics committee and implemented after approval. Any events that occur during the trial that may affect patient safety or the continuation of clinical trials, especially changes in safety, should be reported to the ethics committee. Updates to the investigator's operating manual should be submitted to the ethics committee. A progress report of the clinical trial and a summary of the clinical results after the clinical trial should be submitted to the ethics committee annually.

5. Confidentiality

The original medical records will be kept in the hospital. Electronic data will be stored in the clinical trial public management platform, and personal data will be stored in random numbers. Investigators, research authority personnel, ethics committees, monitors, auditors, and drug regulatory authority inspectors may consult

the subjects' original medical records to verify the clinical trial process and data. The above-mentioned personnel are responsible for the confidentiality of patients' personal information, and violations of disclosure will be punished. The confidentiality of any subject-related identification records will not be used publicly. If clinical trial results are released, identifying information will remain confidential. We will make every effort to protect the privacy of personal medical information to the extent permitted by law.

6. Patient and public involvement

Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial; however, they will not be involved in the recruitment and conduct of the study. Besides, the burden of the intervention will be assessed by patients themselves. After signing an informed consent by the participants, they will be assessed for eligibility and data collection will begin. Dissemination of the general results (no personal data) will be made on demand.

Dissemination plan

The study protocol is published in this journal. The results from this study will be disseminated through manuscript publications and national/international conferences.

Discussion

The most conventional treatment for non-valvular atrial fibrillation is anticoagulation, which is an I, A recommendation. However, in patients at high bleeding risk, the rate of side effects such as bleeding compromises stroke prevention. Left atrial appendage closure (LAAC) is a stroke prevention measure and systemic oral anticoagulation in the prevention of stroke, systemic embolism and cardiovascular death in patients with non-valvular atrial fibrillation (NVAF), according to a large number of clinical trials. , has been shown to be noninferior to warfarin.(22, 26) Because stent exposure is in direct contact with blood, even with combined anticoagulation and antiplatelet therapy, the incidence of device-related thrombosis associated with endocardial devices can range from 3% to 7.2%.(47-50)Transepicardial closure of the left atrial appendage theoretically has a lower risk of device-related thrombosis due to the lack of an intravascular foreign body, and anticoagulants can be discontinued. Caliskan et al(31) advocated discontinuation of warfarin or novel anticoagulant therapy 3 months after treatment for LAA clipping. (51)Kurfirst et al(39) again advocated continuation of anticoagulation for 3 months after surgery; if the patient was in sinus rhythm, anticoagulation should be discontinued at this time. Continued blood flow to the LAA has been shown to increase the risk of stroke in patients undergoing surgical closure of the LAA. The current consensus is that a left atrial appendage stump <10 mm is routinely used as the criterion for success.(52) Once intraoperative transesophageal ultrasound confirms the stable position of the clipping device, and the postoperative residual root is less than 1

cm and/or there is no residual fistula, or the presence of a matte surface due to exposed trabeculae, it can be stopped immediately (53) Anticoagulant drugs.(53) Given the potentially catastrophic nature of cerebrovascular events, a robustly designed study is needed to support discontinuation of OAC after transepicardial closure of the left atrial appendage. It is not currently possible to make strong recommendations to support discontinuation of OAC after surgery.(54) However, for patients with high bleeding risk, it is clinically meaningful to stop anticoagulant drugs after complete closure of the left atrial appendage through epicardial closure, especially for minimally invasive surgery under thoracoscopy, which is more conducive to acceptance. Therefore, the setting of this article is necessary on the basis of high-risk stroke and bleeding risk.

An additional finding was that in a prospective, non-randomized study , patients with epicardial closure of the left atrial appendage compared with endocardial occlusion had a significant decrease in systolic blood pressure at 3 months and 1 year.(43) Although the exact mechanism of this reduction in systemic blood pressure is unclear, the most powerful explanation is the persistent downregulation of the renin-angiotensin-aldosterone system (RAAS) and its interaction with epicardial left atrial appendage clipping, sympathetic nervous system and natriuretic peptide .(55) In addition, Lakkireddy et al(55) found that after transepicardial LAA closure, epinephrine, norepinephrine and aldosterone were significantly downregulated immediately 3 months after surgery. ANP and BNP levels increased significantly at 24 hours and returned to baseline after 3 months. Even adiponectin, free fatty acid, and glucose metabolism are affected by LAA closure surgery. The exact mechanisms of these phenomena are poorly understood. Changes in natriuretic peptides and the autonomic nervous system innervating the left atrial appendage led to the effects of downregulation of the renin-angiotensin-aldosterone system.(56-58)

Left atrial appendage surgery plays a prominent role in patients with contraindications to anticoagulation, reducing the chance of hemorrhage and stroke. At the same time, changes in endocrine and blood pressure during treatment make left atrial appendage clipping surgery an advantageous surgery, especially the more acceptable thoracoscopic left atrial appendage closure. Further clinical evidence is still needed to verify that it is more suitable for subjects with high stroke and high bleeding risk.

It is necessary to design a randomized controlled trial to theoretically randomize patients with nonvalvular atrial fibrillation to thoracoscopic left atrial appendage closure surgery versus oral novel anticoagulants alone to reduce selection bias. However, in the process of clinical practice, there is no such environment in which randomization is performed without the knowledge of patients. Instead, patients choose to receive surgery or oral anticoagulant therapy according to their own wishes. Alternatively, patients are more inclined to surgery because of the confusion caused by multiple bleeding events in the past. In addition, patients who choose to

receive oral anticoagulants without surgery are still a large group, although patients have been informed of the risk of bleeding.

Declaration of interests

None.

Contributors

Cong Ye and Dong Xu: conception of the work. Cong Ye drafted the manuscript. Xuesong Han, Yiming Chen, Hao Ma, Fei Liu, Yang Liu, Yu Yang, Qingfeng Hu, Qing Yao, and Wenting Xie critically revised the work critically for important intellectual content and have read and approved the manuscript. Members of the team will randomly serve as follow-up staff and data statisticians and data monitors at each stage.

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Figure 1 Study flow chart with inclusion and exclusion criteria, as well as outcome measures

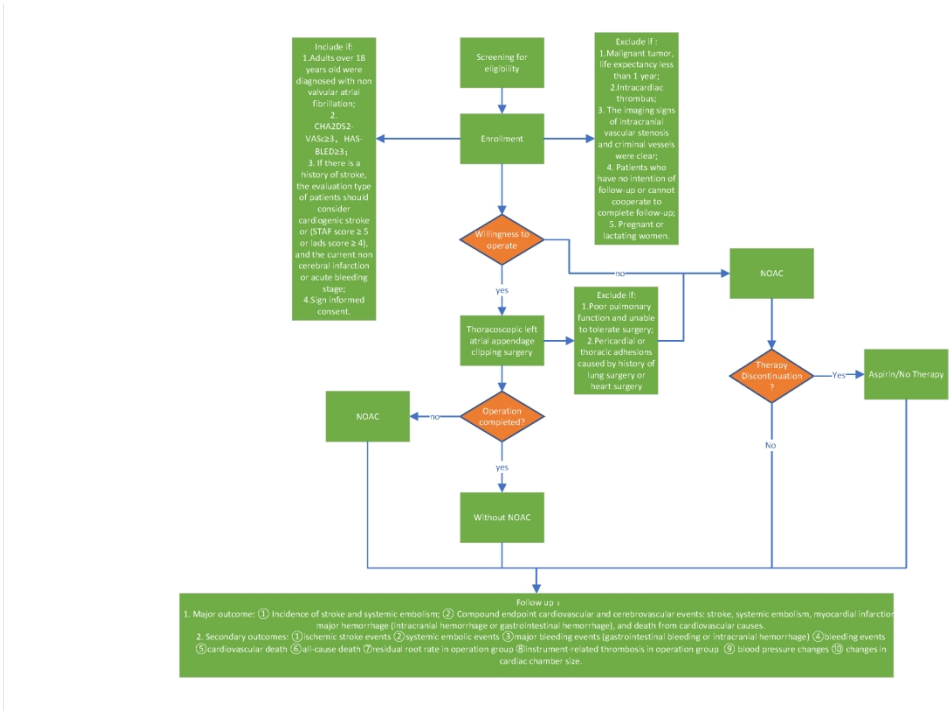

Figure 1 Study flow chart with inclusion and exclusion criteria, as well as outcome measures

297x210mm (200 x 200 DPI)

CHA2DS2-VASc score

Hazard Factor	Points	Score
Congestive heart failure / Left Ventricular Ejection Fraction (LVEF)≤40%	1	
Hypertension	1	
Age ≥ 75 years old	2	
Diabetes mellitus	1	
Stroke or Transient Ischemia Attack (TIA) or Embolism	2	
Vascular disease (prior myocardial infarction, Peripheral arteriosclerosis, or aortic plaque)	1	
Age 65-74 years old	1	
Sex category（Female）	1	
Total score	9	
The highest score is 9. When the CHA2DS2-VASc score is ≥ 2, oral anticoagulant therapy is recommended; when the score is 1, oral anticoagulant or no antithrombotic therapy is acceptable; if there are no risk factors, the patients with 0 score do not need antithrombotic therapy.		

HAS-BLED score

Hazard Factor	Points	Score
Hypertension (H)	1	
Abnormal renal and liver function (A)	1 point each	
Stroke (S)	1	
Bleeding (B)	1	
Labile INRs (L)	1	
Elderly ,Age > 65 years old (E)	1	
Drugs (Combined use of antiplatelet or non-steroidal anti-inflammatory drugs) or alcohol (D)	1 point each	
The annual risk of major bleeding in patients with atrial fibrillation increased significantly with increasing total score. At present, it is clinically believed that a HAS-BLED score ≥ 3 points indicates a high risk of bleeding, but this is not a contraindication to anticoagulation therapy. Attention should be paid to correcting the controllable factors that increase the risk of bleeding, anticoagulation and close monitoring and enhanced follow-up.		

STAF score

Element	Points	Score
Age, y		
> 62	2	
≤62	0	
Baseline NIHSS score		
≥8	1	
< 8	0	
Left atrial dilatation (inner diameter over 35mm)		
Yes	2	
No	0	
Vascular etiology		
Yes	0	
No	3	
1. Vascular etiology, Defined by the absence of symptomatic extra- or intracranial stenosis ≥50%, symptomatic arterial dissection, clinico-radiological lacunar syndrome. 2. This scale is used to distinguish cardiac cerebral embolism from arterial cerebral embolism. Total score is 0-8. If the total score is ≥5 points, it is 90% probability to consider cardiogenic stroke; If the score is less than 5, the diagnosis is inclined to arteriogenic stroke.		

LADS score

Element	Points	Score
Left atrial diameter (mm)		
< 35	0	
35~44	1	
≥45	2	
Age, y		
< 60	0	
60~79	1	
≥80	2	
Diagnosis		
TIA	0	
Stroke	1	
Smoking		
Yes	0	
No	1	
Total score	6	
When the LADS score ≥ 4, the diagnosis was inclined to cardiogenic stroke. The higher the total score, the greater the likelihood of cardiac stroke.		

Informed consent

Name of the research scheme：Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding

Applicant: Beijing Tiantan Hospital, Capital Medical University

CRO：None

Version number：V1.4

Version date：2022–02-21

Informed consent

Dear patients,

You have been diagnosed with atrial fibrillation. After careful discussion by experts of Cardiovascular Surgery and Neurology of Beijing Tiantan Hospital, Capital Medical University, one of the treatment options of oral anticoagulant or transcatheter left atrial appendage occlusion or thoracoscopic left atrial appendage clipping surgery can be chosen to prevent cardiogenic stroke.

We will invite you to participate in a study of stroke prevention in patients with non-valvular atrial fibrillation who are at high risk of stroke and bleeding during thoracoscopic epicardial left atrial appendage clipping. This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University and complies with the principles of the Helsinki Declaration and medical ethics. Participation in this study is voluntary.

Please read this article as carefully as possible before you decide whether to participate in this study. Part of the content covered in this article is determined by the requirements of laws and regulations, and to protect the rights and interests of patients participating in the study, it has been examined and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. It can help you understand the content of the study and why it is conducted, the procedure and duration of the study, and the benefits and discomfort that may be brought to you after participating in the study. If you are inclined to participate in this study, you can also discuss it with your relatives and friends or ask your doctor for an explanation to help you make a decision.

1. Why conducts this research?

As a common arrhythmia, the most serious complication of atrial fibrillation is the occurrence of ischemic stroke caused by thrombosis

and shedding after its hemodynamic changes. Nonvalvular atrial fibrillation is a risk factor for ischemic stroke. The 2016 ESC management guidelines for atrial fibrillation pointed out that when the CHA2DS2-VASc score is ≥2 in men and ≥3 in women, the risk of thromboembolic events is significantly increased, and long-term anticoagulation therapy is recommended (I, A). The safety margin for warfarin is narrow, with a fivefold increased risk of bleeding with warfarin compared to patients who were not anticoagulated. Even with the use of novel oral anticoagulant therapy to reduce the risk of bleeding, there are still adverse events such as thrombosis and bleeding, due to missed doses or improper anticoagulation. In many randomized controlled trials, including subjects receiving new oral anticoagulants or warfarin, the annual incidence of major bleeding events ranged from 2.13% to 3.6%, and the cumulative incidence of annual bleeding events ranged from 14.4% to 25.6%. The discontinuation rate of subjects was as high as 16.6%-25.3% due to bleeding or fear of bleeding. When the risk of bleeding outweighs the potential benefit of oral anticoagulation if the HAS-BLED score is higher than the patient's CHADS2 score, then oral anticoagulation is no longer beneficial for such patients. Therefore, a safe and effective alternative method is urgently needed. Transepicardial left atrial appendage clipping surgery permanently isolates it from the left atrial blood circulation, and its occlusion rate is close to 100%, which is an advantageous method of left atrial appendage closure. In the empirical treatment of left atrial appendage clipping surgery at home and abroad, because of intracardiac implantation without foreign bodies, the complications of instrumental embolism were reduced, and the suggestion to stop anticoagulant drugs was put forward. This new treatment modality reduces the incidence of stroke in patients at high risk of embolism and bleeding and is more beneficial to patients' quality of life. However, more clinical evidence is needed to support this study.

2. How many people will participate in the study?

At least 186 people will participate in this study.

3. Who was selected for the study?

You can participate in this study if you meet the following conditions: Adults over 18 years old, diagnosed with non-valvular atrial fibrillation; CHA2DS2-VASc≥3, HAS-BLED≥3; if there is a history of stroke, consider cardiac stroke, and there is no acute cerebral infarction or bleeding. Whether you can participate in the study needs to be examined by your doctor and finally decided.

4. Who is not suitable to participate in the study?

It is not appropriate for you to participate in this study if you meet any of the following criteria: malignant tumor, life expectancy less than 1 year; intracardiac thrombus; clear imaging signs such as severe carotid atherosclerosis, intracranial vascular stenosis, and criminal blood vessels; presence of patent foramen ovale; other cardiac surgery with thoracotomy; presence of movable aortic plaques (including ascending aorta, aortic arch, and descending aortic thoracic segment); patients with no willingness to follow-up or who cannot cooperate with completion of follow-up; pregnant or lactating women.If you have the above situation, the doctor will also let you know.

5. How long will this study last?

This study will last for 3 years. Follow-up will collect information about your clinical prognosis after treatment. The follow-up period was at least 1 year. You can opt out of the study at any time without losing any of the benefits you should have earned, but it is not recommended. If you decide to quit during the study, we suggest that you consult with your doctor first. In view of your security issues, it is possible to conduct a check before exiting.

6. How was the study conducted?

If you would like to participate in this study, your doctor will review your medical history, ask about past and current treatments and medications, and undergo the following tests to further confirm your suitability for participation in this study:

• Physical examination and medical history inquiry

• Bleeding risk and embolism risk assessment

• Laboratory tests, imaging tests (CT/CTA/MR/MRA, etc.)

• Electrocardiogram for recording electrophysiological activity of the heart

After completing the relevant examinations, it is necessary to conduct a sufficient safety assessment for the individual patient's situation by a neurologist and a cardiac surgeon.

The patients were grouped according to their willingness to undergo surgery. If you enter the left atrial appendage clipping surgery group, we will complete the preoperative examination and post thoracoscopy left atrial appendage clipping surgery, and stop the use of anticoagulant drugs after the operation according to the completeness of the clipping. If you are in the nonsurgical group, we treated you with a new oral anticoagulant and adjusted subsequent medication based on follow-up review results. Throughout the research process, we will collect your health status through a series of monitoring methods and checks to ensure your safety. During the study, your treatment will not be affected or delayed because of the study. After being discharged from the hospital, the patients were followed up by telephone and online.

7. What are my obligations to participate in research?

During the study period, you need to do the following things:

1）Have the obligation to truthfully provide the medical history and "previous participation in clinical trials";

2）take the medicine in strict accordance with the doctor's orders；

3) You need to go back to the hospital for at least 3 clinical visits during the study. (CT, ultrasound, and laboratory tests were performed at the 3rd, 6th, and 12th months of follow-up, respectively).

4) The patient follow-up diary card is filled out by you or your relative. Record the patient's diary card within one week before each visit, and bring the diary card to your research doctor for review during each visit.

5) During the study period, without the permission of the clinician, other anticoagulant drugs may not be added without permission, and the clinician may be consulted as appropriate.

8. What are the costs involved in participating in the research?

(1) Expenses you will be responsible for include:

The examination and treatment expenses for clinical needs during hospitalization are not included in the free range.

(2) Expenses that you are not responsible for include the following:

You need to complete the established follow-up content at 3, 6 and 12 months after joining the study. This study will provide you with free relevant examinations in our hospital (left atrial CTA, craniocerebral CT, cardiac ultrasound).

In addition, to compensate for the inconvenience that may be caused by your participation in this study, you will also pay a certain amount of 200 yuan each time for the transportation expenses incurred by you to participate in the study.

9. What are the benefits of participating in the research for my disease treatment?

The information obtained from this study will help to assess your current condition and follow-up treatment monitoring to develop better treatment strategies. This will help you and other patients with the same disease. If necessary, you can apply to obtain the head CT of this study and the results of laboratory tests to help you further understand your condition.

10. Do I have other treatment options?

In addition to transepicardial left atrial appendage clipping, one can still choose oral anticoagulant therapy, including warfarin and new oral anticoagulants, or transcatheter left atrial appendage occlusion as a means of stroke prevention. This project is a registration study, and whether you participate in this study will not affect your treatment plan.

11. What are the possible risks of participating in research?

As a means of preventing stroke, thoracoscopic left atrial appendage clipping surgery has the characteristics of less trauma, quick recovery, safety and effectiveness. General anesthesia is required during the operation, and there may be complications related to anesthesia, such as respiratory and circulatory system depression or even suspension due to various reasons, arrhythmia, myocardial infarction, pulmonary embolism, adverse drug reactions and cerebrovascular complications (cerebral hemorrhage, cerebral infarction). The operation requires one-lung ventilation, and postoperative complications such as local atelectasis may occur. Pericardiotomy syndrome may be present during the surgical procedure to open the pericardium. However, as an experienced surgical team, it can be prevented and treated in time. If the above situation occurs during the operation, we will immediately notify your family members and start an emergency treatment plan to give timely treatment.

During the research period, you need to be asked by the doctor on time, and perform some physical and chemical examinations and questionnaires, which may cause trouble or inconvenience to you. If your health does suffer from study-related damage as a result of your participation in this study, please notify the study physician immediately and they will be responsible for appropriate treatment for you. The sponsor, Beijing Tiantan Hospital Affiliated to Capital Medical University, will bear the cost of treatment and give you corresponding financial compensation in accordance with relevant

national regulations. Even if you have signed this informed consent form, you still retain all your legal rights.

12. Can I voluntarily choose to participate in and withdraw from the study?

Participation in this study was entirely voluntary. You may refuse to participate in this study, or withdraw from this study at any time during the study. This decision will not affect the doctor's treatment of you, nor will their medical treatment and rights be affected.

Your doctor or investigator may discontinue your continued participation in this study during the course of the study in your best interest.

If you withdraw from this study for any reason, you may also be ordered to undergo laboratory tests and physical examinations, which are beneficial to your health, if deemed clinically necessary by your doctor.

13. What happens if there is new information related to the research content?

Occasionally new information about the research content is available. If there is any new relevant information that may affect your willingness to continue participating in this study, we will promptly notify you and discuss with you whether it is appropriate to continue participating in this study.

14. How will participating in this study affect my life?

You may find follow-up and review visits inconvenient and require special arrangements. Additionally, some tests can make you feel uncomfortable. You can ask your study doctor if you have any questions about the tests and procedures in the study.

You cannot participate in any other clinical studies of drugs or medical devices during the entire study period.

15. Is my personal information confidential?

Your medical records will be kept in the hospital. Investigators, research authority personnel, ethics committees, monitors, and drug regulatory authority inspectors can consult the subjects' original

medical records to verify the clinical trial process and data. The above-mentioned personnel are responsible for keeping your personal information confidential, and violations will be punished for disclosure. Any confidential matters relating to your identification records will not be used publicly. If clinical trial results are released, your identifying information will remain confidential. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. Your name will not be reflected in any reports.

16. How can I get more information?

You can ask any questions about this research at any time. Your doctor in charge will explain and answer all your relevant questions before enrollment and during the study.

17. Related consultation

If you have any questions related to this study, please contact Dong Xu on landline 59975105 or mobile 13910868737.

If you have any questions related to your own rights, or if you would like to report your dissatisfaction and concerns during your participation in this research, please contact the Office of the National Clinical Trials Institute of Beijing Tiantan Hospital, Tel: 010-59975178, or the Ethics Committee Office of Tiantan Hospital, contact Tel: 010-59975692. Email: ttyyirb@163.com.

Subject Consent Statement

I agree to participate in a clinical study of stroke prevention by thoracoscopic left atrial appendage clipping in patients with nonvalvular atrial fibrillation at high stroke risk and high bleeding risk.

Signing here means:

1. I have read this informed consent form and the researcher has explained the study to me.
2. I have discussed and asked relevant questions about this study, and they have been answered to my satisfaction.
3. I understand that I will be able to obtain compensation from the sponsor in the event of research-related damages.
4. I have plenty of time to make a decision.
5. I voluntarily agree to participate in the clinical research presented in this article.
6. I have been informed of the researcher I should consult during the study.

As described in this informed consent form, I consent to hospital supervision, researchers and other relevant personnel having access to my medical and personal information.

Subject's signature: _____ Date: _____

Name in block letters: _____ Contact number: _____

Signature of legal representative (if any): _____Date: _____

The name of the legal representative in block letters: _____

Contact number: _____

Legal representative and patient relationship: _____

Fair Witness Statement:

I was present throughout the informed process, and the contents of the informed consent form and other written materials were accurately explained to the subjects or legal representatives. The subjects or legal representatives fully understood the meaning of the content, and they agreed to participate in the test.

Signature of an impartial witness (if any): _____Date: _____

The name of the impartial witness in block letters: _____

Contact number: _____

Signature of researcher: _____ Date: _____

Name of researcher in block letters: _____

Contact number: _____

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Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

	Reporting Item		Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 1	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 1	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4,105	
Protocol version	#3	Date and version identifier	4,104	

Funding	#4	Sources and types of financial, material, and other support	16,420	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16,415	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16,421	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16,421	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16,419	N/A
Introduction			2, 35	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,36	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,83	
Objectives	#7	Specific objectives or hypotheses	3,88	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3,94	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4,107	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,112	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,128	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4,126	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5,153	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,143-152	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,203	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,106	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9,240	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4,105	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	Non randomized trial
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	Non randomized trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	Unblinded
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	Unblinded
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A	Unblinded
Methods: Data collection, management, and analysis				

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,259	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,282	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11,284	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,290	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,297	

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,300	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A	The team of this study has independent data managers ;Data monitoring is managed through China Trial Management Public Platform
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,302	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13,322	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13,338	
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4,102	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13,318	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,312	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	NOT applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13,345	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16,413	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13,347	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13,350	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14,360	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14,361	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14,361	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix2, 1	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	Not applicable

It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-

Correction: *Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding: study protocol for a non-randomised controlled clinical trial*

Ye C, Han X, Chen Y, *et al*. Stroke prevention of thoracoscopic left atrial appendage clipping in patients with non-valvular atrial fibrillation at high risk of stroke and bleeding: study protocol for a non-randomised controlled clinical trial. *BMJ Open* 2022;12:e063931. doi:10.1136/ bmjopen-2022-063931

This article has been corrected since it was published online. The affiliation numbers 1 and 2 have been merged and updated to "Department of Cardiac Surgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China".

BMJ Open 2023;**13**:e063931corr1. doi:10.1136/bmjopen-2022-063931corr1