A randomized prospective multicenter trial for stroke prevention by prophylactic surgical closure of the left atrial appendage in patients undergoing bioprosthetic aortic valve surgery—LAA-CLOSURE trial protocol

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Patients undergoing surgical aortic valve replacement (SAVR) are at high risk for atrial fibrillation (AF) and stroke after surgery. There is an unmet clinical need to improve stroke prevention in this patient population. The LAA-CLOSURE trial aims to assess the efficacy and safety of prophylactic surgical closure of the left atrial appendage for stroke and cardiovascular death prevention in patients undergoing bioprosthetic SAVR. This randomized, open-label, prospective multicenter trial will enroll 1,040 patients at 13 European sites. The primary endpoint is a composite of cardiovascular mortality, stroke and systemic embolism at 5 years. Secondary endpoints include cardiovascular mortality, stroke, systemic embolism, bleed fulfilling academic research consortium (BARC) criteria, hospitalization for decompensated heart failure and health economic evaluation. Sample size is based on 30% risk reduction in time to event analysis of primary endpoint. Prespecified reports include 30-day

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safety analysis focusing on AF occurrence and short-term outcomes and interim analyses at 1 and 3 years for primary and secondary outcomes. Additionally, substudies will be performed on the completeness of the closure using transesophageal echocardiography/cardiac computed tomography and long-term ECG recording at one year after the operation. (Am Heart J 2021;237:127–134.)

Stroke is a frequent long-term adverse event after aortic valve replacement surgery (SAVR) affecting up to 7% to 15% of patients at 5 year follow-up.[1,2] Given the high burden of atrial fibrillation (AF) after SAVR, emboli related to AF are likely a major source of these strokes and stroke is often the first manifestation of AF.[2,3] Thus, there is an unmet clinical need for better stroke prevention in this patient population.

Based on previous studies ≥90% of AF-related left atrial thrombi are located in the left atrial appendage (LAA),[4] and therefore, LAA occlusion is a tempting method for AF-related stroke prevention in SAVR patients. A slew of observational or underpowered randomized controlled trial data suggests at least 30% stroke risk reduction after cardiac surgery with LAA closure, both at 30 days after surgery as well as in long-term.[5-11] Among elderly patients with AF undergoing coronary bypass, mitral valve or aortic valve surgery, concomitant surgical LAA occlusion was associated with a lower risk of readmission for thromboembolism over 3 years when compared with no LAA occlusion.[11] A recent small underpowered randomized trial suggested up to 70% risk reduction in a composite of post-operative symptomatic ischemic stroke, transient ischemic attack, or imaging findings of silent cerebral ischemic lesions during the median follow-up of 3.7 years irrespective of AF status at enrollment.[12]

Currently, the evidence is insufficient to support routine LAA occlusion during SAVR for AF patients or those at high AF risk postoperatively. The main challenge is to ensure an adequate and durable LAA occlusion with minimal additional risk for patients using sutures, ligation, stapler or specific occlusion devices. EACTS guidelines suggest that devices designed for appendage exclusion should be used rather than a cut-and-sew or stapling technique.[13] Recommendations are based on the findings of meta-analysis of 5 clinical trials including one randomized controlled trial enrolling approximately 1,400 patients with LAA occlusion.[13] Of the 5 studies, only one showed a statistical benefit for LAA occlusion, with 3 giving neutral results and one demonstrating an increased risk.[13] Challenges in achieving adequate LAA occlusion based on postoperative transesophageal echocardiography may explain this heterogeneity.[14] The highest success rate was 93% but most studies have reported only a 55% to 66% rates of successful occlusion when using a variety of methods including stapling, ligation and amputation. The best results have been obtained using devices specifically designed for this purpose.[13]

Another challenge is whether the proper patient population can be identified. Approximately 25% of patients undergoing SAVR have preoperative paroxysmal or permanent AF, however, up to 70% of patients have had at least one episode of AF by the end of first postoperative year.[15] Thus, patients undergoing SAVR have a high postoperative AF burden compared to other types of cardiac surgery such as coronary bypass. Moreover, stroke rates increase with higher CHA_2DS_2-VASc scores[16] and thus it is reasonable to target this enduring treatment for high-risk individuals who may encounter silent AF episodes later in life.

In the LAA-CLOSURE trial, we aim to assess the efficacy and safety of prophylactic surgical closure of LAA in a large-scale randomized controlled clinical trial in SAVR patients at increased thromboembolic risk, but without prior AF (paroxysmal, persistent or permanent) or other indication for oral anticoagulation therapy at the time of surgery.

Materials and Methods

Type and design

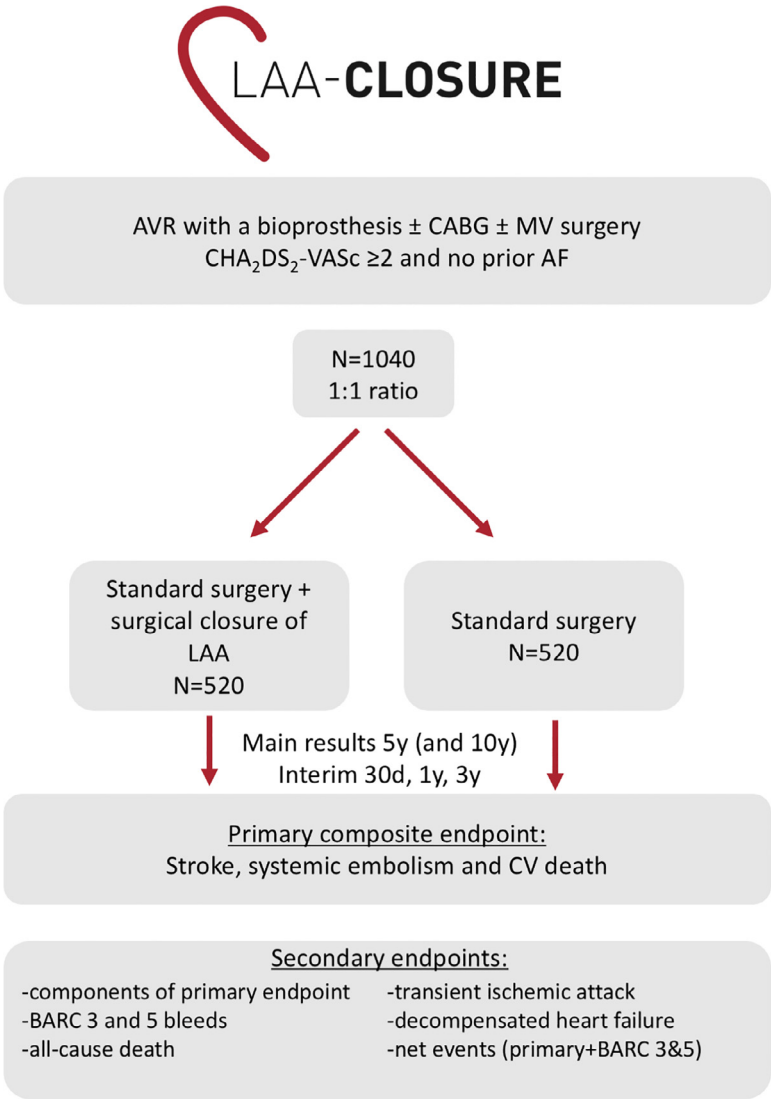
This randomized, prospective, open-label, multicenter trial aims to enroll 1,040 patients undergoing aortic valve replacement with a bioprosthesis. At the time of enrollment, included subjects must have CHA_2DS_2-VASC score ≥2, no history of AF nor indication for permanent anticoagulation. Patients are randomized in 1:1 ratio to standard therapy + surgical closure of LAA vs standard therapy alone.

This is an investigator-initiated academic trial, which received an unrestricted research grant from AtriCure ltd (Mason, OH, USA) covering part of the budget. Other funding sources include Finnish Medical Foundation, Finnish Foundation for Cardiovascular Health, and Turku University Hospital Research Foundation. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. All the publication rights including decision to submit the manuscript for publication remain among investigators. Turku University Hospital (Turku, Finland) is the coordinating site of the trial.

Interventions

'Standard aortic valve replacement ± concomitant surgery' refers to aortic valve replacement with a bioprosthesis according to indications in the current

Figure 1



Flow chart of the LAA-CLOSURE trial. Standard surgery refers to aortic valve replacement according to clinical indications defined in ESC/EACTS guidelines for the management of valvular heart disease. BARC, Bleeding Academic Research Consortium criteria; CABG, coronary bypass; CV, cardiovascular; MV, mitral valve.

ESC/EACTS guidelines for the management of valvular heart disease[12] (*Control group*). The operation as well as the pre- and postoperative care will be performed according to local surgical policies. 'Standard aortic valve replacement ± concomitant surgery with LAA occlusion' (*Active treatment group*) refers the same operation and care as above and surgical closure of LAA using an AtriClip device. All the sites are used to perform Atriclip placement and we do not have a formal roll-in period.

Inclusion and exclusion criteria

Inclusion criteria are: (1) Patients undergoing surgical aortic valve replacement (+/- coronary bypass AND/OR mitral valve surgery) according to clinical indications (ESC/EACTS guidelines for the management of valvular heart disease); (2) Age ≥18 years; (3) No indication for long term anticoagulation at the time of enrollment; (4) CHA_2DS_2-VASC score ≥2; (5) Patient is willing to comply with specified follow-up evaluations; (6) Patient or legally authorized representative has been informed of

the nature of the study, agrees to its provisions and has provided written informed consent, approved by the appropriate Medical Ethics committee or Institutional Review Board. We include bicuspid aortic valve patients but not those undergoing any aortic root procedure

Exclusion criteria include: (1) Age < 18 years; (2) Expected survival < 1 year; (3) History of AF; (4) Indication for long term anticoagulation therapy before the index procedure; (5) Mechanical valve implantation previously or at the index procedure; (6) Any significant medical condition, which in the Investigator's opinion may interfere with the patient's optimal participation in the study.

Randomization and blinding

Upon receipt of the signed written informed consent and satisfactory documentation showing that the patient meets all inclusion and does not meet exclusion criteria, the investigator will open a sealed envelope in numerical order. These envelopes are produced by independent statistician by using https://www.sealedenvelope.com randomization algorithm. There is a stratified block randomization (block size of 10) according to participating center, that is, allocation will be assigned according to a pre-defined randomization list. In each block 5 and 5 patients are randomized to surgical closure of LAA and no closure groups, respectively, in each center. Patients are randomized prior surgical procedure. Patients are considered randomized as soon as the envelope is opened and treatment allocation given.

Endpoints

Primary endpoint is a composite endpoint of stroke, systemic embolism and cardiovascular death at 5 years. Secondary endpoints include each of the following: cardiovascular death, stroke and transient ischemic attack (TIA), hospitalization for acute decompensated heart failure, major bleeding according to Bleeding Academic Research Consortium criteria (BARC 3a, b, c, or 5), any bleeding (BARC 1, 2 3a, b, c, or 5) and surgery-related bleeding (BARC 4).[17] Net adverse events include both the primary composite endpoint and major BARC bleeds. An adjudication committee will adjudicate all the events.

Definitions of endpoints

Cardiovascular death

The primary cause as defined here is the underlying disease or injury that initiated the train of events resulting in death. It includes deaths that result from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

The diagnoses of stroke, TIA and systemic embolism will be confirmed from the patient records, as diagnosed by the treating neurologist. Only a stroke and TIA considered as definite by the treating neurologist will be included for adjudication.

The modified Rankin Scale is used to address stroke disability.

TIA

TIA is defined as a transient (<24 hours) episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.

Systemic embolism

Systemic embolism is defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy.

Major bleeding (BARC criteria 3 and 5)[17]

BARC 3a refers to (1) overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed); (2) any transfusion with overt bleeding. BARC 3b refers to (1) overt bleeding plus hemoglobin drop >5 g/dL* (provided hemoglobin drop is related to bleed); (2) cardiac tamponade; (3) bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid);(4) Bleeding requiring intravenous vasoactive agents. BARC 3c refers to (1) intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); (2) Subcategories confirmed by autopsy or imaging or lumbar puncture; (3) intraocular bleed compromising vision. BARC 5 refers to fatal bleeding.

Hospitalization for heart failure

For the endpoint of hospitalization for acute decompensated heart failure, a patient is required to have an unscheduled hospital admission for a primary diagnosis

of heart failure with a length of stay that either exceeds 24 hours or crosses a calendar day (if hospital admission and discharge times are unavailable). The patient is also required to have typical signs, symptoms, and diagnostic testing results consistent with the diagnosis of heart failure. Laboratory findings consistent with heart failure including elevated natriuretic peptides, radiological evidence of congestion, and either echocardiographic or invasive evidence of elevated filling pressures. In addition to these signs and symptoms, the patient should also receive treatment specifically directed at heart failure, including at least one of the following: (1) significant augmentation in oral diuretic therapy; (2) initiation of intravenous diuretic (even a single dose) or vasoactive agent (eg, vasodilator, vasopressor, or inotropic therapy); or (3) mechanical circulatory support or fluid removal. Significant augmentation of oral diuretic therapy is defined, for example, as the doubling of loop diuretic dose; initiation of maintenance loop diuretic therapy; or initiation of combination diuretic therapy to relieve congestion. Combination diuretic therapy could include: (1) a thiazide-type diuretic (eg, hydrochlorothiazide, metolazone, or chlorothiazide) plus a loop diuretic; or (2) a mineralocorticoid receptor antagonist (eg, spironolactone or eplerenone) plus a loop diuretic. Mechanical fluid removal includes ultrafiltration, hemofiltration, and dialysis as well as thoracentesis or paracentesis for heart failure management.

Anticoagulation therapy

After index surgery, patients are treated according to local practice guidelines as they were treated without surgical closure of LAA. Decisions on the medical therapy remain at the treating physician's discretion. Patients allocated to surgical closure of LAA will not be routinely advised to avoid long-term anticoagulation.

Prespecified trial reporting schedules

- 30 days
- 1 year
- 5 years (main results)
- 10 years if applicable

Prespecified substudies

We have two pre-specified substudies on completeness of LAA closure using transesophageal echocardiography or cardiac computed tomography; and AF occurrence in 7-day ECG-holter 1 year after index surgery. The Core labs for both imaging substudy and 7-day ECG-holter study are at Turku University Hospital/University of Turku. These substudies enroll at selected sites. Alternatives for imaging include transesophageal echocardiography or cardiac CT depending on site's preference.

Study sites

1. Turku University Hospital and University of Turku, Finland
2. St. Antonius ziekenhuis, Nieuwegein, Netherlands
3. Hospital Clinico Universitario de Valladolid, Valladolid, Spain
4. Karolinska University Hospital and The Karolinska Institutet, Stockholm, Sweden
5. Sahlgrenska University Hospital, Gothenburg, Sweden
6. Medisch Spectrum Twente, Enschede, Netherlands
7. Kuopio University Hospital, Kuopio, Finland
8. Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Warsaw, Poland
9. Skåne University Hospital and Lund University, Lund, Sweden
10. Hospital Universitario La Princesa, Madrid, Spain
11. Asklepios Klinik Harburg, Hamburg, Germany
12. Medizinische Hochschule, Hannover, Germany
13. University Medical Center Rotterdam, Rotterdam, Netherlands

Enrollment schedule

The LAA-CLOSURE trial multicenter enrollment began in November 2018. Anticipated end of enrollment is late 2021. Follow-ups for the main results (5 years) will be completed by February 2026. Study reporting will be started 2022.

Statistical analysis

One recent small underpowered randomized trial suggested a hazard ratio (HR) 0.3 (95% CI: 0.1–0.8, $P = .02$) for treatment effect of LAA closure, while a nonrandomized large registry showed HR 0.67 (95% CI, 0.56-0.81; $P < .001$) in 2.6 year follow-up.[12] Moreover, when focusing on patients with CHA_2DS_2-VASC score ≥ 2, the stroke rate lies between 1.35 and 4.93/100 patient years irrespective of preoperative or in-hospital AF.[16] We anticipate a clinically significant 30% risk reduction in the primary endpoint with the occlusion of the LAA. Sample size calculation assumed 109 (21%) primary endpoint event rate in the control group at 5 years (alpha was set to 0.05 and beta 0.90). This was based on the data from STS database as well as pilot data from Turku University Hospital.[1,2] In the general population, the share of cardioembolic strokes is 25% to 30%. However, in patients who have undergone SAVR, the rate of cardioembolic stroke is 48% at a median follow-up of 5 years.[2] Therefore, 520 patients (10% dropout rate) are needed per group, and altogether 1,040 patients will be randomized.

We will perform all analyses in the total population using the intention-to-treat method. We will calculate HRs, 95% confidence intervals, and P values for time-to-event analyses using a Cox proportional-hazards model with

the stratification factor as a covariate. All analyses will be performed using appropriate statistical software such as R statistics software (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software package (SPSS, Inc., Chicago, Illinois, USA).

Discussion

LAA-CLOSURE trial is one of the largest randomized trials on surgical closure of the LAA. The prophylactic approach of the trial focuses on the high AF-risk and stroke-risk patients who will likely encounter AF later in life. Trial is powered to show 30% risk reduction in the primary endpoint of stroke, systemic embolism and cardiovascular death at 5-year follow-up after SAVR. Secondary clinical outcomes will assess the potential additional benefits and harms of the procedure such as the risk for decompensated heart failure, bleeds and AF. Prespecified substudies will assess the achieved completeness of closure and occurrence of AF later in life.

Stroke is a frequent and often deleterious long-term adverse event after SAVR. Observational data suggest 7% to 15% rates of stroke at 5-year follow-up.[1,2] The rate, however, is highly comorbidity-related and it increases with higher CHA_2DS_2-VASc scores[16]. Therefore, we targeted this trial in high stroke-risk patients as defined by CHA_2DS_2-VASc score $\geq$2. Roughly half of strokes after SAVR are considered cardioembolic and often AF-related.[2] New-onset AF (NOAF) is common after SAVR with an incidence of 31% to 74%.[18-24] NOAF is often considered only a temporary, surgery-associated phenomenon, but recent evidence suggests that at least half of the patients with NOAF encounter AF also later in life.[15] AF is often silent in these elderly patients leading to delayed diagnosis and initiation of oral anticoagulation.[3] Based on this background prophylactic closure of LAA could provide stroke protection in this clinical scenario, since LAA is the principal origin of thromboembolism in AF.

Occlusion of LAA may provide stroke protection already shortly after surgery. In intermediate to high surgical-risk patients, 30-day stroke rate in a randomized trial was as high as 6.1%.[25] Early after SAVR, patients are in a prothrombotic state related to the operation, immobilization, and swelling caused by fluid retention.[26,27] Moreover, the initiation of vitamin K antagonist therapy may suppress levels of protein C and S,[28] and increase the risk of thromboembolic complications. Therefore, more efficacious means of preventing thromboembolic complications are needed in this clinical setting.

It is still debatable whether oral anticoagulation can be avoided in patients with LAA occlusion and novel data are needed in this area. ESC/EACTS guidelines for the management of AF do not recommend discontinuation of oral anticoagulation in patients with LAA occlusion.[29] This recommendation derives from data that showed the inability to achieve acceptably high rates of successful occlusion on post-operative transesophageal echocardiography.[13] Nevertheless, cardiac computed tomography data on the study device AtriClip shows favorable closure result.[30,31] LAA-CLOSURE trial has a substudy addressing the completeness of closure result. Selected sites enroll patients for transesophageal echocardiography or cardiac computed tomography to assess the closure result at 3 months after index surgery.

LAA-CLOSURE trial includes patients with or without concomitant CABG and/or mitral valve surgery to mimic real-life SAVR patient population. Concomitant mitral valve surgery may increase the risk of postoperative AF. However, patients with concomitant ascending aortic surgery are excluded because of the risk of emboli originating from the aorta.

Observational study suggested an increased risk for AF after LAA occlusion.[32] Thus, it is important that LAA-CLOSURE trial will address this observation using clinical follow-up of AF occurrence at 3, 12, 24, 36, 48, and 60 months after surgery. In addition, a 7-day ECG-holter substudy is performed in selected sites. These data will provide information not only on temporal risk but also incidence and persistence of AF after SAVR and LAA occlusion – significant for planning of future trials on the topic.

Finally, percutaneous LAA occlusion using specific devices in three randomized controlled trials have demonstrated that patients undergoing the procedure have similar risk of stroke when compared with those on oral anticoagulation (warfarin or non-vitamin K antagonist oral anticoagulant) in the prevention of stroke in nonvalvular AF, with reductions in hemorrhagic stroke and both cardiovascular and all-cause death in over 3-year follow-up.[33] The concept of successful LAA occlusion for stroke prevention, therefore, seems to be of similar efficacy to oral anticoagulation – the best current prevention for AF-related thromboembolic complications, but the efficacy and safety of surgical LAA occlusion need to be explored.

In conclusion, the LAA-CLOSURE trial aims to provide data on a clinically meaningful way to reduce strokes and cardiovascular deaths in patients at high stroke-risk scheduled for SAVR.

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