COMPARE LAAO: Rationale and design of the randomized controlled trial "COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy"

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Background Left atrial appendage occlusion (LAAO) provides an alternative to oral anticoagulation (OAC) for stroke prevention in patients with atrial fibrillation (AF). In patients with a long-term or permanent contraindication for OAC randomized controlled trial (RCT) data is lacking.

Study objectives To assess the efficacy and safety of LAAO in AF patients who are ineligible to use OAC. The co-primary efficacy endpoint is (1) time to first occurrence of stroke (ischemic, hemorrhagic, or undetermined) and (2) time to first occurrence of the composite of stroke, transient ischemic attack (TIA), and systemic embolism (SE). The primary safety endpoint is the 30-day rate of peri-procedural complications.

Study design This is a multicenter, investigator-initiated, open-label, blinded endpoint (PROBE), superiority-driven RCT. Patients with AF, a CHA_2DS_2-VASc score $\geq$2 for men and $\geq$3 for women and a long-term or permanent contraindication for OAC will be randomized in a 2:1 fashion to the device- or control arm. Patients in the device arm will undergo percutaneous LAAO and will receive post-procedural dual antiplatelet therapy (DAPT) per protocol, while those in the control arm will continue their current treatment consisting of no antithrombotic therapy or (D)APT as deemed appropriate by the primary responsible physician. In this endpoint-driven trial design, assuming a 50% lower stroke risk of LAAO compared to conservative treatment, 609 patients will be followed for a minimum of 1 and a maximum of 5 years. Cost-effectiveness and budget impact analyses will be performed to allow decision-making on reimbursement of LAAO for the target population in the Netherlands.

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Summary The COMPARE LAAO trial will investigate the clinical superiority in preventing thromboembolic events and cost-effectiveness of LAAO in AF patients with a high thromboembolic risk and a contraindication for OAC use.

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Background/Introduction

The prevalence of atrial fibrillation (AF) has increased rapidly over the past decades. AF is now prevalent in over 2% of the Dutch population (350.000 patients).[1] Worldwide, 1 in 3 individuals will develop AF at some point in their lifetime.[2] Stroke prevention is one of the cornerstones in the treatment of AF and can be achieved either medically (with oral anticoagulation (OAC) therapy) or mechanical (by occluding the left atrial appendage (LAAO)). The traditional vitamin-K antagonists (VKA) reduce the stroke risk by up to 64%,[3] but have largely been replaced by the more effective and safer direct oral anticoagulants (DOACs).[4–7] Compared to the overwhelming data in the RCTs comparing DOAC to VKA, the evidence for LAAO is still very limited and therefore not (yet) a widely accepted alternative therapy for all AF-patients.[8] The PREDICT-AF and PREVAIL studies showed that LAAO may be equipotent to VKA as a stroke prevention strategy, considering both efficacy- and safety endpoints.[9] In the more recent PRAGUE-17 trial, which included 402 patients at high risk of both stroke and bleeding, LAAO was non–inferior to DOAC in the combined efficacy and safety endpoint of major AF-related cardiovascular, neurologic, and bleeding events.[10] Large RCTs comparing LAAO to DOACs in patients eligible for OAC are ongoing (Occlusion-AF - NCT03642509, CATALYST - NCT04226547, and CHAMPION-AF - NCT04394546). Existing guidelines recommend to consider LAAO only in patients with a high stroke risk contraindicated to use long-term OAC (class IIB recommendation).[2,11] Presently, there is no clear-cut definition of an "absolute" contraindication to OAC, although in up to 5% of patients OAC is discontinued by their physician for this reason.[12,13] Additionally, many patients may have "relative" contraindications and discontinue OAC on their own initiative after (minor) bleeding events or because of fear of bleeding.[14,15] As a result, the proportion of patients currently undertreated for AF-related thromboembolism may be as high as 30%.[1,16,17] Multiple real-world registries confirm the safety and efficacy of LAAO in patients with a contraindication for OAC, with low rates of ischemic and hemorrhagic stroke and low long-term bleeding rates.[18–20] However, RCT-data for LAAO in this frail population is lacking because of a perceived excess bleeding risk in the control group when using OAC, or a perceived excess stroke risk when not using OAC. Based on the current evidence, reimbursement for LAAO under specific circumstances is now granted in many countries worldwide. Therefore, the incentive for physicians and patients to enroll in such RCTs and thereby taking a risk to randomize patients in a control group instead of just schedule the patient for LAAO, is low. These enrolment challenges resulted in the early termination of the ASAP-TOO trial,[21] which studied LAAO in patients deemed not suitable for long-term OAC use. As a result, randomized controlled data are still lacking for this population. Therefore, we designed the COMPARE LAAO trial as part of the Promising Care program of the Dutch government to provide evidence that LAAO in atrial AF patients with a high thromboembolic risk ineligible to use OAC is superior to no treatment or antiplatelet therapy (APT). The study further includes cost-effectiveness and budget impact analyses, all of which will serve to determine whether LAAO should become reimbursed standard of care in the Netherlands.

Methods

Objectives

The primary objective of the COMPARE LAAO trial is to test whether the long-term outcome of LAAO is superior to standard of care regarding prevention of thromboembolic events in patients with AF and contra-indicated to use OAC due to a perceived high bleeding risk. This study has 2 primary efficacy endpoints: (1) the time to first occurrence of stroke (ischemic, hemorrhagic, or undetermined) and (2) the time to first occurrence of the composite of stroke (ischemic, hemorrhagic, or undetermined), transient ischemic attack (TIA) and systemic embolism (SE). The primary safety endpoint will be the 30-day rate of procedural complications, including pericardial effusion requiring pericardiocentesis, any major bleeding including access site bleedings, device embolization, procedural stroke or death, or other severe complications that are considered related to the procedure. To achieve a consistent approach across clinical studies on LAAO, endpoints were defined in accordance with the Munich consensus document.[8,22]

Secondary endpoints include the incidence of device-related thrombus (DRT) at periodically scheduled imaging moments (3 months and once yearly post-procedure). The occurrence of ischemic- and hemorrhagic stroke, mortality (cardiovascular and all-cause), TIA, and SE will be assessed. Previous trials found indications that strokes after LAAO were less disabling,[9,23] therefore the severity of stroke (according to the modified Rankin Scale [mRS][24]) will form a secondary end-

point. Procedural efficacy and left atrial appendage (LAA) sealing efficacy according to manufacturer's definitions at all predefined imaging moments will be compared to expected efficacy rates from large and recent studies and registries.[18,19,25] Minor and major bleeding rates will be obtained during the entire follow-up according to BARC criteria.[26] In addition, net clinical benefit (combining stroke, SE, cardiovascular death, and major bleeding) and weighted net clinical benefit analyses will be performed. Quality of life (QoL), use of (health care) resources, and costs will be compared between the intervention- and control arms. All secondary endpoints and endpoint definitions are listed in appendix A.

Study design

The COMPARE LAAO is a multicenter, investigator-initiated, open-label, blinded endpoint (PROBE), superiority-driven trial. The trial will be conducted in 15 selected centers in the Netherlands and coordinated by the St. Antonius Hospital in Nieuwegein. On-site cardiac surgery is a mandatory pre-requisite for LAAO in the Netherlands, and the selected sites all offer cardiac surgery, interventional cardiology, and electrophysiology and therefore guarantee an optimal combination of support. Centers without implanting experience will be properly trained before participating in the trial. The study aims to include 609 patients in an expected timeframe of 4.5 years. Block-wise randomization with randomly selected block sizes, stratified by study site, is conducted in a 2:1 fashion in favor of the interventional arm. The web-based, automated randomization system of the database-application REDCap is used (Project-redcap.org). REDCap is a secure webplatform for building and managing online databases and surveys.

Study population

A complete overview of in- and exclusion criteria is provided in Table I. Prior to randomization, a patient's contraindication for OAC should be discussed in a multidisciplinary team. Following the EHRA consensus statement on LAA occlusion,[8] medical conditions which might represent contra-indications to long-term OAC may include, but are not limited to:

1. Risk for major bleeding, especially life-threatening or disabling bleeding due to an "untreatable" source of
   a. Intracranial/intraspinal bleeding (eg, diffuse amyloid angiopathy, untreatable vascular malformation)
   b. Severe gastrointestinal- (eg, diffuse angiodysplasia), pulmonary- or urogenital source of bleeding that cannot be corrected
2. Increased bleeding risk; eg, patients with end-stage renal disease (ESRD) with hemodialysis, hematologic disease
3. Severe side effects under OAC

Baseline assessment

Prior to randomization, all patients undergo a baseline assessment including registration of known relevant medical history, a brief physical examination (heart rate, blood pressure) and a transthoracic echocardiogram (TTE). Relevant medical history includes, but is not limited to: Reason of contra-indication to OAC, (severity of) prior bleedings, use of (prior) antithrombotic medication, AF-characteristics, history of coronary vascular disease , history of thromboembolisms (TIA, ischemic stroke, SE), carotid stenosis and/or CEA, CHA_2DS_2-VASc- and HASBLED scores.

Procedure and follow-up

Prior to the procedure, patients will undergo computed tomography (CT)- or trans esophageal echocardiography (TEE)-imaging in order to rule out a LA(A) thrombus.[27] Implantations may be performed with any CE-approved closure device with sufficient evidence on safety and efficacy, currently including the Watchman FLX- and Amplatzer Amulet devices. New devices may be used if adequate performance in at least 1,000 patients with a minimal follow-up of 1 year and published results in a peer-reviewed journal has been shown. The complication rate and number of thromboembolic events for new devices should be similar to currently available CE-marked devices in recent large registries or trials.[18–20,25] Procedures are performed under TEE-guidance using standard-of-care methods.[8,22] All study implanters are trained in percutaneous and transseptal procedures and have completed the manufacturer's physician training program.

Both interventional- and control arm patients will have a minimal follow-up of 1 year, with follow-up moments at 3, 6, and 12 months, and after the first year biannually until the end of the study (max. 66 months). The study ends when all 609 patients have completed the minimal follow-up of 1 year, or as soon as the required number of endpoints has occurred.

After the implant procedure, patients will be prescribed dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) 80 to 100 mg and clopidogrel 75 mg once daily. Check-up visits with CT or TEE imaging take place after 3 months and 1 year. If device endothelialization is adequate and no signs of DRT or large (≥5 mm) peri-device leaks (PDL) are present, clopidogrel will be discontinued at 3 months and ASA may be discontinued after 1 year. Beyond 1 year, ASA may be continued indefinitely at the discretion of the treating physician. After the minimum follow-up of 1 year, patients will undergo CT or TEE imaging once yearly until the study ends. CT imaging will be the recommended standard of care but may be replaced by TEE if required in specific cases.

Table I. Inclusion and exclusion criteria.

Inclusion criteria	
1.	Documented nonvalvular AF (paroxysmal or non–paroxysmal)
2.	CHA_2DS_2-VASc score of 2 or more in men, or 3 or more in women
3.	Considered ineligible for long-term use of OAC as determined by the referring physician team as well as the multidisciplinary team in the study hospital
4.	Suitable for the use of APT: preferably dual APT for at least 3 mo and single APT from 3 until at most 12 mo, but minimally SAPT for 3 months.
5.	At least 18 y of age, and willing and able to provide informed consent and adhere to study rules and regulations and follow-up
Clinical exclusion criteria	
1.	Any planned invasive cardiac procedure within 30 d prior to randomization and 90 d after LAAO interfering with the study follow-up and medication
2.	Contraindications or unfavorable conditions to perform cardiac catheterization or TEE
3.	Stroke within 3 mo prior to inclusion (if not yet clinically stable, and/or without adequate diagnostic or prognostic evaluation, and/or in need of other interventions)
4.	Planned carotid endarterectomy (CEA) for significant carotid artery disease
5.	Major bleeding (BARC criteria > type II) within 1 mo prior to inclusion or longer if it has not been resolved yet
6.	Compelling medical reason to use VKA or NOAC (eg, mechanical heart valve, pulmonary embolism, ventricular aneurysm)
7.	Major contraindications for using APT
8.	(planned) Pregnancy
9.	Life expectancy of less than 1 y
10.	Heart failure NYHA 3 or 4
Echocardiographic exclusion criteria	
1.	Atrial septal malformations, atrial septal defect or a high-risk patient foramen ovale that may cause thromboembolic events
2.	Atrial septal defect repair or closure device or a patent foramen ovale repair or any other anatomical condition as this may preclude an LAAO procedure
3.	Left ventricular ejection fraction <31%
4.	Mitral valve regurgitation grade 3 or more
5.	Mitral valve stenosis (as this defines valvulair AF)
6.	Aortic valve regurgitation grade 3 or more
7.	Aortic valve stenosis (AVA < 1.0 cm^2 or Pmax > 50 mm Hg) (as such patients may require cardiac surgery and/or have a high competing risk of mortality and stroke)

Patients randomized to the control arm continue their current optimal medical therapy, which may include APT or no therapy at all. Patients in both the interventional- and control arm will be approached in-person or by telephone call every 6 months by members of the local study team to check for endpoints and events. In addition, hospital charts and, if applicable, data from other medical practices such as general practitioners will be gathered and checked by these study teams. Figure 1 shows a flowchart depicting the study procedures.

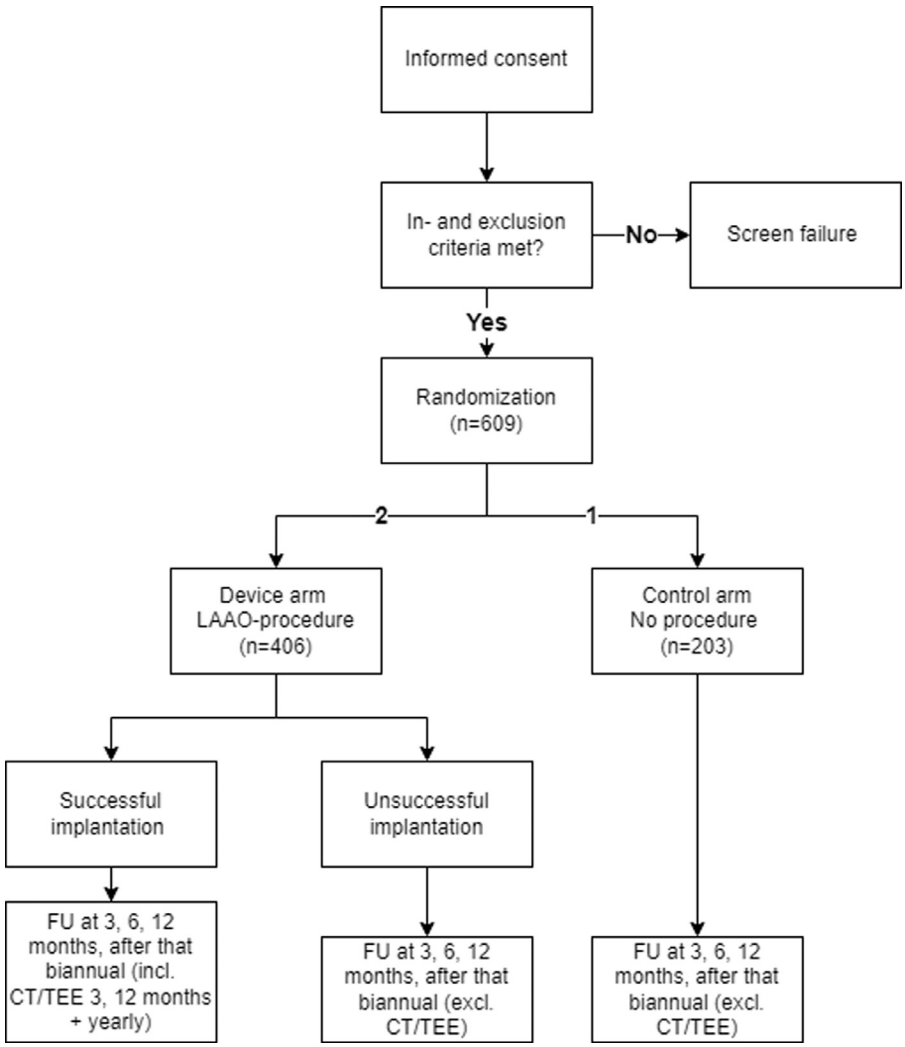
The mean follow-up duration will be approximately 3 years. Questionnaires regarding QoL (using SF-12 and HADS), cost-effectiveness (using iMCQ, iPCQ, and EQ5D5L), and neurologic assessment (QVSFS) will be sent at baseline, 3-, 6- and 12 months, and after the first year biannually by post or email.

In this study, cross-over of patients from the usual care arm to the interventional arm is strongly discouraged. Solely in exceptional cases after the occurrence of the primary endpoint of stroke, it might be decided to perform LAAO if deemed necessary by the responsible physician to protect the patient against thromboembolism originating from the LAA.

Statistical methods

For the 2 primary endpoints hazard ratios and 95% confidence intervals will be calculated with Cox proportional hazards regression analysis. Kaplan-Meier curves will be used to depict the incidence over time. Testing for superiority of LAAO (versus usual care without OAC) with regard to the co-primary efficacy outcome will be performed with (2-sided) logrank tests to test the null hypothesis of identical time-to-event curves across the device and control groups, calculated for each co-primary end point separately. We will use the Hochberg method to preserve the alpha level for significance testing with co-primary outcome. If both *P* values fall below .05, superiority for both outcomes will be claimed. If the largest of the 2 *P* values exceeds .05, superiority for the other end point can only be claimed if its *P* value falls below 025. In all other instances, superiority of LAAO cannot be claimed.

Figure 1



COMPARE LAAO study flowchart.

Sample size calculation

The sample size determination is driven by requirements for testing superiority of LAAO for the co-primary outcome of stroke. With an expected CHA_2DS_2-VASc score of 4 to 5 in the study population, the estimated stroke risk is 6% per year in patients that use ASA.[28] For the sample size calculation, we made the conservative assumption that all patients use ASA and expect that the stroke rate for the median follow-up of 3 years will be at least 18% under usual care. The target relative risk, based on the RCTs PROTECT-AF and PREVAIL[9] showing non–inferiority of WATCHMAN versus OAC, is 0.50 and leads to a reduction of the 3-year stroke rate from 18% under usual care to 9% under LAAO treatment. The conservative approach takes account of the presence of competing non–stroke-related mortality in this population. Under the assumption of an exponential distribution, the hazard ratio equals 0.4752. With 85% power and 2-sided $\alpha < .05$, a sample size of 609 patients is required. Under these assumptions, we expect a total of 72 primary outcomes. The trial is event-driven and is planned to run until 72 primary outcomes have been reached, or futility to proceed occurs.

As the event rate for the other co-primary endpoint of the composite of thromboembolic events is higher than that of stroke alone[28], the power of the trial for this endpoint is expected to be sufficient.

Organizational structure

Steering committee

The steering committee of the COMPARE LAAO trial consists of the chair of the committee (principal investigator of the coordinating center) and 1 principal investigator of each participating hospital. In addition, a neurologist, statistician, and an expert in Health Technology Assessment participate in the steering committee. The committee provides scientific direction and input, addresses policy issues regarding the protocol, and meets periodically to assess the trial progress.

Clinical event committee

A Clinical Event Committee (CEC) with expertise in the field of neurology, interventional cardiology and electrophysiology will review and adjudicate the following primary and secondary end points: All strokes, TIA, SE, death (all-cause), bleeding events and device- and/or procedure-related events which resulted in open cardiac and/or (endo)vascular surgery.

Data safety monitoring board

An independent Data Safety Monitoring Board (DSMB) has been set up to monitor the progress of the study and ensures that the safety of subjects is not compromised. The DSMB will serve in an advisory role to the Steering Committee to ensure safety by reviewing cumulative data from the clinical trial twice yearly for the purpose of safeguarding the interests of trial participants. The DSMB consists of 3 members; 1 biostatistician and 2 cardiologists. The DSMB may recommend revising the study protocol or termination of the trial early based on any perceived safety concerns or in case of futility to proceed. However, the recommendations of the DSMB are not binding.

Funding and trial registration

The COMPARE LAAO trial is registered on ClinicalTrials.gov (NCT trial number: NCT04676880, https://clinicaltrials.gov/ct2/show/NCT04676880) and is approved by the local ethics committees (Medical research Ethics Committees United (MEC-U)). The trial is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. Data will be monitored by an independent monitor. This trial is an investigator-initiated study, funded by a grant of ZonMw/ZINL, a public benefit organization from the Netherlands that was not involved in study design or study processes. The steering committee is solely responsible for the design, data collection, and conduct of this study, all study analyses, the drafting and editing of this paper, and its final contents.

Timeline and present status

The COMPARE LAAO study started enrolment in January 2021 in the coordinating center (St. Antonius Hospital Nieuwegein). Seven of the participating centers started shortly after, whereas the other centers (7) will start as soon as the training programs are finished. At present, 23 patients have been included. The expected time of enrolment is 4.5 years, which means the final inclusion is expected in the second half of 2025. Adding the last year of follow-up, results are expected at the end of 2026.

Discussion

The evidence for LAAO in patient's ineligible for OAC is limited to registries and case series, and therefore there is no solid guideline recommendation (class 2B, level of evidence B).[2,11] Left atrial appendage occlusion (LAAO) is an alternative to OAC therapy for stroke prevention in patients with AF and a high stroke risk. Currently, in both European and American guidelines, its indication is limited to those patients with a long-term contraindication for OAC.[2,11] Surprisingly, this indication is based upon 2 RCTs in an OAC-eligible population comparing LAAO to VKA, demonstrating non–inferiority of LAAO to VKA.[9]

Multiple registry studies have been carried out in recent years. The EWOLUTION (n = 1,020) and the Amplatzer Amulet (n = 1,088) registries both mainly included patients with contraindications for OAC and/or previous significant bleedings (resp. 62% and 83%).[18,20] Both observational studies recorded favorable procedural safety and efficacy outcomes, thereby feeding the hypothesis that LAAO may be superior to no therapy in OAC-ineligible patients. After the FDA approved the Watchman device for OAC ineligible patients, large numbers of LAAO procedures are performed in the US. The NCDR LAAO registry (n = 38,158) recently published the results on procedural safety, whereas efficacy results are awaited.[19] Furthermore, several RCTs investigating LAAO in various populations are currently pending. The CHAMPION AF- (NCT04394546) and CATALYST (NCT04226547) trials randomize patients to LAAO or DOAC and the OPTION trial (NCT03795298) investigates the benefits of catheter ablation combined with LAAO to a standalone catheter ablation with continuation of DOAC afterward. Depending on the results these trials will generate, they might impact the AF-guidelines for these populations, with possible extrapolations to contraindicated patients. However, as it will take several years to finish these trials, there remains an urgent need for randomized controlled data to conclusively answer the question whether LAAO is superior to APT or no therapy for OAC-ineligible patients.

An attempt to address this evidence gap by the investigators of the international ASAP-TOO trial discontinued due to futility in enrolment, most likely due to

physician and patient reluctance to have patients randomized.[21] Nowadays, despite the lack of evidence and in the absence of alternative treatment options, LAAO is generally accepted as a therapy for patients ineligible to use OAC in many countries.[29–31] The Dutch government has not yet granted reimbursement to LAAO therapy for OAC-ineligible AF-patients pending more RCT evidence. Given this lack of reimbursement, enrolment issues are less likely to occur in this trial. Therefore, we expect that the nationwide RCT COMPARE LAAO will provide a valuable and essential source of information to fill the evidence gap.

In the proposed design, we have chosen a co-primary efficacy endpoint; the first including solely stroke (ischemic, hemorrhagic, or undetermined) and the second including both stroke, SE and TIA. As the definition and diagnostic evaluation of TIA is not universal among (stroke) neurologists, it is susceptive to be overdiagnosed.[32–34] In order to achieve as little variability as possible, all TIAs are adjudicated by an experienced stroke neurologist according to the modified EDCT criteria.[32] If misclassification bias nevertheless occurs, it will likely occur in both study arms and therefore lead to a dilution of the effect size, which could result in the need for a larger sample size or an underpowered study. Therefore, we chose to base our sample size calculation for superiority of LAAO versus usual care solely on the end point of stroke. However, as the intention of LAAO is to reduce the risk on all thromboembolic complications of AF, this forms our second co-primary endpoint.

A net clinical benefit endpoint for the primary analysis, as some recent LAAO studies use,[10] would not suit this study design, as the control arm does not receive any treatment at all. However, as LAAO is a preventive intervention, the net clinical benefit between safety and efficacy within the interventional arm is of utmost importance and will therefore be evaluated in the secondary analysis. Concerns about LAAO in OAC-ineligible patients include the procedural risk in this frail population.[8] Procedural complications are relatively scarce, however, together with post-procedural APT they may entail elevated bleeding rates in the first year after LAAO.[9,20] It is therefore important that the benefit of the procedure outweighs the risk of complications. However, net-clinical benefit endpoints must be interpreted with caution as there is no uniformity in the impact weight of different outcome measures.

Limitations

In the current study, all patients deemed unsuitable for OAC may be included and combined into 1 "OAC-ineligible" group. This group may be heterogeneous due to different underlying mechanisms of increased thromboembolic risk and other patient characteristics. This might lead to different efficacy and safety rates in these hypothetical subgroups. Ideally, the research question whether LAAO prevents thromboembolic complications significantly better than no treatment, should be answered for each individual reason for contraindication, but this approach is not feasible due to the large number of patients that would have to be included.

Furthermore, the standard treatment for patients after LAAO consists of DAPT (ASA + clopidogrel) for 3 months and ASA monotherapy until at least 1 year. The therapy of patients in the "standard-of-care" arm often consists of no therapy or (D)APT at the physician's discretion, due to lack of strong guideline recommendations. The difference in treatment regimens between the 2 study arms could lead to a (small) additional therapeutic effect in the prevention of thromboembolic events of post-procedural regimen in the interventional arm, but may also lead to more post procedural bleeding complications. The post-procedural anti–thrombotic regimen for patients with a contraindication for OAC will usually be as minimal as possible. However, the optimal regimen is not yet established and therefore we hold on to the current standard of care treatment.

Lastly, the 2 main causes of stroke are AF and cerebrovascular disease, which may both be present in individual patients. Ideally, a complete neurologic evaluation could exclude patients with carotid artery disease. Logistical and financial restrictions preclude such an approach in this trial, although any overt signs of cerebrovascular disease will be noted at baseline and during follow up.

Summary

The COMPARE LAAO trial is designed to evaluate the safety, efficacy and cost-effectiveness of left atrial appendage occlusion in patients at high risk of atrial fibrillation-related thromboembolism, contra-indicated for long-term treatment with oral anticoagulation.

Appendix a – Study parameters/end points

Definitions of study parameters and endpoints are based on EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion.

Main study parameter/end point

The co-*primary efficacy* endpoints *are:*

- Time to first occurrence of ischemic or hemorrhagic or undetermined stroke.
- Time to first occurrence of the composite of stroke (ischemic or hemorrhagic or undetermined), TIA and systemic embolism.

The primary safety endpoint of the LAAO procedure will be 30-day rate of procedural complications.

Procedural complications will include major procedure-related endpoints within 30-days that require

prolonged hospitalization and/or specific treatment, or that lead to permanent physical or mental disability, including but not limited to: pericardiocentesis, major access site bleeding (BARC), any other major bleeding (BARC), device dislocation from the LAA to the heart or aorta, stroke, death, or other severe complications that are considered due to the procedure.

Secondary study parameters/endpoints

The secondary (efficacy) endpoints are:

- The composite of stroke (ischemic or hemorrhagic), TIA, systemic embolism and cardiovascular death.
- Ischemic stroke
- Disabling stroke
- Hemorrhagic stroke
- Mortality (both cardiovascular and all-cause)
- TIA
- Systemic Embolism
- Major bleeding event rate (according to BARC criteria), both procedural up to 7 days, as well as total
- Minor bleeding event rate (BARC $\leq$ 2), both procedural up to 7 days, as well as total
- Procedural efficacy of LAAO up to 30 days
- Adverse events rate at 30 days, and from 30 days until end of follow up
- LAA sealing efficacy according to manufacturer's definitions at all the predefined LAA CT/TEE imaging moments
- Device related thrombus event rate
- Net-clinical benefit of efficacy and safety end point
- QoL assessments at baseline, 3 and 6 months and after that on a biannual basis in follow up (SF-12, HADS, EQ5D5L)
- Cost-effectiveness analysis at baseline, 3 and 6 months and after that on a biannual basis in follow up (iPCQ and iMCQ)
- Device-related efficacy (at 30 days and from 30 days until end of follow up) and safety (procedural up to 7 days, as well as total) analysis

Definitions of study parameters/endpoints

Stroke

The definition for stroke is based on the standardized definitions for cardiovascular and stroke endpoints events in clinical trials (Hicks et al 2015). All strokes occurring post-enrolment will be recorded as SAEs. All strokes occurring post-randomization will be considered endpoints. Stroke is defined as an acute episode of focal or global neurologic dysfunction caused by cerebral vascular injury as a result of infarction or hemorrhage not caused by trauma. Investigators will classify strokes into 1 of 3 mutually exclusive categories: ischemic, hemorrhagic, or undetermined. Whenever possible, stroke diagnoses should be confirmed using neuroimaging (CT or MRI) to minimize the number of strokes classified as "undetermined."

Ischemic stroke

An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered an ischemic stroke:

1 Rapid onset (or existence on awakening) of a new focal neurologic deficit with clinical (ie, lasting more than 24 hours) or imaging evidence of infarction and not attributable to a non–ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurologic disease)
2 Rapid worsening of an existing focal neurologic deficit that is judged by the Investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non–ischemic etiology. In case imaging is inconclusive, persistent symptoms is defined as duration of $\geq$24 hours or until death.

Hemorrhagic stroke

An acute episode of focal or global cerebral dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage not caused by trauma. Subdural hematomas are Intracranial hemorrhagic events but not strokes.

Undetermined category of stroke

An acute episode of focal or global neurologic dysfunction caused by presumed brain vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic. Strokes of undetermined category will be analyzed as ischemic strokes.

Transient ischemic attack

Focal neurologic symptoms or signs, with total recovery, presumed of ischemic origin, clearly related to a focal brain (or retinal) lesion, lasting less than 24 hours (if no brain imaging is available) and with no new brain lesion (if a brain imaging is available) confirmed by a neurologist. TIAs are diagnosed according to the Modified EDCT (Explicit Diagnostic Criteria for TIA).[32]

Supplementary Table 1 Original EDCT and the Modified Subcriteria C1, C2, and C3

A	Sudden onset of fully reversible neurological or retinal symptoms (typically hemiparesis, hemihypesthesia, aphasia, neglect, amaurosis fugax, hemianopsia, or hemiataxia)
B	Duration <24 h
C*	At least 2 of the following:
	All symptoms are maximal in <1 min (no gradual spread)*
	All symptoms occur simultaneously*
	All symptoms are deficits (no irritative symptoms such as photopsias, pins, and needles, etc)*
	No headache accompanies or follows the neurological symptoms within 1 h*
D	None of the following isolated symptoms (can occur together with more typical symptoms): shaking spells, diplopia, dizziness, vertigo, syncope, decreased level of consciousness, confusion, hyperventilation-associated paresthesia, unexplained falls, and amnesia
E	No evidence of acute infarction in the relevant area on neuroimaging

EDCT indicates Explicit Diagnostic Criteria for TIA; and TIA, transient ischemic attack.

*Modified criteria.

Systemic embolism

An abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (eg, atherosclerosis, instrumentation, or trauma).

Device-related thrombus (DRT)

In line with the recommendations in the EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion, DRT can be detected on both CT and TEE. Multiple comparisons between cardiac CT and TEE for detection of DRT showed that both imaging techniques were equally good (Korsholm et al, Saw et al). Therefore, in this study we will use CT imaging primarily.

There is no uniform definition of DRT in current literature. For this study, we use the following definitions:

- In cardiac CT imaging: DRT is defined as any hypoattenuated thickening (HAT) on the atrial surface of the LAAO device. The cross-sectional area of a HAT is traced at the level of the device disc and related to the disc surface area. The Hounsfield attenuation values of HAT and at the center of the left atrium was measured, and a HAT/left atrium attenuation ratio will be calculated. Images with HAT will be subclassified into low- or high-grade HAT. A high-grade HAT was a priori considered as definite DRT on cardiac CT (Korsholm et al).
- In TEE imaging: DRT is a thrombus adherent to the luminal (left atrial) side of the device and is detected by or confirmed on TEE imaging. It appears as a dense mass with well-defined borders, distinct from endocardium and visualized throughout the cardiac cycle. The surface of the thrombus may appear smooth or irregular but more often may be laminar or pedunculated and partially mobile, where its motion independent of myocardium distinguishes it from artifact. It is important that echocardiographic findings consistent with the process of device endothelialization that looks like a smooth uniform appearance extending over the device surface, becoming continuous with LA endothelial tissue, are not to be confused with thrombus.

Disabling stroke

A stroke, as defined above, that caused neurologic disability compatible with a modified Rankin Scale score (mRS score) >1 at 3 months after symptom onset. In patient with a pre-existing mRS > 1, a stroke that caused an increase in mRS of >1. Fatality within 3 months of stroke onset is included in the definition.

mRS score

The Modified Rankin Score (mRS) is a 6-point disability scale with possible scores ranging from 0 to 5. A separate category of 6 is usually added for patients who expire. The Modified Rankin Score (mRS) is the most widely used outcome measure in stroke clinical trials. Standardized interviews to obtain a mRS score are recommended at 3 months (90 days) following hospital discharge.

1. The patient has no residual symptoms.
2. The patient has no significant disability; able to carry out all pre-stroke activities.
3. The patient has slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help.
4. The patient has moderate disability; requiring some external help but able to walk without the assistance of another individual.
5. The patient has moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual.
6. The patient has severe disability; bedridden, incontinent, requires continuous care.
7. The patient has expired (during the hospital stay or after discharge from the hospital).
8. Unable to contact patient/caregiver.
9. Modified Rankin Score not performed, OR unable to determine (UTD) from the medical record documentation.

Bleeding (BARC criteria)
Major bleeding is defined as BARC > 2

type 0	No bleeding
type I	Bleeding that is not actionable and does not cause the patient to seek treatment
type II	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
type III	a. Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
type IV	CABG-related bleeding within 48 hours
type V	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

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Conflict of interest

L. Boersma is a consultant for Boston Scientific and proctor for Abbott, fees go to the Department. M. Swaans reports proctoring fees for training/educational services to the Department of Cardiology from Boston Scientific, and personal fees from Abbott. The other authors declared no conflict of interests.

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