AMPLATZER* Amulet* Left Atrial Appendage (LAA) Occluder Randomized Controlled Trial

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This trial is intended to evaluate the safety and effectiveness of St. Jude Medical*s AMPLATZERTM AmuletTM device (Amulet) in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism. The trial will…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON47281

Source
ToetsingOnline

Brief title
AMULET IDE

Condition

- Cardiac arrhythmias

Synonym
abnormal heart rhythm, Atrial Fibrillation (AF)

Research involving
Human

Sponsors and support

Primary sponsor: St. Jude Medical
Source(s) of monetary or material Support: St. Jude Medical

Intervention

Keyword: Amulet LAA, Effectiveness, Randomized controlled, Safety

Outcome measures

Primary outcome

The trial has three primary endpoints to compare safety and effectiveness of the Amulet device against the Control device:

Safety

A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months

Effectiveness

A composite of ischemic stroke or systemic embolism through 18 months

Mechanism of Action

Device closure (defined as residual jet around the device <= 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow

Secondary outcome

The trial will also compare the Amulet device to the Control device for the following secondary endpoints:

• A composite of all stroke, systemic embolism, or cardiovascular/unexplained death at 18 months post-implant

• Major bleeding rate at 18 months post-implant: defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC)

definition

• A composite of procedure-related complications, or all-cause death, or major

bleeding through 12 months (superiority analysis)

• A composite of ischemic stroke or systemic embolism through 18 months

(superiority analysis)

• Device closure (defined as residual jet around the device <= 5 mm) at the

45-day visit documented by transesophageal echocardiogram

(TEE/TOE) defined by Doppler flow (superiority analysis)

Study description

Background summary

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder. During AF there are multiple simultaneous waves of contractions, which spread in a chaotic manner through both atria. This arrhythmia results in rapid, uncoordinated contractions, which decrease the blood pumped through the atria. The loss of mechanical efficiency during AF leads to insufficient contraction in the left atrium (LA). Stagnation of blood flow in the LA leads to hypercoagulability and thus increases the risk for thrombus formation in the LA or left atrial appendage (LAA). Approximately 90% of all thrombi in subjects with non-valvular AF (NVAF) forming in the LA originate in the left atrial appendage. The thrombus formation, in turn exposes the patient to thromboembolic events.
Echocardiographic risk factors for LAA thrombus formation include echocardiographic evidence of decreased LAA flow velocity and spontaneous echo contrast within the left atrium and left atrial appendage. The normal flow pattern of the LAA is the ejection of blood from the appendage following atrial contraction at a velocity greater than 40 cm/s2. Agmon et al. found that the relative risk of ischemic stroke was 2.6 times greater in patients with LAA flow velocities < 20 cm/s than those with higher LAA velocities.

Non-valvular AF patients have been assessed to determine the risk of stroke based on the presence of independent risk factors. In a study by Gage et al. the CHADS2 index was shown to be a tool to predict the risk of stroke in subjects with AF. The CHADS2 score assigns one point each for the presence of congestive heart failure, hypertension, age greater than 75, and diabetes

mellitus and two points for history of stroke or transient ischemic attack (TIA). The study found that AF patients who were not treated with anti-thrombotic agents had an increased risk of stroke from 1.5% to 18.2% annually as CHADS2 scores increased from 1 and 6.

A study by Go et al. reviewed outcome data (11,526 patients) in a large primary care setting and confirmed that thromboembolic risk increases progressively with CHADS2 score. The study also noted that oral anticoagulation with warfarin reduces the risk of stroke in most patients with the exception of those at lowest risk (CHADS2 score of zero) and highest risk (CHADS2 >5) for stroke. The more recently developed CHA2DS2-VASc risk assessment scheme, which identifies truly low risk subjects, assigns two points to age >= 75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65 and 74 years and female sex. A recent validation of these risk schemes in more than 90,000 patients without oral anticoagulation (OAC) but on aspirin showed annual ischemic stroke rates ranging from 0.6% in CHA2DS2-VASc = 1 to 4.8% in CHA2DS2-VASc = 4, and more than 12% for CHA2DS2-VASc = 9.

In a meta-analysis conducted by Andersen et al., warfarin was found to be superior to aspirin and placebo in reducing the risk of systemic embolism in subjects with NVAF. Hart et al. reported that adjusted dose warfarin reduces stroke by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22%. The study also reported that risk of intracranial hemorrhage was doubled with adjusted-dose warfarin compared with aspirin.

Recently, new drugs (known as novel oral anticoagulant, or NOAC) have been developed with less dietary and pharmacological interactions than warfarin and no INR monitoring requirements. Major trials such as RE-LY and ROCKET AF demonstrated that dabigatran and rivaroxiban are non-inferior to warfarin in the prevention of stroke or systemic embolism. The ARISTOTLE trial demonstrated apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in subjects with atrial fibrillation. The ENGAGE AF-TIMI trial demonstrated both once-daily dose regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. A number of characteristics that increase a patient*s risk for stroke also increase the patient*s risk for bleeding, therefore an alternative to warfarin and NOAC drugs is needed.

Left atrial appendage occlusion (LAAO) is considered a viable alternative to oral anticoagulation (OAC) therapy for stroke prevention in patients with NVAF. Published evidence supporting LAAO is provided in large part by the major randomized controlled trials PROTECT AF and PREVAIL. Five-year results of PROTECT AF showed superiority of the WATCHMANTM device in mortality and stroke

compared to optimal medical treatment with warfarin.

This clinical trial will study the Amulet device, which is St. Jude Medical*s second-generation LAA closure device. In a comparative study between the ACP and the WATCHMAN devices (40 patients each), Chun et al.31 found the devices to perform similarly. The rate of successful implantation achieved with the ACP device was greater than with the WATCHMAN device (100% vs. 95%) although the difference was not statistically significant. TEE at follow-up revealed a significantly higher incidence of residual peri-device flow (jet > 5 mm) for the WATCHMAN device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events. This finding is consistent with other reports on the ACP device.

The Amulet device is a second-generation ACP device. Early experiences with the Amulet device have been published. Freixa et al. reported successful implantation of the Amulet device in 24 out of 25 patients. Patients who had a successful implant had varying LAA anatomies. The single unsuccessful case was in a patient with a bi-lobar, small and short LAA. No procedural device embolization, stroke or pericardial effusion occurred. At 2-3 months follow-up (21 patients) no stroke, peripheral embolism or bleeding had occurred and TEE showed no residual leak >3 mm in any of the patients. Lam et al. implanted 17 patients with the Amulet device. All devices were successfully implanted. There was one procedure-related pericardial effusion successfully managed with pericardiocentesis. All patients were followed through 90 days. The authors concluded that the implantation of the Amulet device is associated with high success rate and good short-term outcome.
A comparative study Gloekler et al. was conducted, which included 50 ACP devices and 50 Amulet devices. This study showed that the devices performed similarly with respect to safety (combined safety endpoint of surgical bailout, stroke, cardiac tamponade and peri-procedural death: 6% for ACP vs. 8% for the Amulet device). Procedural success was high for both devices (94% and 98% for the ACP and the Amulet device, respectively).

In conclusion, percutaneous LAAO devices have emerged as a feasible option for stroke reduction in AF patients who are at high risk for stroke, and early experience shows that the Amulet device can be safely implanted with good procedural outcomes. Refer to section 6 for a description of the device.

Study objective

This trial is intended to evaluate the safety and effectiveness of St. Jude Medical*s AMPLATZERTM AmuletTM device (Amulet) in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism. The trial will be conducted worldwide under an investigational device exemption (IDE) and is intended to support market approval of the Amulet device in the United States and other countries. The trial is sponsored by St. Jude Medical.

The purpose of the trial is to demonstrate that safety and effectiveness of the Amulet device is non-inferior to that of the Boston Scientific LAAC device (Control) in subjects with non-valvular atrial fibrillation.

Study design

The Amulet IDE trial is a prospective, randomized, multi-center active control worldwide trial. Subjects will be randomized in a 1:1 ratio between the Amulet LAA occlusion device (treatment) or a Boston Scientific LAA closure device (Control).
The randomized trial design was developed to adequately characterize the safety and effectiveness of the Amulet device and will include patients meeting in- and exclusion criteria. Additionally, since there has been no prospective, randomized, device-to-device comparator trial to evaluate LAA closure, the results of this trial are not anticipated to duplicate existing knowledge or data.

Intervention

When it is determined the subject has met all inclusion criteria and no exclusion criteria, the subject may will be randomized in a 1:1 ratio to either the Amulet or Control.

Trained SJM representatives will be present during the Amulet implant procedure. Representatives from Boston Scientific may be present during the Control implant procedure. Site personnel should contact SJM to schedule the implant procedure.
Refer to the Instructions for Use / Directions for Use for the recommended device size, delivery and implantation of the Amulet or Watchman device.

• Procedure must be performed no later than 14 days from the date of randomization
• Procedure will be performed under TEE and angiographic guidance

Study burden and risks

The potential benefit of participating in this clinical trial is close follow-up of the subject by their treating physicians.

The patients will undergo 1 additional TEE examination for study purposes and will have more in-hospital follow-up visits. The importance of this research outweigh the risk of an additional TEE examination and the burden of additional follow-up visits. See question E9 / E9a.

Anticipated adverse events (AEs) associated with study participation and device implants are similar to those of other cardiac catheterization procedures.

There are other possible risks associated with the use of the required medications and testing for the trial, but are also no different from those prescribed outside of this clinical trial.

The trial requires FDA approval and IRB/EC/HREC approval per site, trained physicians specializing in cardiac catheterization procedures, and will utilize a Data and Safety Monitoring Board (DSMB) as an independent oversight committee in an effort to minimize potential risks to subjects. Subjects (preoperatively and postoperatively) will be under the care of a cohesive, multidisciplinary team of medical professionals, and procedures will be furnished in a hospital with an established structural heart disease and/or electrophysiology program.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. 18 years of age or older
2. Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation and the patient has not been diagnosed with rheumatic mitral valvular heart disease
3. At high risk of stroke or systemic embolism defined as CHADS2 score > 2 or a CHA2DS2-VASc
score of > 3
4. Has an appropriate rationale to seek an alternative to warfarin or other anticoagulant medication
5. Deemed by investigator to be suitable for short term warfarin therapy but deemed unable to take
long term anticoagulation, following the conclusion of shared decision making (see inclusion criteria #6)
6. Deemed suitable for LAA closure by a multidisciplinary team of medical professionals (including
an independent non-interventional physician) involved in the formal and shared decision-making
process, and by use of an evidence-based decision tool on oral anticoagulation (final determination must be documented in the subject*s medical record)
7. Able to comply with the required medication regime post-device implant
8. Able to understand and is willing to provide written informed consent to participate in the trial
9. Able and willing to return for required follow-up visits and examinations

Exclusion criteria

1. Requires long-term oral anticoagulation therapy for a condition other than atrial fibrillation
2. Contraindicated for or allergic to aspirin, clopidogrel, or warfarin use
3. Indicated for chronic P2Y12 platelet therapy inhibitor
4. Is considered at high risk for general anesthesia, in the opinion of the investigator, and/or based on past adverse reaction(s) requiring medical intervention or which resulted in prolongation of hospital stay (criterion is only applicable where general anesthesia is planned for the study procedure)
5. Has undergone atrial septal defect (ASD) repair or has an ASD closure device present
6. Has undergone patent foramen ovale (PFO) repair or has a PFO closure device implanted
7. Implanted with a mechanical valve prosthesis
8. Has any of the customary contraindications for a percutaneous catheterization procedure (e.g.
subject is too small to accommodate the TEE/TOE probe or required catheters, or subject has active infection or bleeding disorder)
9. Stroke or transient ischemic attack (TIA) within 90 days prior to randomization or implant procedure (as applicable)
10. Underwent any cardiac or non-cardiac intervention or surgery within 30 days prior to

randomization, or intervention or surgery is planned within 60 days after implant procedure (e.g.
cardioversion, ablation, cataract surgery, etc.)
11. Myocardial infarction (MI) within 90 days prior to randomization
12. New York Heart Association Class IV Congestive Heart Failure
13. Left ventricular ejection Fraction (LVEF) <30%
14. Symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient
or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if
subject has a history of carotid stent or endarterectomy the subject is eligible if there is <50%
stenosis
15. Reversible cause of AF (i.e. secondary to thyroid disorders, acute alcohol intoxication, trauma,
recent major surgical procedures)
16. History of idiopathic or recurrent venous thromboembolism
17. Left atrial appendage is obliterated or surgically ligated
18. Thrombocytopenia or anemia requiring transfusions
19. Hypersensitivity to any portion of the device material or individual components of either the Amulet or Boston Scientific LAA closure device (e.g. nickel allergy)
20. Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial
21. Subject is pregnant or pregnancy is planned during the course of the investigation
22. Active endocarditis or other infection producing bacteremia
23. Subject has had a transient case of AF (i.e. never previously detected, provoked/induced by surgical or catheter manipulations, etc.)
24. Subjects with severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73m2)
25. Subject whose life expectancy is less than 2 years
26. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator*s opinion, could limit the subject*s ability to participate in the clinical trial or to comply with follow up requirements, or impact the scientific soundness of the clinical trial results.;To participate in the trial, subjects must not meet any of the following echocardiographic exclusion criteria:
1. Intracardiac thrombus visualized by echocardiographic imaging
2. Existing circumferential pericardial effusion >2mm
3. Significant mitral valve stenosis (i.e. mitral valve area <1.5 cm2)
4. High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion >15mm
or length > 15mm; excursion defined as maximal protrusion of the ASA beyond the plane of the
atrial septum) or large shunt (early, within 3 beats and/or substantial passage of bubbles i.e. > 20)
5. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch
6. Cardiac tumor
7. LAA anatomy cannot accommodate either a Boston Scientific LAAC or Amulet device, (as

per manufacturer*s IFU.) (i.e. the anatomy and sizing must be appropriate for both devices in order to be enrolled in the trial. This is applicable to all roll-in and randomized subjects).
8. Placement of the device would interfere with any intracardiac or intravascular structure

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2017
Enrollment:	25
Type:	Actual

Medical products/devices used

Generic name:	Amulet Left Atrial Appendage Occluder
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	24-02-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-09-2017

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02879448
CCMO	NL59384.100.16