Rationale and design for AMPLATZER Amulet Left Atrial Appendage Occluder IDE randomized controlled trial (Amulet IDE Trial)

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Aims The Amulet IDE Trial is an ongoing, prospective, randomized, multi-national trial, designed to evaluate the safety and effectiveness of the AMPLATZER Amulet Left Atrial Appendage Occluder for stroke prevention in comparison to the WATCHMAN Left Atrial Appendage Closure Device in patients with non-valvular atrial fibrillation.

Methods Non-valvular atrial fibrillation patients at high risk of stroke ($CHADS_2$ score ≥2 or a CHA_2DS_2-VASc score of ≥3) who are suitable candidates for left atrial appendage occlusion (LAAO) will be fully informed and requested to participate in the trial. A total of 1878 patients at up to 150 sites worldwide will be randomized in a 1:1 ratio between the AMPLATZER Amulet device (investigational) and the Boston Scientific WATCHMAN device (control). Each patient will be followed for 5 years, with follow-up assessments at discharge, 45 days, 3, 6, 9, 12, 18, and 24 months and then annually. The trial has three primary endpoints: A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months (safety); a composite of ischemic stroke or systemic embolism through 18 months (effectiveness); and effective device LAAO, defined as residual jet around the device ≤5 mm at the 45-day visit (mechanism of action).

Summary The Amulet IDE Trial is the first randomized head-to-head LAAO device trial and will provide data for the AMPLATZER Amulet occluder in a population with a high risk of stroke and bleeding. (Am Heart J 2019;211:45-53.)

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder.[1] The loss of mechanical efficiency and enlargement of the left atrium during AF leads to insufficient contraction in the left atrium (LA),[2] with stagnation of blood flow which increases the risk for thrombus formation in the left atrial appendage (LAA). The thrombus formation, in turn, exposes the patient to a risk of embolic events. Percutaneous catheter-based occlusion of the LAA has recently been introduced to reduce the risk of ischemic stroke in patients with non-valvular AF as an alternative to oral anti-coagulation (OAC) therapy with its risk of bleeding. Randomized trials have shown that LAA occlusion (LAAO) may be an alternative to anticoagulation for stroke prevention in warfarin-eligible patients.[3-5] The single-arm AMPLATZER Amulet Observational Study of the Amulet catheter-based LAAO, conducted in 1088 patients at 17 countries outside the US, reported a high implant success rate (99.0%) and a low periprocedural complication rate (3.2%) in a population with a high risk of stroke and bleeding.[6] Additionally, transesophageal echo (TEE) data confirm high effective closure rate (98.2%) during follow-up (67 ± 23 days post) and low rate of device-associated thrombus (1.5%).[5]

The AMPLATZER Cardiac Plug (ACP, Abbott, Plymouth, MN) is the first generation LAAO device that preceded the Amulet device. In a small comparative study between the

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ACP and WATCHMAN (Boston Scientific, Natick, MA) devices Chun et al. found the devices had comparable implant success, procedural characteristics, and safety events.[7] However, TEE at follow-up revealed a significantly higher incidence of residual peri-device leak (jet >5 mm) for the WATCHMAN device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events in this small study. This finding is consistent with other reports on the ACP.[8,9]

Early experiences with the second-generation AMPLATZER device, Amulet (Abbott, Plymouth, MN), have been published.[5,6,10,11] The purpose of the Amulet IDE Trial is to demonstrate the safety and effectiveness of the AMPLATZER Amulet Left Atrial Appendage Occluder in comparison to that of the WATCHMAN Left Atrial Appendage Closure Device in patients with non-valvular AF.

Study design

The Amulet IDE Trial is ongoing, prospective, randomized, multi-national clinical trial designed to evaluate the safety and effectiveness of the AMPLATZER Amulet Left Atrial Appendage Occluder. The trial is conducted under an investigational device exemption (IDE). A total of 1878 of patients will be randomized in a 1:1 ratio between the Amulet (investigational) and Boston Scientific WATCHMAN (control) devices. The control device has received CE Mark and FDA approval, as this is the only device approved in the US, this device was chosen as the comparator. Both devices will be implanted according to the directions/instructions for use as provided by the manufacturers.

The trial will be conducted at up to 150 centers worldwide. Participating centers must have an established structural heart disease and/or electrophysiology program and may enroll up to 20% of the sample size for the trial (375 patients). Anesthesiology support and transesophageal echocardiographic guidance for LAAO are required. Investigators must be trained by the manufacturer on the safe and effective use of both devices prior to performing a procedure and have performed ≥25 interventional cardiac procedures that involve transseptal puncture through an intact septum.

Patient selection and enrollment

Patients in this clinical trial must have non-valvular AF, be at a high risk of stroke or systemic embolism and suitable for implantation with both the investigational and the control device. Patients enrolled in the clinical trial must meet all the inclusion criteria and none of the exclusion criteria, including echocardiographic criteria (Table I).

Patients will undergo screening evaluations as outlined by the inclusion/exclusion criteria. This includes a TEE within 90 days prior to the informed consent. Patients with a prior stroke or TIA are required to have an assessment by a neurologist and submit an MRI or CT post event prior to enrollment. Patients will be considered subjects and enrolled in the trial once the informed consent is signed and the randomization assigned. Randomization is performed by a computer-generated randomization scheme that is stratified by investigational site. The LAA implant procedure must occur within 14 days if randomization (Figure 1). At US sites where the implanting physicians do not have investigational device implant experience, up to 3 patients per implanter may be implanted with the investigational device prior to randomization as part of the Roll-in phase. Patients implanted in the Roll-in phase will have the same data collection and follow-up as randomized patients, but are not included in the cohort of 1878 patients and will be analyzed and reported as separate cohort.

Implant procedure and device description

Patients are required to receive aspirin (81–100 mg) the day before the implant procedure. For patients already taking an anticoagulant prior to the procedure, anticoagulant use may continue uninterrupted without a bridging regimen. The procedure can be done under either local or general anesthesia; however, transesophageal echocardiographic and fluoroscopic guidance are mandatory. During the procedure, a contrast injection is used to confirm that the LAA is of appropriate size for either device, i.e., the landing zone at its widest point must be between 11 and 31 mm. Additionally, the LAA must have a depth from the LAA orifice of at least 10 or 12 mm (depending on device size) to accommodate device placement. The sizing chart for the devices are presented in supplemental tables. If the LAA does not meet these dimensional requirements the procedure will be terminated before device implant and the patient will be followed per the protocol. Peri-procedural echocardiography must verify any post-implantation peri-device leak to assess if the device should be repositioned and to inform post procedure antithrombotic medication regimen. A transthoracic echocardiogram is performed prior to discharge to ensure that the device is positioned correctly and no pericardial effusion is present.

The investigational device is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist (Figure 2). The lobe ranges in diameter from 16 to 34 mm and has stabilizing wires for device placement and retention in the LAA. The disc is larger in diameter than the lobe, ranging from 22 to 41 mm; both the disc and the lobe contain polyester fabric to facilitate closure of the LAA. There are threaded screw attachments at either end of the device for connection to the delivery and loading cable. Radiopaque markers at either end of the device and at the location of the stabilizing wires allow for predictable placement of the device. Both the lobe and the disc will be in contact with the cardiac tissue and blood.

Table I. Amulet IDE Trial inclusion and exclusion criteria

Inclusion criteria

To participate in this clinical trial, patients must meet all of the following 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 $CHADS_2$ score$\geq$ 2 or a CHA_2DS_2-VASc score of $\geq$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 occlusion 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 patient's medical record)
7. Able to comply with the required medication regimen 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

To participate in the trial, patients must not meet any of the following 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. patient is too small to accommodate the TEE/TOE probe or required catheters, or patient 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) $\leq$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 patient has a history of carotid stent or endarterectomy the patient 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. Patient is pregnant or pregnancy is planned during the course of the investigation
22. Active endocarditis or other infection producing bacteremia
23. Patient has had a transient case of AF (i.e. never previously detected, provoked/induced by surgical or catheter manipulations, etc.)
24. Patients with severe renal failure (estimated glomerular filtration rate< 30 ml/min/1.73m^2)
25. Patient 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 patient'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.

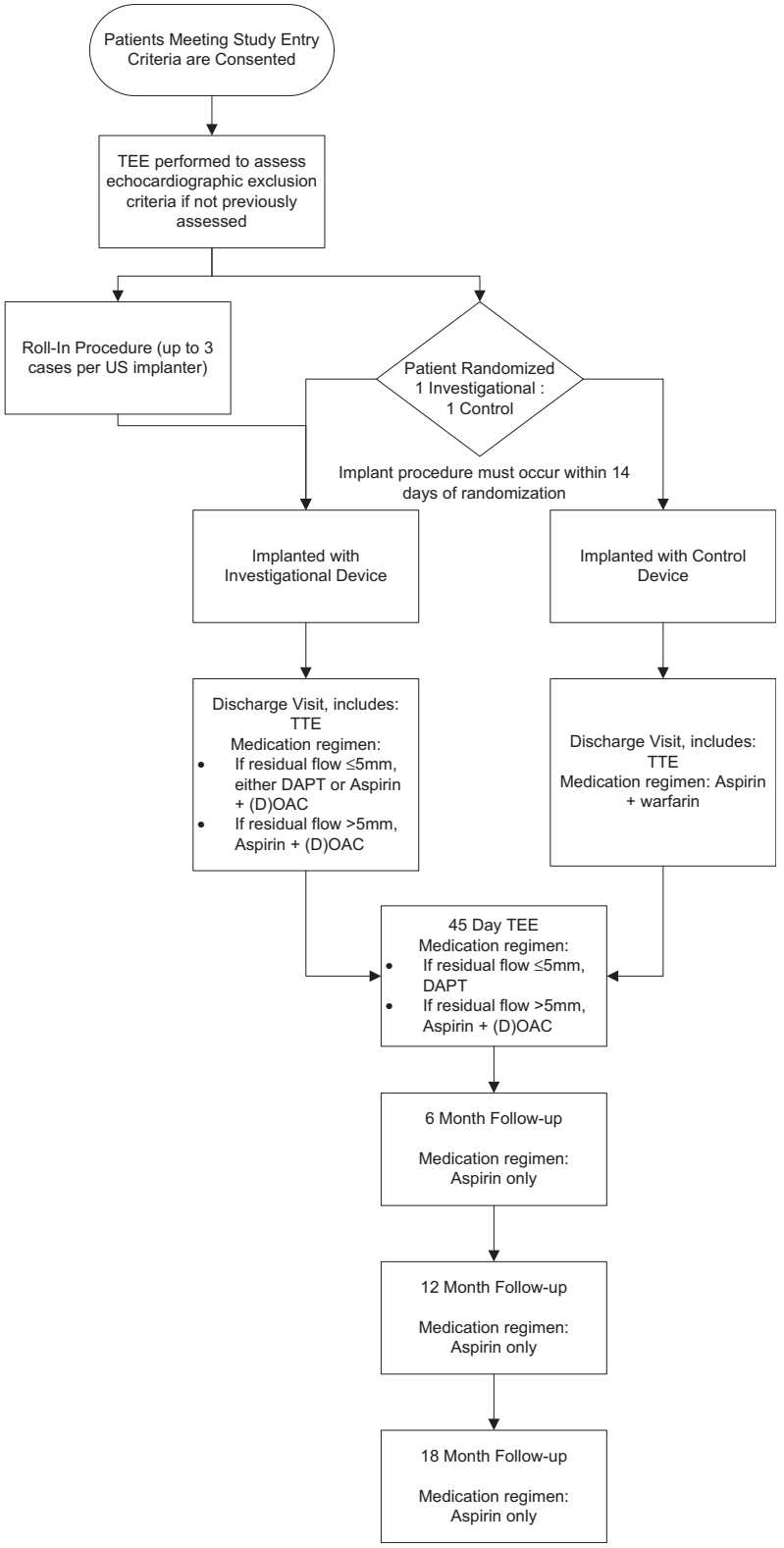
To participate in the trial, patients must not meet any of the following echocardiographic exclusion criteria:

1. Intracardiac thrombus visualized by echocardiographic imaging
2. Existing circumferential pericardial effusion >2 mm
3. Significant mitral valve stenosis (i.e. mitral valve area< 1.5 cm^2)
4. High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion >15 mm or length$\geq$ 15 mm; 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. $\geq$ 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 LAA 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 patients).
8. Placement of the device would interfere with any intracardiac or intravascular structure

Anti-thrombotic medication

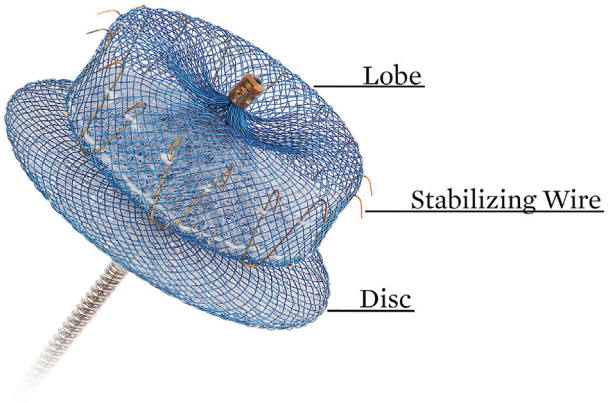
The investigational and control devices have different post-procedural anti-thrombotic medication regimens (Table II). In the 45-day post-procedure period, investigational device group patients receive either dual antiplatelet therapy or aspirin and oral anticoagulant (the latter is required if residual

Figure 1



Trial Flow.

Figure 2



Investigational Device.

jet >5 mm), while the control group patients receive aspirin and warfarin therapy. If the observed residual jet >5 mm remains at the 12 Month Follow-up, investigator discretion is used in determining long term anticoagulation strategy (if any). If a thrombus on the device is detected at any time in either arm, a 4–6-week course of anticoagulation with warfarin is recommended followed by a TEE to evaluate effectiveness of the anticoagulation treatment. In addition to the anti-thrombotic medication, endocarditis prophylaxis is recommended for 6 months following device implantation for both groups.

Data collection and follow-up

At baseline the following data are collected: relevant medical history, $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED risk scores, reason for seeking an alternative to warfarin, neurological and cardiovascular exams including National Institutes of Health Stroke Scale (NIHSS), Barthel Index, modified Rankin Score (mRS), and Questionnaire for Verifying Stroke-Free Status (QVSFS) assessments, and a quality of life assessment by the EQ-5D-5 L.[12] For patients who are randomized and undergo an attempted implant, follow-up schedules are determined by the implant procedure date. For patients who are randomized but do not have implant attempted, follow-up visit schedules will be determined by the randomization date. All enrolled patients will have the following post-procedure required visits: prior to hospital discharge, 45-days, 3-months (phone), 6-months, 9-months (phone), 12-months, 18-months, 24-months, and annually by phone until 5 years. Medication assessments and QVSFS will be conducted at all follow-ups. EQ-5D-5 L will be conducted at all in-person follow-ups following the discharge visit. In the event of a "yes" answer to any question on the QVSFS indicating the possibility of a stroke, assessment by a neurologist will occur. If a stroke or TIA is suspected, an MRI (or CT if MRI is contraindicated) will be obtained along with mRS, NIHSS, and Barthel Index assessments as soon as possible and within 10 days. If an ischemic stroke is confirmed by the neurologist, a TEE is required as soon as possible and within 7 days. For all ischemic strokes and TIAs, an assessment at 90 days post event is required to assess severity.

Endpoints

The primary objective of this trial is to demonstrate that the safety and effectiveness of the Amulet device is non-inferior to that of the WATCHMAN device in patients with non-valvular AF. The trial has three primary endpoints for safety, effectiveness, and mechanism of action. The trial will be successful if all three primary endpoints are met.

The primary safety endpoint is a composite of procedure-related complications, or all-cause death or major bleeding (defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition) through 12 months. This endpoint will be based on event adjudication by the Clinical Events Committee (CEC).

The primary effectiveness endpoint is a composite of ischemic stroke or systemic embolism through 18 months of follow-up. Ischemic stroke is defined as an acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct and does not include TIAs. Systemic embolism is defined as a blood clot that travels through the circulation system and occludes flow in a systemic artery typically with clinical manifestations. This endpoint will be based on event adjudication by the CEC.

The primary endpoint for device mechanism of action is the effective device LAAO rate at the 45-day visit.

Table II. Antithrombotic medication regimen

Group	Investigational		Control	
Observed residual jet	Jet ≤ 5 mm	Jet> 5 mm	Jet ≤ 5 mm	Jet> 5 mm
Post procedure through 45-Day Visit	Aspirin and clopidogrel† OR Aspirin and OAC therapy	Aspirin and OAC therapy	Aspirin and warfarin‡	Aspirin and warfarin‡
45-Day Visit through 6-Month Visit	Aspirin and clopidogrel†		Aspirin and clopidogrel†	
Post 6-Month Visit	Aspirin		Aspirin	

5OAC: Oral anticoagulants, including direct oral anticoagulants Aspirin dose is 81–100 mg, Clopidogrel dose is 75 mg, warfarin dose adjusted to achieve international normalized ratio (INR) of 2.0–3.0 † An alternative antiplatelet may be used if a patient is a non-responder to clopidogrel ‡ Patients enrolled outside the US may take other anticoagulants/vitamin K antagonists in lieu of warfarin.

Effective device occlusion is defined as a residual jet around the device ≤5 mm, documented by TEE. This will be assessed by Doppler flow and evaluated by an independent echocardiography core laboratory.

In addition to the primary endpoints, there are five prespecified secondary endpoints. Each of the primary endpoints has a corresponding secondary endpoint to test for superiority if non-inferiority is demonstrated. Additionally, a composite endpoint of all stroke, systemic embolism, or cardiovascular /unexplained death through 18 months will be tested for non-inferiority of the investigational to the control device. The last secondary endpoint is major bleeding event rate (defined as Type 3 or greater based on the BARC definition) and will test the investigational device for superiority to the control device.

Statistical considerations

Primary analysis populations. The primary safety analysis will be on per-protocol (PP) population, defined as patients who meet trial enrollment criteria and undergo an implant attempt with the device as randomized. The primary effectiveness analysis will be on intent-to- treat (ITT) population, defined as all randomized patients. The primary analysis for device mechanism of action endpoint will include patients who received the device as randomized and who have device LAAO status at 45 days determined by the echocardiography core laboratory.

Sample size calculation

Primary safety endpoint. The trial is powered to show that the investigational device is not inferior to the control device by more than a prespecified non-inferiority margin for the primary safety endpoint. The primary safety endpoint event rate will be estimated by the Kaplan–Meier method. An assumed rate of 15% for this endpoint in each group includes: procedure-related complication rate of 5%, and 12-month all-cause death or major bleeding rate of 10%. The 5% procedure-related complication rate assumption is based on a reported rate of 4.2% in the PREVAIL trial for 7-day procedure-related complications and a peri-procedural complication rate of 4.97% in a large cohort of patients treated with the previous generation of the investigational device (ACP).[4,13] The 10% rate of all-cause death or major bleeding assumption is based on a 12-month all-cause mortality rate of 4.7% and major bleeding rate of 5.3% reported in the PREVAIL Trial[14,15] A 5.8% non-inferiority margin represents a 1.39 relative risk. A sample size of 1746 randomized patients provides 90% power to declare non-inferiority of the investigational device at the 2.5% significance level, assuming 2% of patients are randomized but not treated and 7.5% of patients are withdrawn or lost-to-follow-up at 12 months. The sample size was calculated by simulations in the R software.

Primary effectiveness endpoint. The trial is powered to show that the investigational device is not inferior to the control device by more than a prespecified non-inferiority margin for the primary effectiveness endpoint. The primary effectiveness endpoint event rate will be estimated by the Kaplan–Meier method. The 18-month rate of ischemic stroke or systemic embolism is assumed to be 4.2% based on the reported of 4.2% rate of ischemic stroke and systemic embolism in the PREVAIL trial (2014 Boston Scientific WATCHMAN Left Atrial Appendage Closure Therapy Advisory Panel Meeting[15]). A 3.2% non-inferiority margin was chosen, which represents a relative risk of 1.76. The assumed endpoint event rate and non-inferiority margin allow for a maximum of event rate of 7.4%, equivalent to an annualized event rate of 5.1 events per 100 patient-years. Based on the expected distribution of patients' $CHADS_2$ score, the expected event rate with untreated AF is 6.5 events per 100 patient-years. A meta-analysis of six trials of warfarin compared with placebo estimated a stroke (ischemic or hemorrhagic) rate of 2.2 events per 100 patient years. Additionally, annualized rates for stroke or systemic embolism on warfarin or a direct OAC therapy reported in clinical trials range from 1.1 to 2.6 events per 100 patient-years.[16-20] Therefore, the non-inferiority margin ensures the rate observed with the investigational device will be at most twice the rate expected with OAC therapy. A sample size of 1878 patients provides 90% power to declare non-inferiority of the investigational device at the 2.5% significance level, assuming 10% of patients are

withdrawn or lost-to-follow-up at 18 months. The sample size was calculated by simulations in the R software,

Primary endpoint for device mechanism of action. The trial is powered to show that the investigational device is not inferior to the control device by more than a prespecified non-inferiority margin for the mechanism of action endpoint. The endpoint will be evaluated as a binomial proportion. The effective device LAAO rate is assumed to be 95%. This assumption is based on a weighted rate calculated from the reported rates of warfarin cessation at 45 days in the PREVAIL trial (91.9%), PROTECT AF trial (86.8%), and CAP trial (95.8%) (2014 Boston Scientific WATCHMAN Left Atrial Appendage Closure Therapy Advisory Panel Meeting and the EWOLUTION registry (99.3%)[21,22]). Using the Farrington Manning approach, a sample size of 1258 will yield 90% power to declare non-inferiority of the investigational device at the 2.5% significance level.

Therefore, a sample size of 1878 patients will provide at least 90% power (92% for safety, 90% for effectiveness, and 97% for device mechanism of action) to declare non-inferiority for each of the primary endpoints at a 2.5 significance level, and the overall power to demonstrate success in all three primary endpoints is 80%.

Analysis plan

Formal statistical tests of the non-inferiority will be carried out on each of three primary endpoints. For each of the primary endpoints, the difference between the observed rates will be presented (investigational minus control) with either the 97.5% upper confidence bound (safety and effectiveness endpoints using Greenwood's method to calculate standard errors) or the 97.5% upper confidence bound (endpoint of device mechanism of action using the Farrington-Manning method). If the safety endpoint's upper confidence bound is less than 5.8%, then non-inferiority of investigational to control on safety will be claimed to have been met; if the effectiveness endpoint's upper bound is less than 3.2%, then non-inferiority of investigational to control on effectiveness will be claimed to have been met; if the device mechanism of action endpoint's lower bound is greater than −3%, then non-inferiority of investigational to control on this primary endpoint will be claimed to have been met.

Missing data due to premature withdrawal will be handled by several approaches, including multiple imputation and tipping point analysis. Results from the various approaches for handling missing data will be compared to assess sensitivity of analysis results to missing data. To account for the effect of potentially different use of anticoagulant medication on the primary effectiveness endpoint, additional sensitivity analyses will be performed, including (1) repeating the primary analysis by excluding those patients who experience a primary effectiveness endpoint event or withdraw or die before 45-day visit, (2) changing the time origin to the date of the 45-day follow-up visit in the Kaplan–Meier analysis, and (3) a Cox proportional hazard regression treating warfarin or other OAC use as a time-varying covariate.

Study management, assessments, and adjudication

The trial is sponsored and funded by Abbott, manufacturer of the Amulet device. The data collection, monitoring, and analysis are performed by the sponsor. The study chairman and steering committee in concert with the study sponsor designed the trial and are responsible for its conduct and analysis. The authors are solely responsible for the drafting and editing of the paper and its final contents. The trial started enrollment in August 2016 and is expected to be completed in 2019 with follow-up to assess the primary endpoints completing in 2020.

An independent Data and Safety Monitoring Board (DSMB), composed of experts in cardiology, electrophysiology, interventional cardiology, neurology and statistics will monitor trial progress including regular reviews of the trial safety and make recommendations regarding study modification or termination.

An independent CEC will review and adjudicate adverse events pertaining to the primary and secondary endpoints, including all reported bleeding (major and minor) and neurologic events. The CEC is composed of physicians specializing in electrophysiology, interventional cardiology, neurology, and neuroradiology. The CEC will be blinded to the investigational group.

An external, independent Echocardiography Core Laboratory will be utilized to analyze echocardiographic imaging, as required, during the trial. Because the devices differ in their echocardiographic appearance, it will be impossible to maintain blinding for members of the echo core lab. They will remain blinded to all other clinical/imaging data for the subjects.

Discussion

The Amulet IDE Trial is the first large, randomized clinical trial to evaluate the Amulet device's safety and effectiveness in a randomized trial of patients with AF who have a rationale for seeking an alternative to warfarin. This clinical trial will contribute important prospective comparative data between the Amulet and WATCHMAN devices.

Following FDA approval of the WATCHMAN device, standard of care treatment for patients who seek a non-pharmacologic alternative to warfarin is the WATCHMAN device. The intended patient population for this trial are those already indicated for LAAO, therefore this trial is randomized against the FDA approved WATCHMAN device.

The PROTECT AF and PREVAIL trials demonstrated safety and effectiveness of the WATCHMAN device. These studies also demonstrated a learning curve with

respect to implant success and procedural safety. WATCHMAN implant success rates improved from 90.9% to 95.1% and complication rates decreased from 8.7% to 4.5% as operators gained experience.[3,4] It should be noted that comparisons of this trial with PROTECT AF and PREVAIL trials will need to consider differences in patient populations. The PROTECT AF and PREVAIL trials had as entry criterion a $CHADS_2$ score $\geq$ 1, whereas this trial uses criteria based on those used for Medicare reimbursement. Patients in the Amulet IDE Trial will have either a $CHADS_2$ score $\geq$2 or CHA_2DS_2-VASc $\geq$3 and an appropriate rationale to seek an alternative to warfarin or other anticoagulation. As the Amulet IDE Trial provides the first experience implanting the Amulet device, operators will need to learn implant techniques for this new device relative to the control device. Therefore, extensive operator training and a Roll-in phase are being utilized in this trial.

A key aspect that this trial will also provide insight into is the impact of differing medication regimens post-implant on safety and effectiveness. To assess this impact on the primary effectiveness endpoint, a Cox proportional hazards model will be used to analyze ischemic stroke or systemic embolism events, with OAC therapy use being a time-varying covariate. The relative risk of ischemic stroke or systemic embolism for the investigational versus control device will be estimated.

A limitation of this trial design is the time between required evaluations for a thrombus on the device. While this trial will systematically evaluate for a thrombus on the device using TEE at 45 days and 1 year, an interim evaluation is not specified unless an ischemic stroke occurs or a thrombus is suspected.

Summary

The Amulet IDE Trial is the first large randomized head-to-head LAAO device trial and will provide evidence of the AMPLATZER Amulet occluder's safety and effectiveness relative to the WATCHMAN device in a population with a high risk of stroke and bleeding.

Declarations of interest

DL: personal fees from Abbott, during the conduct of the study; personal fees from Biotronik, grants from Biosense Webster, personal fees from Janssen, grants from Pfizer, outside the submitted work.

SW: grants from Boston Scientific, grants from St. Jude Medical, grants from Abbott, grants from Amgen Inc., grants from Biotronik, grants from Terumo Inc., grants from Symetis SA, grants from Edwards Lifesciences, grants from Bayer AG, outside the submitted work.

DT: personal fees from Abbott, outside the submitted work.

LS: nothing to disclose.

JC: reports other from Abbott, during the conduct of the study; other from Abbott, outside the submitted work.

MG: personal fees from Abbott, outside the submitted work.

HG: employee of Abbott.

KB: employee of Abbott.

JH: personal fees from Abbott, outside the submitted work.

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Supplementary data

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