Safety of Oral Anticoagulation Therapy withdrawal after Successful Cardiac Ablation in Patients with Atrial Fibrillation and Associated High Risk Factors for Embolic Events
(OAT Pilot Study)

Sponsor:	BIOSENSE WEBSTER, INC. 3333 Diamond Canyon Road Diamond Bar, CA 91765
EudraCT:	2012-003745-15
Version:	3.0 - October 21, 2013

1.0 Protocol Agreement Form

Study Title: Safety of Oral Anticoagulation Therapy Withdrawal after Successful Cardiac Ablation in Patients with Atrial Fibrillation and Associated High Risk Factors for Embolic Events (OAT Pilot Study)

I, the undersigned have read and understand this clinical study, including the appendices. I will conduct the clinical study in accordance with appropriate in-country ethical and regulatory considerations and will strictly follow the study procedures. I will ensure that all persons assisting in this study are adequately informed about the protocol, study product(s), and their clinical study-related duties and functions. I will provide all information to other investigators and hospital staff involved in the study.

I agree to maintain all information supplied by Biosense Webster, Inc. in confidence and when information regarding this study is presented to an institutional review board (IRB; or equivalent; eg, ethics committee [EC] or ethics board [EB]), it will describe the confidential nature of all study-related material.

Principal Investigator	**Signature**	**Date**
Sub-Investigator	**Signature**	**Date**
Sub-Investigator	**Signature**	**Date**

2.0 Contact Details

Sponsor:
Biosense Webster, Inc.
3333 Diamond Canyon Road
Diamond Bar, CA 91765
USA
Tel +1 909-839-8500
Fax +1 909-839-8804

[redacted]

Table of Contents

3.0 Protocol Summary

Title:	Safety of Oral Anticoagulation Therapy Withdrawal after Successful Cardiac Ablation in Patients with Atrial Fibrillation and Associated High Risk Factors for Embolic Events (OAT Pilot Study)
Design:	Prospective, multicenter, randomized (1:1), controlled, two-arm unblinded study. Patients undergoing successful cardiac ablation for atrial fibrillation who remain AF recurrence-free 3 months after successful ablation and continue to meet the inclusion/exclusion criteria will be screened for enrollment in the trial. After fulfilling all of the inclusion/exclusion criteria, patients who consent to participate in the study and remain AF recurrence-free will be randomized to one of two study arms: (1) OAT Withdrawal (Test) Group or (2) OAT (Control) Group and participate in the Evaluation Period (12 months).
Objective:	The objective of this study is to determine the safety of discontinuing oral anticoagulation therapy in high risk patients who have had a successful cardiac ablation and remain AF recurrence free for 3 months post ablation.
Hypothesis:	High risk subjects who have successful cardiac ablation and remain free from AF recurrence for 3 months post ablation procedure can discontinue their OAT without an increased risk of thromboembolic events as compared to those who remain on OAT.
Enrollment:	Up to 100 subjects will be enrolled in this study.
Clinical Sites:	Up to 10 sites in the United States and Europe will be included.
Subject Population:	Patients who have undergone successful cardiac ablation for AF that are 3months post procedure and remain free from AF recurrence. Eligible patients who sign the study informed consent form will be randomized (1:1) into one of two study arms: • **OAT Withdrawal (Test) Group:** discontinue OAT during the Evaluation Period • **OAT (Control) Group:** continue OAT during the Evaluation Period
Inclusion/Exclusion Criteria:	**Inclusion Criteria:** 1. Successful cardiac ablation for AF 2. Documented freedom from AF recurrence (symptomatic or asymptomatic arrhythmic recurrences lasting longer than 30 seconds) 3 months after successful cardiac ablation (AF recurrence during 3-month blanking period is excluded). 3. Patient must have been on a commercially approved anticoagulation therapy for at least two (2) months prior to randomization in the OAT Study. Commonly prescribed Oral Anticoagulation and Antiplatelet therapies for use in this study are listed in Appendix A. For patients enrolled in Germany,

only those who are prescribed therapies listed in Appendix A can be enrolled in this study.

4. $CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc score ≥ 3
5. Left ventricular ejection fraction > 25%
6. LA size ≤ 65
7. High risk for thromboembolic events (i.e., $CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc score ≥ 3 and require OAT before undergoing cardiac ablation)
8. Able and willing to comply with all pre- and follow-up testing and requirements
9. Signed informed consent form
10. Age 18 years or older

Exclusion Criteria:

1. OAT required for reasons not related to AF (i.e., prosthetic valve, PV stenosis, previous pulmonary embolism, presence of spontaneous echo contrast [SEC] at standard echo performed at 3-months follow-up).
2. Any cardiac surgery within the past 60 days (2 months) or valvular cardiac surgical procedure at any time (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
3. Previous myocardial infarction (MI), or a percutaneous coronary intervention PCI within the past 3 months
4. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months)
5. Documented left atrial thrombus
6. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or COPD) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms
7. Significant medical problem that in the opinion of the investigator would preclude enrollment in this study
8. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal)
9. Acute illness or active systemic infection or sepsis
10. Unstable angina
11. Contraindication to anticoagulation (i.e., heparin, warfarin or another commercially available anticoagulation medication)
12. History of blood clotting or bleeding abnormalities
13. Life expectancy less than 360 days (12 months)
14. Uncontrolled Heart Failure or NYHA Class III or IV heart failure
15. Enrollment in a clinical study evaluating another device or drug, within the past 6 months
16. Unable or unwilling to comply with protocol requirements

Endpoints:

Primary

Composite endpoint represented by the occurrence of any major thromboembolic event (stroke [i.e., ischemic, hemorrhagic or cryptogenic] that is an acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥24 hours or resulting in death) or major hemorrhagic complication (major bleeding) during the 12-month Evaluation Period.

Secondary:

- Minor bleeds
- Hospitalization with any thromboembolic or major hemorrhagic event
- All cause mortality
- QoL (SF-36)
- AF recurrence
- Repeat ablation for AF

Study Duration: 2 years (1 year enrollment period and 1year follow-up)

4.0 Acronyms/Abbreviations and Study Definitions

Table 1. Acronyms and Abbreviations Used in the Study Protocol

Acronym / Abbreviation	Expanded Term
AAD	AntiArrhythmic Drug
ACC/AHA	American College of Cardiology/American Heart Association
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
EB	Ethics Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HM	Holter Monitor
ILR	Implantable Loop Recorder
HRS	Heart Rhythm Society
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
LA	Left Atrium
LAA	Left Atrial Appendage
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
OAT	Oral Anticoagulation Therapy
PAC	Physician Advisory Committee
PI	Principal Investigator
PLAX	Parasternal Long Axis
PV	Pulmonary Vein
PVAI	Pulmonary Vein Antrum Isolation
QoL	Quality of Life
RA	Right Atrium
RFCA	Radiofrequency Catheter Ablation
RV	Right Ventricle
SAE	Serious Adverse Event
SEC	Spontaneous Echo Contrast
SMC	Safety Monitoring Committee
SOC	Standard of Care
SOP	Standard Operating Procedure
SR	Sinus Rhythm
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography

Table 2. Study Definitions

Term	Definition
AF Recurrence	Recurrence of an AF episode, which is an episode of AF ≥ 30 seconds in duration. Atrial fibrillation and atrial flutter (including atypical flutter) are considered episodes of AF.
Asymptomatic (Silent) AF	Documented by ECG without subject symptoms.
Documented AF Episode	Documentation obtained with an arrhythmia monitoring tool. This may include ECG, TTM, HM, or telemetry strip. Reporting of a symptomatic episode by subjects is **not** considered as a documented episode.
High-burden Paroxysmal AF	AF episodes that last less than 30 days. Episodes may terminate spontaneously or via cardioversion.
High-risk	$CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc score ≥ 3
Long Standing Persistent AF	Longstanding persistent AF is defined as continuous AF of >12 months duration.
Major hemorrhagic complication	• Stroke is an acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥ 24 hours or resulting in death. o Stroke (i.e., ischemic, hemorrhagic or cryptogenic) occurrence. Stroke is categorized as ischemic or hemorrhagic or cause unknown (based on computed tomographic or magnetic resonance imaging or autopsy). o Fatal stroke is defined as death from any cause within 30 days of stroke. o Severity of stroke will be assessed by modified Rankin score at discharge from hospital and at 3 to 6 months later. • Bleeding (major) is defined by ≥ 1 of the following criteria: o Bleeding associated with reduction in hemoglobin level of at least 2.0 g/L; o leading to transfusion of at least 2 U of blood or packed cells; or o symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, GI bleeding, intra-articular bleeding, or pericardial bleeding. • Bleeding (life-threatening) if ≥ 1 of the following criteria are met: o fatal, symptomatic intracranial bleed; o reduction in hemoglobin level of at least 5.0 g/L; o transfusion of at least 4 U of blood or packed cells; o associated with hypotension requiring the use of intravenous inotropic agents; or o necessitated surgical intervention.
Minor hemorrhagic event (Minor Bleeds)	Clinical bleeds that do not fulfill the criteria for major bleeds
Paroxysmal AF	Paroxysmal AF is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤48 h duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Permanent AF	The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it

Term	Definition
	refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.
Persistent AF	Persistent AF is defined as continuous AF that is sustained beyond 7 days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥48 h of AF, but prior to 7 days, should also be classified as persistent AF episodes.
Successful Cardiac Ablation	After Cardiac Ablation, no symptomatic or asymptomatic AF recurrence ≥ 30 seconds (without increased or new AADs) following the 3-month blanking period.
Symptomatic AF	Symptom(s) which is/are exhibited by the subject, which make them seek medical attention, and are concurrent with a documented episode by ILR, ECG, TTM, HM, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (eg, rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.
Thromboembolic Event	Any documented clinical event due to the embolic occlusion of an artery in the brain or other organs.

5.0 Introduction

5.1 Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of between 0.9% and 2.5% in the general population and an increasing incidence with age.[2,3] This arrhythmia is associated with an increased risk of thromboembolic complications and in particular of ischemic stroke. The rate of this complication varies from fewer than 2 to more than 10 strokes per 100 patient-years without antithrombotic therapy.[4, 5] The stroke risk increases in the presence of cardiovascular diseases, such as rheumatic mitral stenosis, or prosthetic cardiac valves. Furthermore, patients with non-valvular AF, a history of previous thromboembolism, advanced age, hypertension, diabetes mellitus, and heart failure have an increased risk of stroke.[6] Thromboembolic complications generally result from left atrium thrombi, the left atrial appendage (LAA) being the most common source of thrombus formation, with an incidence of 91% in patients with non-valvular AF.[6,7] The pathogenesis of LAA thrombi has not been fully elucidated, but the relative stasis of the blood within the appendage, due to its anatomy and altered function during AF (reduced contraction, filling dynamics), is thought to play a major role.[8]

Adjusted-dose warfarin is highly effective in preventing stroke, and reduces risk by 62% versus placebo in patients with non-valvular AF;[9] however, it increases the risk of major bleeding by 1.2% per year.[6] The absolute reduction in stroke risk is reported to be 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[9]

Although the efficacy of warfarin in preventing stroke in AF patients has been clearly demonstrated, oral anticoagulation is still underused in clinical practice for several reasons. Firstly, oral anticoagulation therapy carries a substantial risk of hemorrhage; this could be underestimated in clinical practice, considering the restrictive selection criteria used in randomized trials, in which patients with lower risk of bleeding are often enrolled. For example, in the SPINAF trial only 7% of the 7982 patients initially screened were enrolled.[10] Moreover, the risk of hemorrhage is strictly related to the patient's age. Indeed, the incidence rate of major hemorrhage has been found to rise from 1.5 per 100 patient-years for patients younger than 60 years to 4.2 per 100 patients-years for patients older than 80 years (hazard ratio of 2.7).[11] In a meta-analysis of major randomized trials of oral anticoagulation therapy, the mean age of patients was 69 years, and only 20% of participants were older than 75 years.[9]

By contrast, in clinical practice this latter group of patients represents more than 50% of the population that needs to be treated with anticoagulation therapy.[7] The second reason for the underuse of oral anticoagulation is that this therapy, specifically warfarin, is associated with restrictions in everyday life, as it requires frequent monitoring of the INR level in order to adjust the therapeutic dosage. Finally, it is well known that a considerable percentage of patients are unable to comply with oral anticoagulation therapy. In warfarin-treated patients, discontinuation of this therapy occurs at rates of up to 38% a year and approximately 50% of strokes occur during inadvertent therapeutic lapses or in subjects who temporarily or permanently cease therapy.[8]

The benefit of oral anticoagulation is more substantial in patients who are at high risk for stroke. Despite this benefit, a considerable portion of these patients may have relative or absolute contraindications to warfarin treatment that prevent use of the recommended anticoagulation therapy. Indeed, it has been reported that 46% of elderly Medicare beneficiaries have contraindications to warfarin, such as previous hemorrhage, blood dyscrasia, and renal or hepatic disease.[12] Recently, new medications for oral anticoagulation therapy have been developed and approved for use. Two recent clinical trials compared the use of rivaroxaban (ROCKET AF study) and dabigatran (RE-LY study) with warfarin in patients with AF. In the ROCKET AF Study, rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism, with similar rates for adverse events and bleeding.[13] In the RE-LY Study, dabigatran compared with warfarin was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.[14] The net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) versus no treatment in a "real world" AF population was presented in a recently published study. Using a modeling analysis based on a nationwide cohort study, Banerjee, et al found that when the risk of bleeding and stroke are both high, these new anticoagulants appear to have a greater net clinical benefit compared to warfarin.[15] The management of these patients remains challenging; however, and alternative methods of treatment to reduce embolic stroke need to be considered.

Since the late 1990s, catheter ablation has offered a minimally-invasive, non-pharmacological therapeutic option to patients with AF. Over a short period of time this procedure has become a more commonly performed ablation technique that is used throughout the world in appropriately selected patients. Haïssaguerre, et al demonstrated that the majority of AF is initiated by ectopic foci found primarily in the pulmonary veins;[16] however, different approaches have since been developed to electrically confine the triggers in the pulmonary veins (pulmonary vein isolation [PVI]). Success rates of approximately 75% have been reported in many studies that compared radiofrequency catheter ablation with AADs for the treatment of AF.[17-21] Still, the role of anticoagulation therapy in preventing atrioembolic stroke after PVI remains unclear and no universally accepted recommendations exist for anticoagulation therapy after successful ablation of atrial fibrillation.

After undergoing radiofrequency ablation of atrial fibrillation, all patients receive oral anticoagulation therapy for a minimum of 3 months (ie, "blanking period"). For those taking warfarin, their INR is monitored to maintain the appropriate therapeutic range (2-3, target 2.5). Following the "blanking period," considerations for the use of warfarin fall into several categories, with the $CHADS_2$ or CHA_2DS_2-VASc score commonly used as a predictor of thromboembolic events following catheter ablation of AF.[22] For patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 0, there is general agreement that warfarin therapy may be discontinued after the "blanking period." On the contrary, for patients with $CHADS_2$ or CHA_2DS_2-VASc score >1, the recommendations for long-term anticoagulation therapy remain controversial. In many centers, it is common practice to withdraw warfarin, if no symptomatic or asymptomatic arrhythmic recurrences are documented, post-ablation pulmonary stenosis is excluded, and the $CHADS_2$score is equal to 1. The results of recent observational trials seem to confirm the value and safety of this strategy.[23-27] However, this approach, although reasonable, is substantially empirical and not based on data from randomized clinical trials. In high-risk patients with $CHADS_2$ score ≥ 2, different strategies have been used. In a few centers, warfarin is stopped after 3 to 6 months for patients with an apparently successful procedure.[28] However in the majority of centers, anticoagulation therapy is continued indefinitely despite the absence of documented atrial fibrillation episodes.

5.2 Rationale

Currently, only limited data regarding the benefit of continuing oral anticoagulation therapy (OAT) in patients who undergo radiofrequency catheter ablation (RFCA), have successful procedures, and remain free from recurrences of atrial fibrillation are available. There are no published, randomized trials regarding continuation or discontinuation of OAT after catheter ablation of AF. Observational or interventional studies that assess OAT withdrawal and OAT continuation do not present a comparison of appropriate patient groups (ie, patients with successful ablation and no OAT are compared to patients on OAT, most or all of whom had early AF recurrence).[24, 27] Furthermore, most studies used warfarin as OAT and very few thrombotic events were reported for patients with successful ablation, either on or off OAT.[23, 24, 27] If considering only patients continuing in sinus rhythm (SR), with comparable baseline stroke risk, it is unlikely that these studies[23, 24, 27, 29] would have detected any difference in event rates between OAT withdrawal and OAT continuation groups. To better understand the effect of OAT withdrawal following successful cardiac ablation, a well-controlled study of subjects at high risk of thromboembolic events that includes an appropriate comparison group and long-term follow-up should be conducted.

The OAT Pilot Study is a randomized, controlled study aimed at understanding the need for continued OAT in high-risk subjects who have successfully undergone cardiac ablation by assessing the risk of thromboembolic events after OAT withdrawal versus OAT continuation.

5.3 Risk Analysis

The risks posed during the conduct of this study are expected to be comparable to those anticipated with the use of OAT according to current AF management guidelines.[6, 30-33] Anticoagulation therapies have been approved for many decades and the risks and complications are well known. Depending on a patient's risk factors, anticoagulation therapy is recommended for a period of time after undergoing an ablation procedure.[31] For the OAT Pilot Study, appropriate measures have been implemented to minimize the risk to subjects, while still providing the possible benefits of the two treatment options.

Description and Analysis of Risks:

The OAT Pilot Study will assess the risks associated with subjects randomized to one of two study arms, OAT Withdrawal (Test) Group or OAT (Control) Group. No additional risks are anticipated for subjects randomized to the OAT arm of the study as these subjects will continue with their current physician-prescribed OAT. The major risk for subjects continuing OAT during the Evaluation Period is the risk of major bleeding and hemorrhagic stroke.[31] The main risks for subjects discontinuing OAT during the Evaluation Period is the increased risk of a thromboembolic event. This risk is higher in subjects with a history or previous thromboembolism, advanced age, hypertension, diabetes mellitus and heart failure.

Minimization of Risks:

The criteria for subject selection, study methods, personnel selection, facilities, and training that have been specified in this study are intended to minimize the risk to enrolled subjects. Subjects will be carefully screened prior to study enrollment to confirm compliance with the study inclusion and exclusion criteria. In addition, prior to randomization, all patients will undergo further AF monitoring to confirm they are AF recurrence free for 3 months following catheter ablation. Once enrolled, additional AF monitoring and clinic follow-up visits are required for each subject to ensure an appropriate level of safety monitoring. Patients experiencing AF recurrence during the study will be treated per the investigator's discretion.

Additionally, safety data will be evaluated periodically during enrollment and follow-up by a physician review committee functioning as a Global Safety Monitoring Committee (GSMC) for this study.

Potential Benefit:

There is no direct benefit expected for subjects enrolled in the OAT arm of the study. Subjects enrolled in the OAT withdrawal arm may experience an increase in their quality of life due to the elimination of complications associated with OAT. Overall, the information gathered during the conduct of this study may be of benefit in the future for the treatment of patients with AF.

6.0 Study Hypothesis

High risk subjects who have successful cardiac ablation and remain free from AF recurrence for 3 months post ablation procedure can discontinue their OAT without an increased risk of thromboembolic events as compared to those who remain on OAT.

7.0 Objective

The objective of this study is to determine the safety of discontinuing oral anticoagulation therapy in high risk patients who have had a successful cardiac ablation and remain AF recurrence free for 3 months post ablation.

8.0 Pilot Study Plan

8.1 Study Design

This is a prospective, multicenter, randomized (1:1), controlled, two-arm, unblinded, pilot study, evaluating the incidence of thromboembolic and hemorrhagic complications after withdrawal of OAT compared to continuation of OAT in subjects who have undergone successful cardiac ablation.

8.2 Treatment Groups

Patients who have undergone successful cardiac ablation for symptomatic AF that are 3 months post procedure (AF recurrences during the 3 month blanking period immediately after cardiac ablation are acceptable), remain free from AF recurrence, fulfill the study inclusion/exclusion criteria, and consent to participate will be considered for study participation and may be enrolled. Enrolled subjects will be randomized (1:1) into one of the two treatment groups described below and participate in the study Evaluation Period (12 months).

- **OAT Withdrawal (Test) Group:** discontinue OAT during the Evaluation Period (from randomization through 12-months follow-up)
- **OAT (Control) Group:** continue OAT during the Evaluation Period (from randomization through 12-months follow-up)

The test group will be compared to the control group in terms of the safety endpoints including the incidence of thromboembolic events or major hemorrhagic complications, minor bleeds, hospitalizations, and all cause mortality. Additional endpoints will be evaluated including QoL, AF recurrence and repeat ablation procedures for AF. Planned statistical analysis of these endpoints is described in the Statistical Analysis Section (13.0) of this protocol.

8.3 Number of Centers

Up to 10 sites will be included in the study. Total subject enrollment is expected to be 100. All subjects enrolled will be followed through 12 months after randomization or until AF recurrence.

8.4 Study Duration, Completion, and Termination

- **Duration:** The study duration is anticipated to be 2 years; 1 year to complete screening/enrollment, and 1 year to complete follow-up for all subjects.
- **Completion:** The study will be considered complete when all subjects either complete their 12-month study visit, withdraw/discontinue the study, become lost to follow-up.
- **Termination:** The study may be terminated prematurely at the discretion of the Sponsor, on statistical grounds, or on the advice/recommendation of the Safety Monitoring Committee. The Sponsor may also terminate a site prior to study completion if it believes the site is no longer capable of participating (eg, cannot fulfill subject enrollment goals, site suspension by IRB or equivalent).

9.0 Subject Selection and Disposition

9.1 Recruitment and Screening Procedures

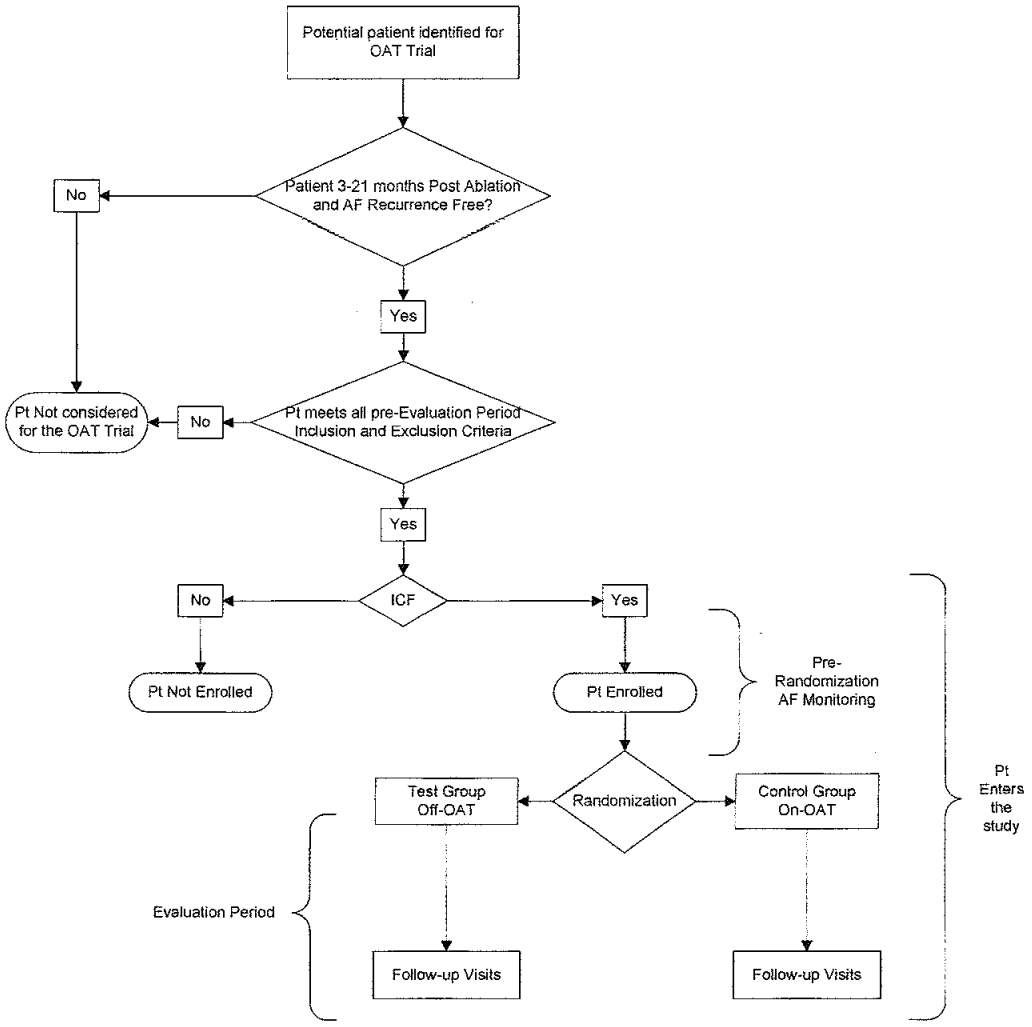
Patients who have undergone a successful cardiac ablation procedure using devices commercially available and remain AF recurrence free should be screened by the investigator or a member of the designated study staff to determine study eligibility. All high-risk ($CHADS_2 \geq 2$ or CHA_2DS_2-VASc $\geq$

3) patients who have had successful cardiac ablation for the treatment of symptomatic AF, remain free from AF recurrence 3-21 months after cardiac ablation may be eligible for inclusion in the study (Refer to Figure 1, Study Flow Chart). A screening log, maintained at each study site, will be used to document the patients reviewed for potential enrollment into the study. The screening log should be completed for any patient considered for study inclusion, regardless of whether the patient is selected or not, as this will allow better management of the study enrolment rate.

9.2 Informed Consent and Enrollment Procedures

If a patient is deemed eligible and is willing to participate in the study, the investigator or designated member of the study staff will properly obtain a written informed consent form (ICF) from the patient prior to study enrollment. The ICF and any revisions must have prior approval of the study site's institutional review board (IRB) or equivalent (eg, ethics committee [EC] or ethics board [EB]). Patients who sign the informed consent form will be considered enrolled in the study. A sample ICF for this study is provided in a separate document. No patient should undergo any study-specific tests or exams that fall outside the standard of care without first signing the informed consent document for this study. After signing the study's ICF, enrolled subjects will undergo further AF monitoring to confirm freedom from arrhythmia recurrence. Subjects who are deemed free from arrhythmia recurrence and qualify for enrollment according to the study inclusion and exclusion criteria will be randomized to one of the two study arms and followed through the Evaluation Period (12 months).

Figure 1.0 Study Flow Chart



9.3 Study Inclusion Criteria

Candidates for this study must meet **ALL** of the following criteria:

1. Successful cardiac ablation for symptomatic AF refractory to antiarrhythmic drug therapy
2. Documented freedom from AF recurrence (symptomatic or asymptomatic arrhythmic recurrences lasting longer than 30 seconds) 3 months after cardiac ablation (AF recurrence during 3-month blanking period is excluded).
3. Patient must have been on a commercially approved anticoagulation therapy for at least two (2) months prior to randomization in the OAT Study. Commonly prescribed Oral Anticoagulation and Antiplatelet Therapies for use in this study are listed in Appendix A. For patients enrolled in Germany, only those who are prescribed therapies listed in Appendix A can be enrolled in this study.
4. $CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc ≥ 3
5. Left ventricular ejection fraction > 25%
6. LA size ≤ 65
7. High risk for thromboembolic events (ie, $CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc ≥ 3 and require OAT before undergoing cardiac ablation)
8. Able and willing to comply with all pre- and follow-up testing and requirements
9. Signed informed consent form
10. Age 18 years or older

9.4 Study Exclusion Criteria

Candidates for this study will be EXCLUDED from the study if **ANY** of the following conditions apply:

1. OAT required for reasons not related to AF (ie, prosthetic valve, PV stenosis, previous pulmonary embolism, presence of spontaneous echo contrast [SEC] at standard echo performed at 3-months follow-up).
2. Any cardiac surgery within the past 60 days (2 months) or valvular cardiac surgical procedure at any time (ie, ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
3. Previous myocardial infarction (MI), or a percutaneous coronary intervention PCI within the past 3 months
4. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months)
5. Documented left atrial thrombus
6. Significant pulmonary disease, (eg, restrictive pulmonary disease, constrictive or COPD) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms
7. Significant medical problem that in the opinion of the investigator would preclude enrollment in this study
8. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal)
9. Acute illness or active systemic infection or sepsis
10. Unstable angina
11. Contraindication to anticoagulation (ie, heparin, warfarin or another commercially available anticoagulation medication)
12. History of blood clotting or bleeding abnormalities
13. Life expectancy less than 360 days (12 months)
14. Uncontrolled Heart Failure or NYHA Class III or IV heart failure
15. Enrollment in a clinical study evaluating another device or drug, within the past 6 months
16. Unable or unwilling to comply with protocol requirements

9.5 Randomization

All subjects who have signed the study ICF will be required to undergo AF monitoring just prior to randomization. This pre-randomization AF monitoring is designed to verify that the subject is not experiencing symptomatic or non-symptomatic AF recurrence. Pre-randomization AF monitoring will be conducted by Holter Monitor. For subjects with an implantable cardioverter defibrillator (ICD) or artificial cardiac pacemaker, interrogations for the duration of seven (7) days of and within 30 days of randomization will be accepted.

Subjects who are found to be free from AF recurrence during pre-randomization AF monitoring will be randomized (1:1) into one of the two study arms: (1) OAT withdrawal or (2) OAT continuation and followed during the study Evaluation Period (12 months). Randomization will be stratified by gender and region (Europe and North America).

9.6 Subject Disposition

Evaluable Subjects

- **Enrolled Subjects:** subjects who sign the study's informed consent form
- **Randomized Subjects:** subject who remain free from arrhythmia recurrence after signing the study ICF and are randomized into one of the study arms (OAT withdrawal or OAT).
- **Completed Subjects:** enrolled subjects who have not been discontinued, withdrawn or lost-to-follow-up from the study prior to the final (12 month) study visit.
- **Lost to Follow-up Subjects:** subjects who are enrolled and randomized, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject, two (2) by documented telephone calls, and one (1) written attempt sent by registered mail).
- **Discontinued:** Subjects that have arrhythmia recurrence at any time during the Evaluation Period will be discontinued. Discontinued subjects are exited from the study prior to completion of all follow-up visits; however, they will remain in the analysis cohort until the time at which they are discontinued from the study.
- **Withdrawn Subjects:** Subjects may be withdrawn for reasons stated below in Section 9.7. Withdrawn subjects are exited from the study prior to completion of all follow-up visits; however, they will remain in the analysis cohort until the time at which they are withdrawn.

Non-Evaluable Subjects

- **Excluded:** Subjects found to not meet one of the study inclusion/exclusion criteria after the being enrolled.

9.7 Subject Withdrawal

The investigator may remove a subject from the study for any of the following reasons: withdrawal is in the subject's best interest, subject preference, concurrent illness, noncompliance, or any other situation the investigator deems a compromise to the integrity of the study. Subjects will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or the institution.

If a subject is removed from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the Investigator must comply with all reporting requirements described in Section 12 and must follow the subject until the AE/SAE has resolved or stabilized.

10.0 Study Endpoints

10.1 Primary Endpoint

The primary endpoint is a composite endpoint represented by the occurrence of any major thromboembolic event (stroke [i.e., ischemic, hemorrhagic or cryptogenic] that is an acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥24 hours or resulting in death) or major hemorrhagic complication (major bleeding) during the 12-month Evaluation Period.

10.2 Secondary Endpoints

The secondary endpoints supporting the study objective are:

Safety Endpoints:

- Minor bleeds
- Hospitalization with any thromboembolic or major hemorrhagic event
- All cause mortality

Additional Endpoints:

- QoL (SF-36)
- AF recurrence
- Repeat ablation for AF

11.0 Treatment Description

11.1 Prior Ablation Procedure

Subjects enrolled in the OAT Pilot Study have previously undergone successful cardiac ablation in accordance with institutional standards of care (SOC). SOC is the clinical work flow and process that physicians follow in their practice when using commercially available devices (without any mandated protocol requirements) as required by the investigator's institution.

11.2 Medication Management

11.2.1 OAT Management

Prior to enrollment in the OAT Pilot Study, subjects' OAT should be administered at the discretion of the investigator and in accordance with current AF management guidelines.[6; 30-32] Subjects should continue their physician-prescribed regimen for OAT until they are enrolled in the OAT Pilot Study. Subjects randomized to the OAT (Control) Group should continue their current OAT regimen; however, changes are allowed per the investigator's discretion (i.e., from one type of OAT to another) during the Evaluation Period. All commercially approved OAT medications may be prescribed to subjects in the OAT (Control) Group. Subjects in the OAT Withdrawal (Test) Group who resume OAT during the Evaluation Period, regardless of the reason, will be discontinued from the study at the time when OAT therapy is resumed.

11.2.2 AAD Management

AADs are defined as class I or class III. Subjects on a stable AAD regimen are allowed to remain on their current AAD regimen. Subjects' AAD regimen should remain constant over the course of the study.

11.2.3 Use of Additional Medications

The use of additional medications during the study will be at the discretion of the investigator for clinical indications.

11.3 Management of Arrhythmia Recurrence

If there is AF recurrence after the subject is randomized to one of the study arms, the subject should be treated according to institutional Standards of Care (SOC), which is defined as the clinical work flow that physicians follow in their practice (without any mandated protocol requirements) and the processes required by the investigator's institution. Subjects who experience an AF recurrence and/or undergo a repeat ablation or resume OAT (for subjects in the OAT Withdrawal [Test] Group) for AF will be discontinued from the study.

11.4 Schedule of Examinations

11.4.1 Study Visits

Table 3 displays the required schedule for subject treatments and evaluations for the test and control groups. Sites participating in this study have been selected on the basis of their capabilities to successfully carry out these assessments.

Table 3. Summary of Subject Assessments

	Enrollment	Randomization	Evaluation Period			
Assessments	**Screening/Enrollment (within 30 days prior to randomization)**	**Baseline/ Randomization**	**3-Month Follow up Visit (+/- 2 week)**	**6-Month Follow up Visit (+/- 2 weeks)**	**12-Month Follow up Visit (+/- 4 weeks)**	**Unscheduled Visit**
Informed Consent Form	✓					
Inclusion/Exclusion Review	✓	✓				
Clinic Visit	✓	✓	✓	✓	✓	✓
Demographics	✓					
Medical History	✓		✓	✓	✓	✓
12 lead ECG		✓	✓	✓	✓	✓
CT/MRI Scan[1]			✓[1]	✓[1]	✓[1]	✓[1]
Pregnancy Test		✓[2]				
AF Monitoring	✓[3,4]		✓[4]	✓[4]	✓[4]	
Blood Draw • INR[5]		✓	✓	✓	✓	✓
QoL		✓[6]	✓		✓	
Medication: • Concomitant Medications		✓	✓	✓	✓	✓
• Anticoagulation		✓	✓	✓	✓	✓
• AAD		✓	✓	✓	✓	✓
Adverse Events	✓[7]	✓	✓	✓	✓	✓

1. A CT/MRI Scan should be performed to exclude PV stenosis for subjects who are symptomatic.
2. In pre-menopausal women only, if the subject may be pregnant according to menstrual period history. Test must be performed within 72 hours of pre-randomization.
3. A 7-Day Holter Monitor is required at screening during the pre-randomization AF monitoring. Subjects with an ICD or pacemaker may use interrogations for the duration 7 days and within 30 days prior to randomization.
4. Refer to the AF Monitoring description (Section 11.4.2, Subject Assessment Details) for additional information regarding when subjects are required to monitor their heart rhythm for each visit.
5. Only applicable for subjects randomized to the OAT arm.
6. Prior to randomization
7. Once a subject has signed the ICF, all adverse events associated with study required assessments must be collected.

11.4.2 Subject Assessment Details

12-lead Electrocardiogram (ECG)

Data from 12-lead ECG recordings will be collected as described in Table 3. Data from unscheduled ECG's between two consecutive follow-up visits will be collected at the next scheduled visit. A copy of the ECG should be filed in the subject's medical chart with the participating investigator.

Cardiac Computed Tomography (CT) / Magnetic Resonance Imaging (MRI)
A cardiac multi slice CT or MRI should be performed on symptomatic subjects to exclude PV stenosis.

AF Monitoring: Holter Monitor (7-day)
All subjects who have signed the study ICF are required to undergo AF monitoring prior to randomization. The pre-randomization AF monitoring will be conducted by Holter Monitor.

- **Screening/Enrollment:** Subjects will be provided with a 7-day Holter Monitor to confirm that they are free from AF recurrence prior to randomization into one of the study arms. At the end of the Holter Monitoring period, subjects are to send their Holter Monitor to the core lab for analysis.
  - (Subjects are permitted to remove their Holter Monitor during certain activities of daily living during which wearing the device would not be recommended or is impractical (e.g., bathing). However, subjects must be encouraged to be as compliant as possible with Holter Monitoring so that heart rhythm status data can be captured consistently and completely.)

- **Follow-up Visits:** Subjects who are randomized to the off-OAT cohort, it is strongly recommended that some type of continuous monitoring should be performed to screen for asymptomatic AF at regular intervals as noted in the 2012 HRS Expert Consensus Statement[33]. At minimum, AF monitoring duration should be for no less than 48 hours and no less frequent than every 6 months. The outcome of the AF monitoring must be clearly documented in the source document and eCRFs. If there is a recurrence of AF, the subject should be treated as described in Section 11.3 – Management of Arrhythmia Recurrence.

For subjects with an implantable cardioverter defibrillator (ICD) or artificial cardiac pacemaker, interrogations for the duration of and within the windows for AF monitoring will be accepted.

Pregnancy Test
A urine sample pregnancy test must be obtained within 72 hours prior to randomization in pre-menopausal women only, if the subject may be pregnant by the history of their menstrual period.

Quality of Life Questionnaire
The SF-36 Questionnaire must be completed by the subjects prior to randomization and at specified follow-up visits according to Table 3.

Adverse Events (AEs)
Any untoward medical occurrence in a subject whether or not there is a relationship between the AE and the drug therapy administered will be documented and reported to the Sponsor as outlined in the Adverse Events Reporting Section (12.0) of this protocol.

Medication
All concomitant medication will be documented in the subject's chart and reported on the appropriate electronic case report form(s) (eCRF[s]). Any new medications or changes to existing medication will also be captured in the eCRFs. In case an AE is related to intake of drugs, details must be provided on the appropriate eCRF(s), including the AE form.

11.4.3 Unscheduled Visits

If a subject returns for visit outside of the protocol-defined visit windows provided in the Study Visits Section (11.4.1) of this protocol, the visit will be considered "unscheduled". If the unscheduled visit is for any purpose other than a repeat ablation procedure, an unscheduled visit CRF must be completed and the subject must also return for their next scheduled study visit. A list of the requested/recommended assessments that should be performed during the unscheduled visits is included in Table 3.0. If the unscheduled visit is for arrhythmia recurrence, the subject must be discontinued from the study as previously indicated in the Subject Disposition Section (9.6) of this protocol. All appropriate forms (eg, Final Status Form) must be completed for subjects that are discontinued due to arrhythmia recurrence within the Evaluation Period.

11.5 Core Laboratories for Evaluation Tests

A core laboratory will be used for the objective evaluation of Holter Monitor data. Initial evaluations will be performed by technical personnel trained in the evaluation of these tests, and will be reviewed by a cardiologist or an experienced EP technician. AF episodes will be evaluated per the definitions provided in this protocol.

12.0 Adverse Event Reporting and Documentation

Adverse event information will be collected throughout the study and will be recorded on the eCRFs by the study investigator or study coordinator per the reporting requirements outlined in table 8: AE Reporting Requirements below. Each AE must be reported regardless of classification, seriousness, intensity, outcome or causality. All AEs will be monitored until they are adequately resolved or explained in accordance with prevailing regulatory requirements.

12.1 Definitions / Classifications

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs or symptoms (including abnormal laboratory value, or other medical event) in subjects, whether or not related to study medication. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline, are adverse events if the investigator determines they are clinically significant.

NOTE: Specifically for drug-related AEs (adverse drug reaction; ADR) the following definition applies: Regarding marketed medicinal products, a drug-related AE or adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. All drugs taken per protocol requirements will be considered for AE reporting.

NOTE: AF recurrence by itself is considered a recurrence of disease (pre-existing condition) and therefore does not meet the definition of an AE, unless it is a worsening compared to the preexisting condition; and unless AF recurrence meets at least one of the conditions for an SAE.

Serious Adverse Event (SAE):
A SAE is an event that:

- Lead to a death.
- Lead to a serious deterioration in the health of a subject that:
  - — resulted in a life-threatening illness or injury;
  - — resulted in a permanent impairment of a body structure or a body function;
  - — required in-patient hospitalization or prolongation of existing hospitalization; or
  - — resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: A planned hospitalization for a pre-existing condition (without serious deterioration in health) is not considered a serious adverse event. An AE would meet the criterion of "hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay). Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

Unanticipated Adverse Event:

An unanticipated AE is a serious event not previously identified in nature, severity or degree of incidence, or any other unanticipated serious problem associated with the commercially approved OAT that relates to the rights, safety or welfare of subjects.

Adverse Events (AE) associated with OAT can be found in the package insert for commercially approved drugs (listed under Adverse Reactions). AEs deemed related to OAT that are not found within the package insert will be considered unanticipated AEs.

Anticipated Adverse Events:

All AEs listed in the package insert for a subject's prescribed OAT will be considered anticipated adverse events for purposes of this study.

12.2 Causality

Regarding the causality of each OAT-related AE, the investigator will assess and evaluate the causality of the AE as related to the use or discontinuation of OAT according to the following classifications:

Table 4: Adverse Event Causality Classifications

Definitely	The drug directly caused or contributed to the AE
Probably	The drug likely caused or contributed to the AE
Possibly	The drug may have caused or contributed to the AE
Not Related	The drug did not cause or contribute to the AE

12.3 Intensity / Severity

Regarding the intensity/severity of each AE, the investigator will assess and evaluate the relationship according to the following definitions:

Table 5: Adverse Event Intensity or Severity Definitions

Mild	Any event that results in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure, or that requires intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is life threatening and results in permanent impairment of a body function or damage to a body structure, or that requires significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

12.4 Outcome

Regarding the outcome of each AE, the investigator will assess and evaluate the relationship according to the following classifications:

Table 6: Adverse Event Outcome Classifications

Classification	Definition
Resolved without sequelae	Subject fully recovered with no observable residual effects
Resolved with sequelae	Subject recovered with observable residual effects
Improved	Subject's condition improved, but residual effects remain
Unchanged	AE is ongoing
Worsened	Subject's overall condition worsened
Death	Subject died as a result of the AE

12.5 Adverse Event Documentation and Reporting Requirements:

AE information will be collected throughout the study and will be recorded on eCRFs. The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the Adverse Events Section (12.0) of this protocol. All AEs must be assessed by the study investigator and properly documented by completing the subject's medical records (source documents) and appropriate eCRF. Additional documentation may be requested by the Sponsor, including but not limited to, a written subject narrative detailing the clinical course of the AE, a copy of any correspondence with the local EC/EB, and extracts from medical records (patient identifies removed). All AEs will be monitored until they are adequately resolved or explained.

Table 8: AE Reporting Requirements

Type of Adverse Event	Reporting Requirements
Non-Serious and Anticipated Adverse Events	Report to Sponsor within **7 days** of awareness
Serious Adverse Events	Report to Sponsor within **24 hours** of awareness
Unanticipated AEs	Report to Sponsor within **24 hours** of awareness
Subject Death	Report to Sponsor within **24 hours** of awareness

The Sponsor will confirm that (serious) AEs are reported as required to the:

- **To Institutional Review Board (or equivalent):** The site is responsible for ensuring that all (serious) AEs are fully recorded and reported to the IRB (or equivalent) according to the local requirements.

- **To Global Safety Monitoring Committee (GSMC):** The sponsor will forward all reported SAEs to the GSMC. The GSMC will evaluate whether the event is unanticipated, the seriousness, the relationship with/to the OAT (as applicable), and the perceived risk for the other study centers. The GSMC will determine whether the event is drug-related. Additional detail regarding the GSMC is provided in the Study Management Section (15.0) of this protocol.

13.0 Statistical Analysis Plan

13.1 Study Objective

The objective of this study is to assess whether the patients who discontinued OAT after a successful AF ablation are not inferior to the group of patients who continued OAT after a successful AF ablation in terms of the composite endpoint of all ischemic and hemorrhagic events.

13.2 Primary Endpoint

The primary endpoint is a composite endpoint represented by the occurrence of any major thromboembolic event (stroke [i.e., ischemic, hemorrhagic or cryptogenic] that is an acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥24 hours or resulting in death) or major hemorrhagic complication (major bleeding) during the 12-month Evaluation Period.

13.3 Sample Size

A total sample size of 100 (50:50) subjects will be enrolled in this pilot study. This is a pilot study and is not statistically powered to make a statistical inference.

13.4 Analysis Population

The study contains two treatment arms with subjects either discontinuing OAT or continuing OAT. The primary analysis will be based on the intent-to-treat principle where subjects will be analyzed by the group to which they are randomized, regardless of actual treatment received. Lost-to-follow-up, discontinued, and withdrawn / early termination subjects will also be included in this analysis.

13.5 Analysis by Subject Disposition

The number of subjects that are enrolled, excluded, discontinued, prematurely withdrawn from the study, and lost to follow-up will be summarized and listed by randomization group, by gender, and by study site.

13.6 Demographic and Baseline Characteristics

The descriptive statistics of demographic and baseline characteristics include but are not limited to (1) age; (2) gender; (3) race; (4) ethnicity; (5) medical history conditions; and (6) AF history and will be presented overall and by randomization group. The descriptive statistics including number of subjects, mean, median, 25th and 75th percentiles, minimum, maximum and standard deviation will be presented for continuous variables. Frequency and percentage will be presented for categorical variables. The Fisher exact test will be used to examine the categorical demographic and baseline characteristics between two randomization groups. Wilcoxon rank sum test will be used for the continuous variables.

13.7 Endpoint Analyses

13.7.1 Primary Endpoint Analysis

The primary endpoint is the occurrence of any thromboembolic event or major hemorrhagic complications during the 12-month Evaluation Period.

The Kaplan-Meier method will be used to model the time to the first occurrence of any thromboembolic event or major hemorrhagic complications during the 12-month Evaluation Period following randomization. The survival probabilities of the occurrence of any thromboembolic event or major hemorrhagic complications at the 12 month follow-up along with the corresponding 95% confidence intervals will also be presented. The equality of the survival curves between two randomization groups will be tested by the Log-rank test.

This analysis will include all subjects in the analysis population and account for censored observations. Subjects lost to follow-up, withdrew or discontinued prior to reaching their primary endpoint will be censored at their last visit.

Descriptive statistics such as 25th percentile, median and 75th percentile of time to the first occurrence as well as the 95% confidence intervals around the median time will be presented overall and by randomization groups.

The number and proportion of subjects experiencing occurrence of any thromboembolic event or major hemorrhagic complications will be summarized overall and by two randomization groups at 12 month follow up. The Fisher exact test will be used to compare the proportions between the two randomization groups.

13.7.2 Analysis of Secondary Endpoints

Descriptive statistics including frequency and percentage for categorical secondary endpoints will be presented. The categorical secondary endpoints include minor hemorrhagic events (minor bleeds), hospitalization with any thromboembolic or major hemorrhagic event, all cause mortality, AF recurrence and repeat ablation procedures for AF.

The 95% confidence intervals for binary outcome will be computed using exact binomial method. Descriptive statistics and 95% confidence intervals will be presented overall and by randomization groups. The proportion of the occurrence will be compared between randomization groups using the Fisher exact test.

Descriptive statistics for continuous endpoints will include number of subjects, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum. These continuous secondary endpoints include the index scores of the SF-36. Change from baseline for the index score of the SF-36 will be compared between two randomization groups using the Wilcoxon rank sum test.

13.7.2.1 Minor Hemorrhagic Events (Minor Bleeds) (%)

A minor hemorrhagic event (minor bleed) is defined as clinical bleeds that do not fulfill the criteria for major bleeds. Descriptive statistics and type of minor hemorrhagic event will be summarized and listed by randomization groups.

13.7.2.2 Hospitalization with any thromboembolic or major hemorrhagic event (%)

Descriptive statistics and type of event will be summarized by randomization groups.

13.7.2.3 All Cause Mortality (%)

Descriptive statistics of subjects who die during the 12-month Evaluation Period will be summarized by randomization groups. Causes of death will be listed and summarized by randomization groups.

13.7.2.4 AF Recurrence

Descriptive statistics of subjects experiencing the recurrence of AF during the 12 month Evaluation Period will be summarized by randomization group.

13.7.2.5 Repeat Ablation for AF

Descriptive statistics of subjects undergoing repeat ablations for AF during the 12-month Evaluation Period will be summarized by randomization groups.

13.7.2.6 Quality of Life

SF-36
Quality of life (SF-36®) at 3 and 12months after randomization will be compared to baseline. Change from baseline in physical component summary (PCS) and mental component summary (MCS) will be calculated and tested.

13.7.3 Interim Analyses

There are no interim analyses planned for this study.

14.0 Administrative Responsibilities

14.1 Ethics Committee/Institutional Review Board (EC/IRB) Review

Before initiating this study, the Sponsor will work with the investigator to obtain approval from the EC/IRB (or equivalent) and fulfill any local, applicable requirements for notification to competent authorities. The investigator will obtain written and dated approval from the responsible EC/IRB (or equivalent) for the study protocol (or amendment[s]) and informed consent before enrollment of subjects. Biosense Webster and the EC/IRB (or equivalent) must approve in writing any changes to the protocol that affect the rights safety and/or welfare of the subjects, or may adversely affect the validity of the study.

A signed copy of the EC/IRB (or equivalent) Approval Form and a signed copy of the EC/IRB (or equivalent) approval letter addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the study by their EC/IRB (or equivalent).

14.2 Informed Consent

The investigator will obtain written and dated approval from the responsible EC/IRB (or equivalent) for the study informed consent form (ICF template is provided in a separate document). A patient's informed consent must be obtained and documented per institutional, EC/IRB (or equivalent), and applicable regulatory requirements. The informed consent may be translated as appropriate.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the investigator or designee. Patients should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the study. A patient or his/her legal representative must be given ample time and opportunity to inquire about details of the study and all questions about the study should be answered to the satisfaction of the patient or their representative.

Prior to participation in the study, the investigator or designated member of the research team will obtain written informed consent from the subject. The background of the proposed study and the potential benefits and risks of the study should be explained to the subject. The subject or legal representative must sign the ICF prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The written ICF should be signed and personally dated by the patient or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee) and this process should also be documented in the subjects' medical records. If the patient or his/her legal representative is unable to read the consent form, a witness should be present during the entire informed consent discussion. After the informed consent form is read to or by the patient and signed by the patient or his/her legal representative, the witness should also sign the consent form, attesting that informed consent was freely given by the patient or his/her legal representative.

The patient or his/her legal representative must receive a copy of the signed and dated informed consent form. An original copy of the EC/IRB-approved ICF must be maintained by each investigator in a designated study administrative file and a copy should be filed in the subjects medical records.

14.3 Subject Confidentiality

All information and data sent to Biosense Webster concerning subjects or their participation in this study will be considered confidential. During this study, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities. Information and data collected and used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. No information that can be used to identify subjects will be collected. Only authorized Biosense Webster personnel or representative, local government authorities, or federal agencies (eg, U.S. FDA) acting in their official capacities will have access to these confidential files.

14.4 Study Monitoring

The clinical site will be monitored periodically by Sponsor personnel or an appropriately qualified and trained designee for protocol adherence, accuracy of eCRFs, verification with source documents and compliance with applicable regulations. If data entry or source documentation errors are discovered during the site visit, corrections will be made at that time by the site personnel. The monitor will create electronic data clarification queries to request data clarification or data correction, if at the time of the site visit, corrections cannot be made. The Principal Investigator will sign off for the accuracy of the final data reported to the Sponsor.

Each monitoring visit may include, but is not limited to, the following:

- Verification that the informed consent was properly obtained for all subjects and completed prior to any study required test(s)
- Confirm that randomization procedures are being followed
- Source document verification against the eCRFs
- Verification of a complete Regulatory Binder; Delegation of Responsibility Log, etc.
- Identification and management of any issues or problems with the study

Biosense Webster may request further documentation such as investigator and/or electrophysiology (EP lab procedure notes when complications or product malfunctions are observed. To this end, the investigator and institution must permit inspection of the study files and subjects' eCRFs by Sponsor personnel.

14.5 Management of Protocol Amendments

All instructions described in this study protocol are to be followed. If an amendment is required, it must be made in written form and receive approval from persons (or their designee if they are no long available to review and approve the protocol) and authorities who approved the original protocol. Administrative changes (which do not affect patient's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

14.6 Management of Protocol Deviations

The investigator will not deviate from the protocol without **prior notification to and written approval** from Biosense Webster, Inc. except or in unforeseen, isolated instances to protect the safety and well being of the subject. In medical emergencies, prior approval for protocol deviations will not be required, but the Biosense Webster clinical operations personnel must be notified within 5 days of the deviation. All protocol deviations will be documented and followed up according to the applicable Standard Operating Procedures (SOPs). Any evident pattern of non-compliance with respect to applicable standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the site will be asked to withdraw.

14.7 Data Management

The Sponsor or designee will perform all data management activities for this trial. These activities include development and validation of a clinical database, into which all study data will be entered. The Sponsor or designee will be responsible for ensuring overall integrity of the data and database.

14.7.1 Data Collection

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during this trial. The eCRFs will be developed to capture the information outlined in this protocol. Data collected on these eCRFs will be analyzed as defined in the study protocol. Modification of the eCRFs will only be made if deemed necessary by Biosense Webster.

14.7.2 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that study data are properly recorded on each subject's eCRFs and related documents.. The investigator is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRFs will be monitored by Biosense Webster personnel, or an appropriately qualified and trained designee, at regular intervals throughout the trial. The investigator and institution must permit the inspection of any trial-related documentation and eCRFs by such representatives and/or responsible government agencies.

All eCRFs should be completed by the designated site personnel within14 days of the subject visit. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines within this study protocol.

14.7.3 Source Documentation

Source documents will serve as the basis for monitoring the eCRFs. Source documents may include subject's medical records, hospital charts, clinical charts, the investigator's subject study files, admissions and discharge summaries, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms.

If no standard hospital or office document exists to capture information that may be unique to this study, a worksheet may be developed to record this information, which shall be signed by the PI at the given site and serve as the source document for unique study data.

Electronic subject records will be considered source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records will have to be printed and added to the subject's paper file. A print-out of an eCRFs cannot be used as source documentation.

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained on source documentation:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes on the day of entry into the study including the name of the study sponsor (Biosense Webster), protocol number, clinical site identifier, subject number assigned and a statement that consent was obtained.
- Dated and signed notes from each study visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- AEs reported and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results, etc.
- Notes regarding protocol-required medication and prescription medications taken during the study (including start and stop dates).

- Study subject's condition upon completion of or withdrawal from the study.

14.7.4 Data Verification and Review

All eCRFs will be subjected to automated and manual validation checking for omitted data, gross data inconsistencies, and timeliness of reporting. Biosense Webster, Inc. will employ a clinical trials database on a server, available to site and sponsor personnel over an Internet connection. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data entry errors.

14.7.5 Final Data Analysis

All exported datasets for analyses will undergo a final data review prior to final database lock. Once all critical data are monitored and locked, the final analyses of study data will be performed.

14.7.6 Confidentiality and Protection of Study Data

To ensure confidentiality, protection, and attribution of the clinical study data, only trained and authorized sponsor and site personnel will be assigned unique user accounts and passwords to access the clinical trial database. Each user account is designed to allow appropriate user rights and access level with the clinical trials database system.

14.7.7 Publication Policy

Publication of study results will be coordinated between Biosense Webster, Inc. and the Physician Advisory Committee members. Authorship will be determined by Biosense Webster prior to development of any manuscript.

15.0 Study Management

15.1 Sponsor Responsibilities

The Sponsor (Biosense Webster, Inc. or an appropriately qualified and trained designee (ie, a CRO that has been contracted by Biosense Webster, Inc. to assist with study management) will be responsible for the following:

- Investigator selection
- Inform investigator of his/her responsibilities
- Selection of members of the Physician Advisory Committee (PAC) and the Global Safety Monitoring Committee (GSMC)
- Ensure that appropriate training/information is provided to the study investigators and
- Staff
- Obtain study contracts with investigators/hospitals, CROs and other involved parties
- Preparing (and modifying, if needed) study documents including but not limited to the protocol, eCRFs and ICF template
- Completing pre-study site assessments and approvals
- Monitoring the study throughout its duration
- Database input, management and maintenance
- Conducting all communications to applicable authorities
- Informing Investigators of their responsibilities
- Preparing reports summarizing the status of the clinical study which will be supplied to the Principal Investigator at each site
- Ensure that all AEs are reported by the study investigators and where appropriate, are reported to the other investigators and relevant regulatory authorities

15.2 Investigator Selection

Biosense Webster will select investigators qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. Furthermore, each investigator is expected to make a self assessment of his/her qualifications after considering the study protocol and demands of the study. The investigator's signature on the Protocol signature page constitutes an affirmative assertion that he/she is qualified to conduct the study and constitutes the investigator's commitment to abide by the study protocol requirements.

15.3 Investigator Training

Training of appropriate clinical site personnel will be the responsibility of the Sponsor. To ensure uniform data collection and protocol compliance, Sponsor personnel or designee will present to the study site personnel including but not limited to reviewing the applicable Good Clinical Practice (GCP) guidelines, the protocol, the case report form and data collection process, randomization process, and the safety and complaint reporting processes.

15.4 Investigator Responsibilities

- Work with CRO to obtain IRB/EC approval
- Provide the Sponsor with:
  - Annual IRB (or equivalent, eg, EC/EB) approval letters and IRB (or equivalent, eg, EC/EB) approved consent forms
  - Fully executed Clinical Study Agreement
  - Completed Financial Disclosures
  - Curriculum vitae for Investigator(s) and relevant study staff
  - Copy of the annual report to the EC/IRB from the investigator
- Completing the appropriate training the study protocol prior to enrolling and treating subjects
- Obtain informed consent form and enroll patients
- Perform medical procedures per protocol
- Order all tests required by the study protocol
- Adhere to the study protocol
- Follow subjects until the end of the study protocol
- Complete eCRFs on time, completely and accurately
- Allow the Sponsor direct access to source documents to perform monitoring duties, and to perform audits
- Maintain records and provide reports according to the local legislation/regulations
- Share all relevant study-related information with colleagues involved in this study
- Inform the appropriate entities (eg, Sponsor, Biosense Webster, Inc.'s Complaints Management Department, the EC / EB) in a timely manner regarding the occurrence of any AEs

At a minimum, the records listed below are to be maintained by the investigator:

- Study protocol and all amendments
- Signed Clinical Study Agreement
- IRB/EC approval letter, including approved ICF document
- IRB/EC membership list
- Correspondence relating to the study
- CVs for all investigator(s)
- Site personnel delegation of authority/responsibility
- Clinical Monitor/Site Visit sign-in log
- Subject enrollment log
- Lab certification and lab test normal ranges (pregnancy test, INR)
- Reports (e.g. annual reports, final reports from investigator and Sponsor)

The following records must be maintained for each subject enrolled in the study:

- Signed patient ICF
- All completed CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death

The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur while the subject is enrolled in the study. Biosense Webster reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

15.5 Physician Advisory Committee (PAC)

The responsibilities of the PAC include:

- Consultation on study design, protocol development, and investigator training
- Ensure investigators compliance with the protocol
- Provide support regarding emergent issues:
  - Advising the Sponsor of any unforeseen medical issues identified during the clinical study
  - Addressing patient medical concerns or conditions raised by investigators as related to the use of the continuation/discontinuation of OAT
- Review of evidence results (assist in data interpretation)
- Publication Committee (strategy and consultation)

15.6 Global Safety Monitoring Committee (GSMC)

All AEs will be monitored until they are resolved or explained. Each AE will be reported regardless of severity, outcome, or causality. To minimize risks to subjects enrolled in the clinical investigation, the sponsor will convene a formal Global Safety Monitoring Committee (GSMC) to review the safety data and recommend appropriate action(s) to ensure subject safety.

The GSMC is tasked with adjudicating severity and causality of adverse events. Activities related to the collection of source documentation and narrative writing for events presented for adjudication by the GSMC will be performed by the sponsor or designee. In addition to reviewing individual adverse events, the GSMC may also review the accumulated safety data for the clinical investigation. Sponsor or designee will collect and compile the information packets or listings for the GSMC to review. Biosense Webster will manage the GSMC.

16.0 Regulatory / Ethical Considerations

16.1 Basic Principles and Standards

This clinical study will be conducted according to applicable regulatory requirements and good clinical practice (GCP) guidelines including but not limited to:

- ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice 21 CFR
- Declaration of Helsinki
- ICH E6 Good Clinical Practice
- Medical Device Directive 93/42/EC
- MEDDEV 2.12-1 Guidelines on a Medical Devices Vigilance System

16.2 Record Retention and Archiving

Each site will be asked to maintain study records for at least two years after the study is completed unless otherwise instructed by local requirements. The Sponsor will maintain study records according to the applicable Biosense Webster procedures.

17.0 References

1. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulation therapy, warfarin, compared with dibigatran. Am Heart J 2009;157:805-810e2.

2. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004; 90: 286-292.

3. Miyasaka, Y., et al., Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006; 114:119-25.

4. Wolf PA, Dawber TR, Thomas HE, Kannel WB; Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973-7.

5. Flegel KM, Shipley MJ, Rose G Risk of stroke in non-rheumatic atrial fibrillation. Lancet 1987;1:526-9.

6. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006; 114: e257-354.

7. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; 61: 755-9.

8. Al-Saady, N. M., O. A. Obel, et al. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999; 82: 547-54.

9. Hart RG, Benavente O, et al.Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999; 131: 492-501.

10. Emmerich J, Le Heuzey JY, et al. Indication for antithrombotic therapy for atrial fibrillation: reconciling the guidelines with clinical practice. Eur Heart J 2005; 7: C28-C33.

11. Torn M, Bollen WL, et al. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med 2005; 165: 1527-32.

12. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. J Am Coll Cardiol 2004; 43: 929-35.

13. Patel MR, Mahaffey KW, Garg J, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365:883-891.

14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361 (12):1139-1151.

15. Banerjee A, Deirdre L, Torp-Pedersen C, Lip GYH. Net clinical benefit of new oral anticoagulants (dabigitran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study. Thromb Haemost 2012; 107:584-589.

16. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le MA, Le MP, Clementy J (1998) Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 339 659-666.

17. Bonanno C, Paccanaro M, La Vecchia L, Ometto R, Fontanelli A. Efficacy and safety of catheter ablation versus antiarrhythmic drugs for atrial fibrillation: a meta-analysis of randomized trials. J Cardiovasc Med 2010;11:408–418.

18. Nair GM, Nery PB, Diwakaramenon S, Healey JS, Connolly SJ, Morillo CA. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2009; 20(2):138-44.

19. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol 2009;2:349-361.

20. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. Circ Arrhythmia Electrophysiol 2009;2(6):626-33.

21. Noheria A, Kumar A, John V. Wylie JV, Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. Arch Intern Med 2008;168(6):581-586.

22. Chao TF, Lin YJ, Tsao HM, Tsai CF, Lin WS, Chang SL, Lo LW, Hu YF, Tuan TC, Suenari K, Li CH, Hartono B, Chang HY, Ambrose K, Wu TJ, Chen SA. CHADS(2) and CHA(2)DS(2)-VASc Scores in the Prediction of Clinical Outcomes in Patients With Atrial Fibrillation After Catheter Ablation. Am Coll Cardiol. 2011 Nov 29; 58(23):2380-5.

23. Oral H, Chung A, Ozaydin et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation 2006; 114: 759-65.

24. Nademanee K, Schwab MC, Kosar EM, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol 2008; 51:843-9.

25. Rossillo A, Bonso A, Themistoclakis S, et al. Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. J Cardiovasc Med.2008; 9: 51-5.

26. Corrado A, Patel D, Riedlbauchova L, Fahmy TS, Themistoclakis S, Bonso A, Rossillo A, Hao S, Schweikert RA, Cummings JE, Bhargava M, Burkhardt D, Saliba W, Raviele A, Natale A. Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. J Cardiovasc Electrophysiol.2008; 19:807-11.

27. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WI, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol. 2010 Feb 23;55(8):735-43;

28. Prystowsky E, Themistoclakis S, Brachmann J, Callans D, Connolly S, Lip GY, Waldo AL. Anticoagulation issues. In Natale A, Raviele A (eds): Atrial fibrillation ablation. Blackwell Futura.2007:41-50.

29. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. J Cardiovasc Electrophysiol 2009; 20: 988-93.

30. Calkins H, Chair, Brugada J, Co-Chair, (2007) HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. Heart Rhythm 4:1-46.

31. Camm JA, Kirchhof P, Lip GY, *et al.* Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the european society of cardiology (ESC). Eur Heart J 2010; 31:2369-2429.

32. Wann SL, Curtis AB, January CT, *et al.* 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 123:104-123.

33. Calkins, H., Kuck, K.H., Cappato, R., et al. (2012) HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. J Interv Card Electrophysiol.: Mar 2012; 33(2):1-87

Appendix A: Commonly Prescribed Oral Anticoagulation and Antiplatelet Therapies

In all countries, apart from Germany, any commercially available OAT may be prescribed.
In Germany only patients who are prescribed therapies included on the following list may be included in this study.

Anticoagulation Medications
Warfarin sodium
Dabigatran etexilate mesilate
Rivaroxaban
Phenprocourmon

Antiplatelet Medications
Clopidogrel hydrochloride
Clopidogrel besilate
Clopidogrel hydrogen sulphate
Prasugrel hydrochloride
Ticagrelor
Acetylsalicylic acid