

Accepted Manuscript



Rationale and design of the Apixaban for the reduction of thrombo-embolism in patients with Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial

Renato D. Lopes, Marco Alings, Stuart J. Connolly, Heather Beresh, Christopher B. Granger, Juan Benezet Mazuecos, Giuseppe Boriani, Jens C. Nielsen, David Conen, Stefan H. Hohnloser, Georges H. Mairesse, Philippe Mabo, A. John Camm, Jeffrey S. Healey

PII: S0002-8703(17)30127-8
DOI: doi: [10.1016/j.ahj.2017.04.008](https://doi.org/10.1016/j.ahj.2017.04.008)
Reference: YMJJ 5435

To appear in: *American Heart Journal*

Received date: 3 February 2017
Accepted date: 21 April 2017

Please cite this article as: Lopes Renato D., Alings Marco, Connolly Stuart J., Beresh Heather, Granger Christopher B., Mazuecos Juan Benezet, Boriani Giuseppe, Nielsen Jens C., Conen David, Hohnloser Stefan H., Mairesse Georges H., Mabo Philippe, Camm A. John, Healey Jeffrey S., Rationale and design of the Apixaban for the reduction of thrombo-embolism in patients with Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial, *American Heart Journal* (2017), doi: [10.1016/j.ahj.2017.04.008](https://doi.org/10.1016/j.ahj.2017.04.008)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Trial Design**Rationale and design of the Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial**

RCT# NCT01938248

Renato D. Lopes, MD, MHS, PhD,¹ Marco Alings, MD, PhD,² Stuart J. Connolly, MD,³ Heather Beresh,³ Christopher B. Granger, MD,¹ Juan Benezet Mazuecos, MD,⁴ Giuseppe Boriani, MD, PhD,⁵ Jens C. Nielsen, MD, DMSc,⁶ David Conen, MD, MPH,^{3,7} Stefan H. Hohnloser, MD,⁸ Georges H. Mairesse, MD,⁹ Philippe Mabo, MD,¹⁰ A. John Camm, MD,¹¹ and Jeffrey S. Healey, MD³

¹Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC; ²Working Group on Cardiovascular Research, Utrecht, The Netherlands; ³Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Canada; ⁴Hospital Universitario Fundación Jimenez Díaz-Quironsalud, Madrid, Spain; ⁵Cardiology Division. Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena University Hospital, Modena, Italy; ⁶Aarhus University Hospital, Aarhus, Denmark; ⁷Department of Medicine, University Hospital, Basel, Switzerland; ⁸Department of Cardiology, Johann Wolfgang Goethe University Hospital, Frankfurt, Germany; ⁹Cliniques du Sud Luxembourg, Arlon, Belgium; ¹⁰Hôpital Pontchaillou, Rennes, France; ¹¹St. George's University of London and Imperial College London, London, United Kingdom.

Short title: ARTESiA Rationale and Design

Address for correspondence: Renato D. Lopes, MD, MHS, PhD, Duke Clinical Research Institute, Box 3850, 2400 Pratt Street, Room 0311 Terrace Level, Durham, NC 27705. E-mail: renato.lopes@duke.edu; Phone: 919-668-8241; Fax: 919-668-7056.

ABSTRACT

Background: Device-detected subclinical atrial fibrillation (AF) refers to infrequent, short-lasting, asymptomatic AF that is detected only with long-term continuous monitoring.

Subclinical AF is common and associated with an increased risk of stroke; however, the risk of stroke with subclinical AF is lower than for clinical AF, and very few patients with subclinical AF alone have been included in large AF anticoagulation trials. The net benefit of anticoagulation in patients with subclinical AF is unknown.

Design: ARTESiA is a prospective, multicenter, double-blind, randomized controlled trial, recruiting patients with subclinical AF detected by an implanted pacemaker, defibrillator, or cardiac monitor, and who have additional risk factors for stroke. Patients with clinical AF documented by surface electrocardiogram will be excluded from the study. Participants will be randomized to receive either apixaban (according to standard AF dosing) or aspirin 81 mg daily. The primary outcome is the composite of stroke, transient ischemic attack with diffusion-weighted magnetic resonance imaging evidence of cerebral infarction, and systemic embolism. Approximately 4000 patients will be enrolled from around 230 clinical sites, with an anticipated mean follow-up of 36 months until 248 adjudicated primary outcome events have occurred.

Summary: ARTESiA will determine whether oral anticoagulation therapy with apixaban compared to aspirin reduces the risk of stroke or systemic embolism in patients with subclinical AF and additional risk factors.

Key Words: apixaban, aspirin, atrial fibrillation, oral anticoagulation, stroke

Background

Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide. The presence of AF increases the risk of stroke, and AF-related strokes are associated with higher mortality than strokes unrelated to AF. About one sixth of strokes are attributable to documented AF (1).

Modern pacemakers and implantable cardioverter defibrillators (ICDs) can continuously monitor atrial rhythm. In patients with a pacemaker but without evidence for AF, device-detected atrial high-rate arrhythmias are common (2,3). These episodes, referred to as subclinical AF, are typically asymptomatic, of short duration (minutes to hours), and infrequent (4). Thus, subclinical AF differs from permanent, persistent, and paroxysmal AF diagnosed by various forms of surface electrocardiogram (ECG) monitoring. However, although subclinical AF is associated with stroke, the increase in risk appears to be somewhat lower than that with clinical AF (3,5).

Subclinical AF and stroke risk

Several studies have shown an association between the presence of subclinical AF and the risk of stroke. The summarized results of the trials that have investigated the risk of stroke associated with subclinical AF have recently been published (4). In the Mode Selection Trial in Sinus Node Dysfunction study, patients with sinus node dysfunction were randomized to dual chamber rate-modulated or single chamber ventricular pacing. In a subgroup analysis of this study, the presence of subclinical AF, defined as an atrial rate >220 bpm and lasting ≥ 5 minutes, was independently associated with death or non-fatal stroke (5). In the Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS) trial, patients with an indication for a pacemaker or an ICD and an additional risk

factor for stroke were included (2). Subclinical AF was defined as an episode of a rapid atrial rate >170 bpm, lasting ≥ 20 seconds. At the end of a mean follow-up of 1.4 years, at least one episode of subclinical AF was observed in 47% of patients. In this study, the presence of subclinical AF was associated with thromboembolic risk, and this risk was related to the burden of subclinical AF. Subclinical AF duration of >5.5 hours/day (the median value in the study) doubled the risk for thromboembolic events to 2.4%/year, while no increase in stroke risk was observed in patients with a lower burden of subclinical AF (2).

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing (ASSERT) study included patients 65 years and older with a history of hypertension, a recent pacemaker or ICD implant, and no history of AF. Subclinical AF was defined as an episode of a rapid atrial rate >190 bpm, lasting >6 minutes. Within 3 months after implantation, subclinical AF was detected in 10% of the patients. During a mean follow-up of 2.5 years, subclinical AF was detected in 35% of the patients. The presence of subclinical AF during the first 3 months after pacemaker implantation was associated with a fivefold increase in the risk of developing clinical AF, and a 2.5-fold increase in the risk for ischemic stroke or systemic embolism (3).

Although subclinical AF is associated with stroke, this risk appears to be low compared to the stroke risk in patients with similar risk profiles and clinical AF. In TRENDS, the mean CHADS₂ score was 2.2, and the stroke rate in patients with episodes of subclinical AF was 2.4%/year (2). In ASSERT, the mean CHADS₂ score was 2.2 and 2.3 in patients with and without subclinical AF, respectively. In patients with a baseline CHADS₂ score >2 and subclinical AF detected between enrollment and 3 months, the annual stroke rate was 3.78% (3). Although this represents an almost fourfold increase compared to the annual stroke risk of

patients without subclinical AF during the first 3 months after pacemaker implantation, this is substantially lower than the >5.9% annual stroke risk of patients with clinical AF and a CHADS₂ score >2 (6). Thus, after adjustment for risk factors for stroke, subclinical AF may be associated with a lower absolute stroke risk compared with clinical AF.

Anticoagulation therapy for stroke prevention in AF and subclinical AF

The overall efficacy of anticoagulation therapy for stroke prevention in AF has been well established (7). More recently, the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention have been established in pivotal phase 3 trials with thousands of patients (8-11). Overall, when compared with warfarin, NOACs significantly reduced the risk of stroke, intracranial hemorrhage, and mortality, with similar risk for major bleeding but increased risk of gastrointestinal bleeding (12). However, there were very few subclinical AF patients enrolled in any of these large trials. Patients with pacemakers especially tend to be extremely elderly and may have a high bleeding risk from anticoagulation. Thus, it is unknown whether there is a positive risk/benefit ratio for oral anticoagulation in patients with subclinical AF, and this question can only be conclusively answered by means of a randomized clinical trial. The rationale for such a trial is further supported by the observation that with prolonged monitoring via an implanted device, subclinical AF is frequently observed. For example, in ASSERT, the cumulative incidence of a subclinical AF episode of greater than 6 minutes by 3.5 years was almost 50%. Increasingly, physicians are using implanted devices such as the Medtronic Reveal recorder to detect arrhythmias in patients and even in those without symptoms. It is also likely that in the near future, detection of subclinical AF-like episodes will be possible by means of wearable devices such as smart watches. The increasingly common

detection of subclinical AF and subclinical AF-like episodes will require better understanding of the role of anticoagulation in subclinical AF.

Given the uncertainty of the risk/benefit ratio of oral anticoagulation for stroke prevention in patients with device-detected subclinical AF, specific recommendations in most guidelines for AF management are scarce and rarely similar. The 2014 Canadian Cardiovascular Society Guidelines recommend oral anticoagulation therapy for patients with subclinical AF who are ≥ 65 years of age, with a CHADS₂ score ≥ 1 and episodes that last more than 24 hours, or for shorter episodes only if the patient is high risk, such as having a history of recent cryptogenic stroke (13). The 2016 European Society of Cardiology Guidelines, on the other hand, indicate that it is unclear whether subclinical AF implies the same therapeutic requirements as clinically overt AF, and recommend that patients with subclinical AF should undergo further ECG monitoring to document AF before initiating AF therapy (14). Few patients with subclinical AF were enrolled in the trials that studied anticoagulation in patients with AF. Thus, the question of whether this therapeutic approach is beneficial for patients with subclinical AF remained to be investigated in a large randomized trial. A four-country survey in Canada and Europe showed a heterogeneity in the opinions of cardiologists involved in the care of patients with pacemakers toward the role of anticoagulation therapy in patients with subclinical AF (15). Importantly, most of them were willing to enroll patients in a randomized trial.

The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial was designed to determine whether treatment with apixaban compared to aspirin reduces the risk of stroke or systemic embolism in patients with subclinical AF and additional risk factors for stroke. The favorable risk/benefit ratio of apixaban shown in previous AF studies (Apixaban for Reduction in Stroke and Other

Thromboembolic Events in Atrial Fibrillation [ARISTOTLE] and Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment [AVERROES]) (8,16) supports the hypothesis that prophylactic apixaban will have a net beneficial effect in patients with subclinical AF.

Methods

Study overview

ARTESiA (ClinicalTrials.gov # NCT01938248) is a prospective, multicenter, double-blind, randomized controlled trial that will recruit patients with subclinical AF detected by either a pacemaker, ICD, or insertable cardiac monitor, and who also have other risk factors for stroke and no requirement for anticoagulation therapy. Eligible, consenting patients will be enrolled and randomized to receive aspirin or apixaban. The study will be conducted at approximately 230 sites in the United States, Canada, and Europe.

This trial will be conducted in compliance with the study protocol, principles laid down in the Declaration of Helsinki, and Good Clinical Practice guidelines as defined by the International Conference on Harmonization where applicable. Prior to patient participation, written informed consent will be obtained from each patient or the patient's legally accepted representative, and will comply with the Declaration of Helsinki and applicable local regulations.

Study population

The ARTESiA trial will include approximately 4000 participants. Key inclusion and exclusion criteria are shown in **Table I**. Device interrogation output (i.e., an episode log) documenting at least one episode of subclinical AF ≥ 6 minutes in duration will be required as

evidence of eligibility. The subclinical AF episode may have occurred at any time in the past. If the episode lasted < 6 hours, electrogram documentation will also be collected for central verification. Episodes of subclinical AF ≥ 6 hours will not require electrogram documentation because previous studies have shown that there is a very high correlation between such reports and true subclinical AF (17). For these longer episodes, device logs will be considered sufficient documentation to confirm eligibility. Patients with any single episode of subclinical AF > 24 hours in duration at any time prior to enrollment will not be included.

In addition to having subclinical AF, eligible patients must satisfy the following study criteria for stroke risk: A) previous stroke, or transient ischemic attack, or systemic embolism, or age 75 years or greater; B) age 65-74 and two additional risk factors; or C) age 55-64 and three additional risk factors (**Figure 1**). The risk factors for stroke are female sex, hypertension, heart failure, diabetes, and vascular disease (coronary artery disease, peripheral artery disease, or aortic plaque) (**Table II**).

Randomization, treatment, and follow-up

Enrolled patients will be randomized (interactive web-based) in a 1:1 ratio between aspirin and apixaban (**Figure 2**). Double-blind treatment will be achieved using a double-dummy technique. Each patient will take three study pills per day: a single aspirin or placebo aspirin and two doses of apixaban or placebo apixaban. Apixaban dosage will be 5 mg twice daily (or 2.5 mg twice daily for patients having 2 or more of the following characteristics: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL). During the course of the trial, apixaban dosage will be down-titrated if patients develop 2 or more of these dose reduction criteria. Those assigned to aspirin will receive a dose of 81 mg once daily.

Follow-up will occur at 30 days after enrollment, at 6 months after enrollment, and every 6 months thereafter until the end of the study, with an anticipated mean follow-up of approximately 36 months. As this is an event-driven study, the precise termination of follow-up will occur once 248 adjudicated primary efficacy outcome events have occurred.

Study outcomes

The primary efficacy outcome is a composite of stroke and systemic embolism. Stroke will be defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours, unless supported by clear evidence of cerebral infarction on diffusion-weighted magnetic resonance imaging. Available neuroimaging studies will be considered to support the clinical impression and to determine whether there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Stroke includes transient ischemic attack with corresponding evidence of cerebral infarction on diffusion-weighted magnetic resonance imaging (18). Stroke disability will be classified using the modified Rankin Scale at day 7 or at hospital discharge (whichever comes first), and again at the next scheduled follow-up visit following the event.

A systemic arterial embolism will be considered to have occurred where there is clear evidence of abrupt occlusion of a systemic artery consistent with an embolic event. It will not include arterial occlusions that are not embolic, nor will it include pulmonary embolism. In addition to clinical signs and symptoms consistent with embolic arterial occlusion, there should be at least one of the following objective findings of arterial embolism: surgical report indicating

evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy reports.

The main safety outcome will be the occurrence of clinically overt major bleeding as defined by the International Society of Thrombosis and Haemostasis criteria: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; or bleeding causing an acute fall in hemoglobin level of ≥ 2 g/dL or leading to transfusion of two or more units of whole blood or red cells (19).

Secondary outcomes will include ischemic stroke, myocardial infarction, vascular death, total death (vascular and non-vascular), the composite of stroke, myocardial infarction, systemic embolism and total death, and the composite of stroke, myocardial infarction, systemic embolism, total death, and major bleeding. All primary events and major bleeding will be adjudicated.

Device interrogation data will be collected throughout study follow-up to allow for a better understanding of AF burden and subclinical AF frequency and duration in this population. In addition, the following cardiovascular outcomes that are common in this patient population will be assessed: clinical AF (detected by surface ECG), hospitalization for heart failure, cardioversion, and ablation for AF.

Sample size calculation and statistical analysis

Among ASSERT patients with risk factors similar to patients who will be enrolled in ARTESiA, the annual rate of stroke and systemic embolism was 2.75%. Assuming an event rate of 2.75% per year in the proposed population with an anticipated mean follow-up period of 3

years and using a two-sided significance level of 0.05, a sample size of 3719 is required to provide 80% power to detect a 35% relative risk reduction, allowing for a combined dropout and crossover rate of 8.5% over the course of the study. The study will enroll approximately 4000 participants. A total of 248 primary outcome events will be required.

The analysis of the main trial results will be performed following the intention-to-treat principle (i.e., all patients randomized in the study will be included in the analysis). Patients will be included in their assigned treatment groups regardless of the actual treatment they received. An on-treatment analysis will include all treated subjects (randomized subjects who received at least one dose of the assigned study drug). In this analysis, subjects will be categorized to the treatment group to which they were assigned unless they received the incorrect treatment. Subjects who received the incorrect treatment will be excluded from this analysis population. Follow-up will be censored at 6 days after discontinuation of study medication.

The rates of the primary efficacy outcome (stroke or systemic embolism) and primary safety outcome (major bleeding) will be presented for the two treatment groups using the Kaplan-Meier method, and comparisons between the groups will be performed using a log-rank test. Adjusted and unadjusted treatment effects as measured by the hazard ratio with two-sided 95% confidence interval will be derived by the Cox proportional hazards model. Six subgroup analyses of the main trial study outcome are prespecified to compare (1) patients whose longest baseline episode of subclinical AF is longer vs. shorter than the median value for the study population, (2) patients with different CHA₂DS₂-VASc scores, (3) patients <75 and ≥75 years of age, (4) patients with and without a prior history of stroke or transient ischemic attack, (5) patients with a chronic pacemaker/ICD/cardiac resynchronization therapy (≥ 2 years) vs. newly implanted pacemaker/ICD/cardiac resynchronization therapy (< 2 years) vs. insertable cardiac

monitor, and (6) patients with ICD vs pacemaker vs insertable cardiac monitor. Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective non-stratified Cox proportional hazards model used in the main analysis. Significant interactions in the analysis of the primary outcome will be interpreted as “flags” to prompt further investigation. Following the test of interaction, treatment effect will be estimated separately within each level of a subgroup variable using a stratified Cox proportional hazards model.

Steering and Data Monitoring Committees

The ARTESiA Steering Committee comprises the national leads from each participating country and oversees the design, execution, analysis, and reporting of the study, and will assign appropriate responsibilities to the other committees. The Steering Committee holds the primary responsibility for publication of the study results. This committee will convene regularly by teleconference for meetings to address policy issues and monitor study progress, execution, and management.

An independent Data Monitoring Committee, composed of one neurologist, two cardiologists, one thrombosis expert, and one statistician, will review serious adverse events, adverse drug effects, and primary outcome data on a 6-month basis and reports to the Steering Committee. Two formal interim analyses will be done after 82 and 164 primary outcome events have occurred.

The Data Monitoring Committee may in exceptional circumstances recommend termination of the study for a safety concern that is assessed to outweigh potential benefits. No

formal boundaries will be used for terminating the study for safety reasons, but clear and consistent evidence of net harm that overrides any benefit should be apparent. In the case that risk outweighs benefit in these two important outcomes, the committee may recommend that the study be stopped early for “harm.”

The modified Haybittle-Peto rule will be used to guide the decision regarding early stopping: a reduction of 4 standard deviations ($\alpha = 0.00006$) in the analysis of the primary outcome at the first interim analysis or 3 standard deviations ($\alpha = 0.0027$) at the second interim analysis. If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be conducted after at least 3-6 months to confirm the boundary remains crossed and that the trend in treatment effect is not temporary. The α -level for the final analysis will remain the conventional 0.05 given the paucity of interim analyses, their extremely low α -levels, and the requirement for confirmation with subsequent analyses.

Support

ARTESiA is an investigator-initiated study, supported by grants from the Canadian Institutes for Health Research, Canadian Stroke Prevention Intervention Network, the Bristol-Myers Squibb and Pfizer Alliance, Hamilton Health Sciences Foundation, and Medtronic, Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Discussion

Subclinical AF is characterized by relatively short episodes of atrial high-rate arrhythmias that are detected only with continuous monitoring and are mostly asymptomatic.

Subclinical AF differs from clinically overt AF, which occurs more often, with symptoms, and is documented on ECG. Several studies have shown an association between the presence of subclinical AF and the risk of stroke (2–5).

However, there is debate on the minimum duration of subclinical AF that is required to confer this stroke risk. For eligibility in the ARTESiA trial, subclinical AF episode duration between 6 minutes and 24 hours was chosen based primarily on the ASSERT study, since it was observed that episodes of subclinical AF lasting at least 6 minutes were associated with an increased risk of stroke, and when episodes of subclinical AF were longer than 24 hours, this risk was much higher. A recent publication of the Canadian Cardiovascular Society recommended oral anticoagulation therapy for patients with subclinical AF lasting >24 hours when the patient is aged ≥ 65 years or with CHADS₂ score ≥ 1 , or for shorter episodes if the patient is considered to be at high risk (13). The 2016 European Society of Cardiology Guidelines limit the consideration of oral anticoagulants in patients with subclinical AF, except for special circumstances (14).

A recent review on stroke prevention in patients with subclinical AF suggests anticoagulating patients with subclinical AF if a history of ischemic stroke is present (20). Observations from the ASSERT II trial, however, may challenge the importance of history of ischemic stroke in this setting. Using an implantable loop recorder, the ASSERT II trial studied the prevalence of subclinical AF among older individuals without pacemakers. With an annual incidence of 34.4%, subclinical AF episodes ≥ 5 minutes were common in asymptomatic elderly patients. Patients with prior stroke were not more likely to have subclinical AF than patients without prior stroke (21). The current need for scientific evidence investigating stroke prevention in device-detected subclinical AF has been highlighted (22).

Whether subclinical AF is the same direct risk factor for stroke as clinical AF or is only a risk marker with a different mechanism is unclear. Therefore, patients with subclinical AF may respond differently to anticoagulants than patients with clinical AF. Results from TRENDS, the Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT) study, and a time-dependent analysis for ASSERT all indicate that there is no clear temporal association between episodes of subclinical AF and stroke (2,23,24). The absence of a temporal relationship between subclinical AF and the occurrence of stroke challenges the conventional understanding of a mechanistic relationship between atrial stasis, clot formation, and embolism. Stroke in patients with subclinical AF may be delayed or may be caused by a different factor. IMPACT was the first trial of anticoagulation in device-detected subclinical AF but used a complex treatment strategy, stopping treatment if no further subclinical AF episodes were seen in a period of time (24). Early initiation of anticoagulation based on device-detected subclinical AF did not improve outcomes, in part because of temporal dissociation between AF and stroke, and possibly because of stroke mechanisms independent of subclinical AF (25). In this trial, a possible explanation for the lack of observed benefit of the monitoring strategy is that the idea that stroke risk increases for a defined period after subclinical AF may be incorrect. Previous data have suggested that in the majority of cases of subclinical AF-associated stroke, no AF occurred within 1-3 months of the stroke. Another important issue was the use of a composite primary outcome including stroke and major bleeding. The components of this composite outcome may have offset each other, which could have contributed to a neutral result (25). In clinical practice, the relationship between subclinical AF and stroke is likely complex, and different for different patients: in some, a temporally linked, causal relationship, while in others, simply a marker of stroke risk. Therefore, the results of the

IMPACT trial do not support urgent initiation or any later withdrawal of anticoagulation in response to incident subclinical AF or its termination, and argue instead for anticoagulation based on more comprehensive, individualized assessment of risk and benefit. Additional studies like ARTESiA will help elucidate stroke mechanisms in patients with advanced heart disease to inform anticoagulation decision making for AF detected by implanted cardiac rhythm management devices.

Apixaban is a factor Xa inhibitor that has been shown to be effective in a variety of conditions where oral anticoagulation can be used, including the reduction of venous thromboembolism and stroke. In the AVERROES and ARISTOTLE trials, apixaban was effective and safe for patients with non-valvular AF compared with aspirin or dose-adjusted warfarin (8,16). The Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment (AMPLIFY-EXT) study showed that extended use of apixaban was safe, with similar rates of major bleeds when compared to placebo (26). Thus, the consistently favorable risk/benefit ratio of apixaban led to the selection of apixaban in the design of ARTESiA.

Aspirin was chosen as the control for the ARTESiA study because it is a common medication for secondary prevention in this population of patients with multiple risk factors, and modestly reduces the risk of ischemic stroke. Instead of combining the use of apixaban and aspirin, which would likely increase the risk of bleeding events in these patients, we have chosen to compare apixaban with aspirin. Our study, however, will allow the use of open label aspirin up to 100 mg/day in addition to study medication in situations where the treating physician considers aspirin to be appropriate.

Finally, patients who develop symptomatic clinical AF documented by surface ECG during the study period should be taken off the study drug and switched to non-study anticoagulant therapy as recommended by current guidelines. If a clinical indication for anticoagulation or dual antiplatelet therapy arises, the study drug will be discontinued or interrupted. If patients develop subclinical AF with episode duration > 24 hours, the decision to discontinue blinded study drug and start non-study anticoagulant therapy will be left to the discretion of the investigator. Participants will continue with follow-up and may restart study medications if and when the clinical indication for these other therapies resolves. Unblinding of study medication will be avoided unless knowledge of the treatment allocation is required to make an urgent treatment decision.

Conclusions

The ARTESiA trial will compare apixaban with aspirin to reduce the risk of stroke in patients with subclinical AF and additional risk factors for stroke. The study findings will generate evidence to address this gap in scientific knowledge and will help inform antithrombotic strategies for these patients.

Disclosures

Dr. Lopes's disclosures are available at https://dcricri.org/about-us/conflict-of-interest/COI-Lopes_2016.pdf. Dr. Alings has served on advisory boards/speaker bureau for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer. Dr. Connolly has received consulting fees and research support from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Bayer, Portola, Medtronic, St. Jude Medical, and Daiichi Sankyo. Dr. Granger has received consulting and research funding from Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Bayer/Janssen, and Daiichi Sankyo. Dr. Mazuecos has received speaking and consulting fees from St. Jude Medical. Dr. Boriani has received speaker fees from Medtronic, Boston Scientific, and Boehringer Ingelheim. Dr. Nielsen has received a speaker fee from Biotronik and consultant fee from Boston Scientific. Dr. Conen has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, Bayer, Bristol-Myers Squibb and Daiichi Sankyo; he also has received consultant and/or speaker fees from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. Dr. Hohnloser has received consulting fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, Cardiome, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Portola, Sanofi Aventis, Servier, St. Jude Medical, and Zoll; research grants from Sanofi Aventis and St. Jude Medical; and lecture fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Sanofi Aventis, St. Jude Medical, and Medtronic. Dr. Mairesse has received speaker fees, served on advisory boards, or received travel grants from Bayer, Boehringer Ingelheim, Biotronik, Daiichi Sankyo, Johnson & Johnson, Livanova, Medtronic, Menarini, Pfizer/BMS, and St. Jude Medical. Dr. Mabo has received consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Daiichi Sankyo, Medtronic, Boston

Scientific, and LivaNova. Dr. Camm has receiving consulting fees from Bayer Healthcare, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Gilead, Menarini, Johnson & Johnson, Medtronic, Pfizer/Bristol-Myers Squibb, Sanofi Aventis, Servier, and St. Jude Medical; research grants from Sanofi Aventis and Daiichi Sankyo; and lecture fees from Bayer Healthcare, Boehringer Ingelheim, and Daiichi Sankyo, St. Jude Medical, Boston Scientific and Medtronic. Dr. Healey has received research grants from Bristol-Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim, Medtronic, Boston Scientific, and St. Jude Medical. The other authors have no disclosures.

References

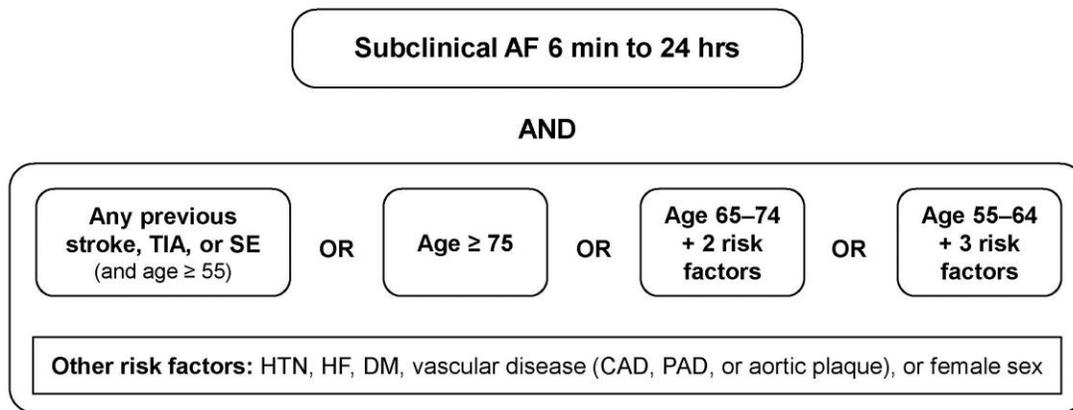
1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8):983-8.
2. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;2(5):474-80.
3. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366(2):120-9.
4. Hess PL, Healey JS, Granger CB, et al. The role of cardiovascular implantable electronic devices in the detection and treatment of subclinical atrial fibrillation: a review. *JAMA Cardiol* 2017;2(3):324-31.
5. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MObde Selection Trial (MOST). *Circulation* 2003;107(12):1614-9.
6. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285(22):2864-70.
7. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154(13):1449-57.
8. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981-92.

9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883-91.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139-51.
11. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093-104.
12. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383(9921):955-62.
13. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2014;30(10):1114-30.
14. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18(11):1609-1678.
15. Bami K, Nielsen JC, Alings M, et al. Current attitudes towards oral anticoagulant use to treat cardiac device patients with subclinical atrial fibrillation: Results from a four-nation physician survey. *J Innov Cardiac Rhythm Manage* 2015;15:1969-75.
16. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364(9):806-17.
17. Kaufman ES, Israel CW, Nair GM, et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;9(8):1241-6.

18. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke* 2009;40(6):2276-93.
19. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4.
20. Camm AJ, Simantirakis E, Goette A, et al. Atrial high-rate episodes and stroke prevention. *Europace*. 2016 Oct 4. pii: euw279. [Epub ahead of print].
21. Healey JS. ASSERT-II: Sub-clinical AF (SCAF) in older asymptomatic patients. Paper presented at: American Heart Association Scientific Sessions; Nov. 12-16, 2016; New Orleans, LA.
22. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society. *J Am Coll Cardiol* 2014;64(21):e1-76.
23. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129(21):2094-9.

24. Martin DT, Bersohn MM, Waldo AL, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J* 2015;36(26):1660-8.
25. Healey JS, Lopes RD, Connolly SJ. The detection and treatment of subclinical atrial fibrillation: evaluating the IMPACT of a comprehensive strategy based on remote arrhythmia monitoring. *Eur Heart J* 2015;36(26):1640-2.
26. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368(8):699-708.

Figure 1. Eligibility criteria for the ARTESiA trial. AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes; HF, heart failure; HTN, hypertension; PAD, peripheral artery disease; SE, systemic embolism; TIA, transient ischemic attack.



ACCEPTED

Figure 2. ARTESiA trial design. AF, atrial fibrillation; bid, twice daily; ISTH, International Society of Thrombosis and Haemostasis; OAC, oral anticoagulant; OD, once daily; TIA, transient ischemic attack. *A 2.5-mg dose of apixaban will be given twice daily for subjects who have 2 or more of the following characteristics: age \geq 80 years, weight \leq 60 kg, or serum creatinine \geq 1.5 mg/dL.

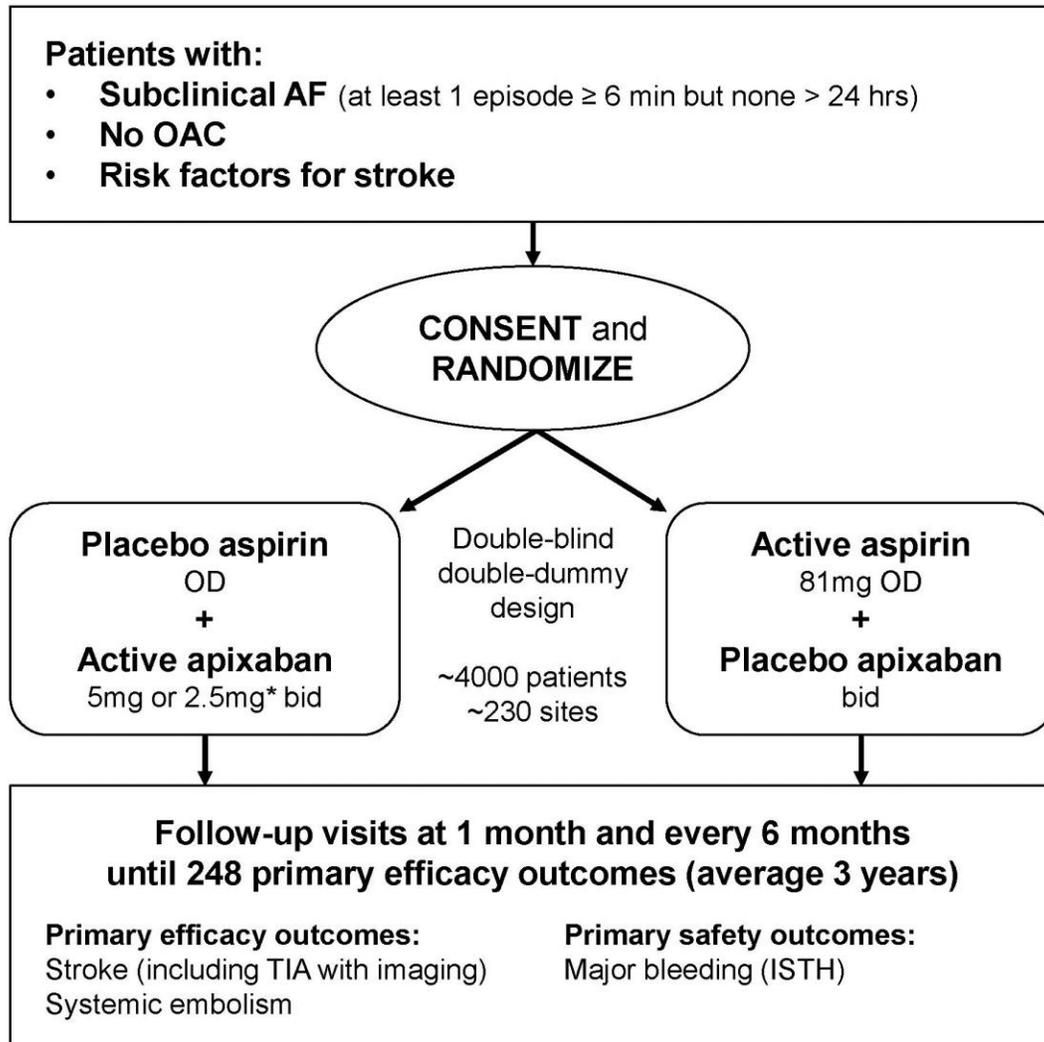


Table I. Key inclusion and exclusion criteria.

Inclusion Criteria	<ol style="list-style-type: none"> 1. Permanent pacemaker or defibrillator with atrial lead (with or without resynchronization) or a single-chamber device with an AF detection algorithm similar to those employed in implantable loop recorders, or insertable cardiac monitor capable of detecting SCAF 2. At least one episode of device-detected SCAF ≥ 6 minutes in duration (atrial rate > 175/min if an atrial lead is present), but no single episode > 24 hours in duration at any time prior to enrollment. SCAF requires at least one episode of electrogram confirmation (unless ≥ 6 hours in duration) 3. Age ≥ 55 years 4. Risk factors for stroke (any of the following): <ul style="list-style-type: none"> • Previous stroke, TIA, or SE • ≥ 75 years old • 65-74 years old + at least 2 risk factors* • 55-64 years old + at least 3 risk factors* <p>*Risk factors: female gender, hypertension, heart failure, diabetes, vascular disease (coronary artery disease, peripheral artery disease, or aortic plaque)</p>
Exclusion Criteria	<ol style="list-style-type: none"> 1. Clinical atrial fibrillation documented by surface ECG (12 lead ECG, Telemetry, Holter) lasting ≥ 6 minutes, with or without clinical symptoms 2. Mechanical valve prosthesis, recent (within past 6 months) deep vein thrombosis or pulmonary embolism or other condition requiring treatment with an anticoagulant 3. Allergy to aspirin or apixaban 4. Severe renal insufficiency (serum creatinine > 2.5 mg/dL [221 μmol/L] or a calculated creatinine clearance < 25 ml/min) 5. Serious bleeding in the last 6 months or at high risk of bleeding (this includes, but is not limited to: prior intracranial hemorrhage, active peptic ulcer disease, clinically significant thrombocytopenia or anemia, recent stroke within past 10 days, documented hemorrhagic tendencies or blood dyscrasias) 6. Moderate to severe hepatic impairment 7. Ongoing need for combination therapy with aspirin and clopidogrel (or other combination of two platelet inhibitors) 8. Meets criteria for requiring lower dose of apixaban AND also has ongoing need for <i>strong</i> inhibitors of both CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir or clarithromycin) 9. Ongoing need for strong dual inducers of both CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) 10. Received an investigational drug in the past 30 days 11. Participants considered by the investigator to be unsuitable for the study for any of the following reasons: <ul style="list-style-type: none"> • Not agreeable for treatment with either aspirin or apixaban or anticipated to have poor compliance on study drug treatment • Unwilling to attend study follow-up visits • Life expectancy less than 2 years due to concomitant disease 12. Women who are pregnant, breast-feeding or of child-bearing potential without an acceptable form of contraception in place (sterilization, abstinence or other method with less than 1% failure rate)

Table II. Guidance for stroke risk factors.

Risk Factor	Guidance
Stroke or TIA	Any clinical history of stroke (signs or symptoms \geq 24 hours) or TIA (signs or symptoms $<$ 24 hours) OR CT or MRI evidence of prior silent infarction (with or without symptoms).
Systemic arterial embolism	Any clinical history of systemic arterial embolism.
Hypertension	Any history of hypertension requiring antihypertensive treatment OR 2 blood pressure readings $>$ 140/90 (either value) on separate days taken after 5 minutes rest and which would, in the opinion of the treating physician, require treatment with antihypertensive therapy.
Heart failure	Clinical heart failure diagnosed at any time OR a left ventricular ejection fraction $<$ 50%.
Diabetes	Known history of diabetes OR currently taking insulin or any oral diabetic medication OR HbA1c $>$ 8% OR fasting blood sugar $>$ 14 mmol/L.
Vascular disease	Evidence of atherosclerosis on coronary angiogram, nuclear testing, or stress testing, or evidence of aortic or peripheral arterial disease using ultrasound, CT, or MRI imaging. Vascular disease need only be present, not necessarily flow-limiting or symptomatic.

CT = computed tomography; HbA1c = glycated hemoglobin; MRI = magnetic resonance imaging; TIA = transient ischemic attack.