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Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation

Luigi Di Biase[1,2,3,4], David Callans[5], Karl Georg Hæusler[6], Gerhard Hindricks[7], Hussein Al-Khalidi[8], Lluis Mont[9], Jens Cosedis Nielsen[10], Jonathan P. Piccini[11], Ulrich Schotten[12,13], and Paulus Kirchhof[13,14,15]*

[1]Albert Einstein College of Medicine, Montefiore Hospital, NY, USA; [2]Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, TX, USA; [3]Department of Biomedical Engineering, University of Texas, Austin, TX, USA; [4]Department of Cardiology, University of Foggia, Foggia, Italy; [5]Hospital of the University of Pennsylvania, Philadelphia, USA; [6]Center for Stroke Research Berlin & Department of Neurology, Charité—Universitätsmedizin Berlin, Germany; [7]Abteilung für Rhythmologie, Herzzentrum Leipzig GmbH, Leipzig, Germany; [8]Department of Biostatistics & Bioinformatics, Duke University School of Medicine, USA; [9]Hospital Clinic Barcelona, Barcelona, Spain; [10]Department of Clinical Medicine, Aarhus University Hospital, Denmark; [11]Duke University, Division of Cardiology Duke University Medical Center, Durham NC, USA; [12]University Maastricht, Department of Physiology, Maastricht, Netherlands; [13]Atrial Fibrillation NETwork association (AFNET), Münster, Germany; [14]University of Birmingham Institute of Cardiovascular Sciences, SWBH and UHB NHS Trusts, Birmingham, UK; and [15]Department of Cardiovascular Medicine, Hospital of the University of Münster, Münster, Germany

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Aims Catheter ablation is the most efficacious rhythm control therapy in atrial fibrillation (AF) patients. There is growing evidence that catheter ablation procedures are best performed during continuous oral anticoagulation, but outcomes are variable depending on the anticoagulation strategy or agent chosen. Specifically, there is a need to evaluate the peri-procedural use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients undergoing catheter ablation of AF. The AXAFA-AFNET 5 trial will test whether peri-procedural anticoagulation therapy using apixaban is a safe alternative to vitamin K antagonist (VKA) therapy for patients undergoing catheter ablation of AF.

Methods and results AXAFA-AFNET 5 is a randomized, prospective multi-centre study conducted in Europe and the USA. A total of 650 patients scheduled for AF ablation will be randomized 1:1 to undergo AF ablation on continuous treatment with the NOAC apixaban or with a VKA. Patients can undergo AF ablation after at least 30 days of continuous effective anticoagulation or after exclusion of atrial thrombi by transoesophageal echocardiogram. The trial includes a post-ablation magnetic resonance imaging substudy that will quantify silent brain lesions that can occur in neurologically asymptomatic patients after AF ablation. Patients will be followed on continuous anticoagulation for 3 months after the ablation. The primary outcome parameter of AXAFA-AFNET 5 is a composite of all-cause death, stroke, and major bleeding events.

Conclusion The results of AXAFA-AFNET 5 will provide evidence informing about the safety of apixaban in ablation patients and on its efficacy including effects on silent brain lesions. AXAFA – AFNET 5 is an investigator-initiated trial sponsored by AFNET. The trial is supported by the DZHK (German Centre for Cardiovascular Research) and by the BMBF (German Ministry of Education and Research) and by Bristol-Myers Squibb/Pfizer Alliance.

Keywords Atrial fibrillation • Ablation • Oral anticoagulation • Apixaban • Warfarin • Un-interrupted • Stroke • Bleeding

* Corresponding author. Tel: +44 121 414 7042.; fax: +44 121 414 5887. *E-mail address*: p.kirchhof@bham.ac.uk
Dr Luigi is the International Co-Chief Investigator and Paulus Kirchhof is the International Chief Investigator.

Introduction

Catheter ablation is an important rhythm control strategy in atrial fibrillation (AF) patients.[1,2] There is growing evidence that catheter ablation procedures are best performed during continuous oral anticoagulation. This is reflected in current consensus statements and guidelines.[3,4] Several non-randomized trials have proposed uninterrupted vitamin K antagonists (VKAs) instead of interrupted anticoagulation for prevention of stroke during AF ablation.[5–7] This was followed by a randomized controlled trial (RCT) using continuous VKA therapy.[8] Data on non-vitamin K antagonist oral anticoagulants (NOACs) mainly arise from observational data sets with diverse results,[9–18] and more recently from a medium-sized (200 patients) RCT on rivaroxaban, which is the only randomized trial published so far evaluating NOACs.[19] Information on the effectiveness and safety of uninterrupted NOAC therapy (e.g. with apixaban) is scarce and more data are needed. The limited information available is promising.[20,21] Thus, the growing number of patients scheduled for catheter ablation for AF on NOACs are faced with different anticoagulation options,[22] and therefore potentially prone to bleeding and thromboembolic complications.[23,24] Randomized, controlled trials comparing continuous NOAC to continuous VKA in patients undergoing AF ablation are needed to better inform clinical practice.

While peri-procedural anticoagulation with vitamin K antagonists seems to reduce the incidence of overt ischemic strokes, bleeding events, and 'silent' brain lesions,[8–12,25,26] the impact of NOAC therapy during ablation procedures on the latter has never been studied in RCTs.[11,21]

Therefore, we conduct the AXAFA-AFNET 5 trial to determine the safety of continuous anticoagulation using the factor Xa inhibitor apixaban compared to continuous VKA therapy in patients undergoing catheter ablation for AF, including a systematic assessment of cognitive function and brain magnetic resonance imaging (MRI) evaluation in a large portion of the patients.

Objectives

To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of AF in the prevention of peri-procedural complications.

Study design

AXAFA-AFNET 5 is an investigator-initiated, prospective, parallel-group, randomized, open, blinded outcome assessment (PROBE) interventional multi-centre study (*Figure 1*) conducted in European and US American ablation centres. The trial tests whether peri-procedural anticoagulation therapy using the novel, oral, direct factor

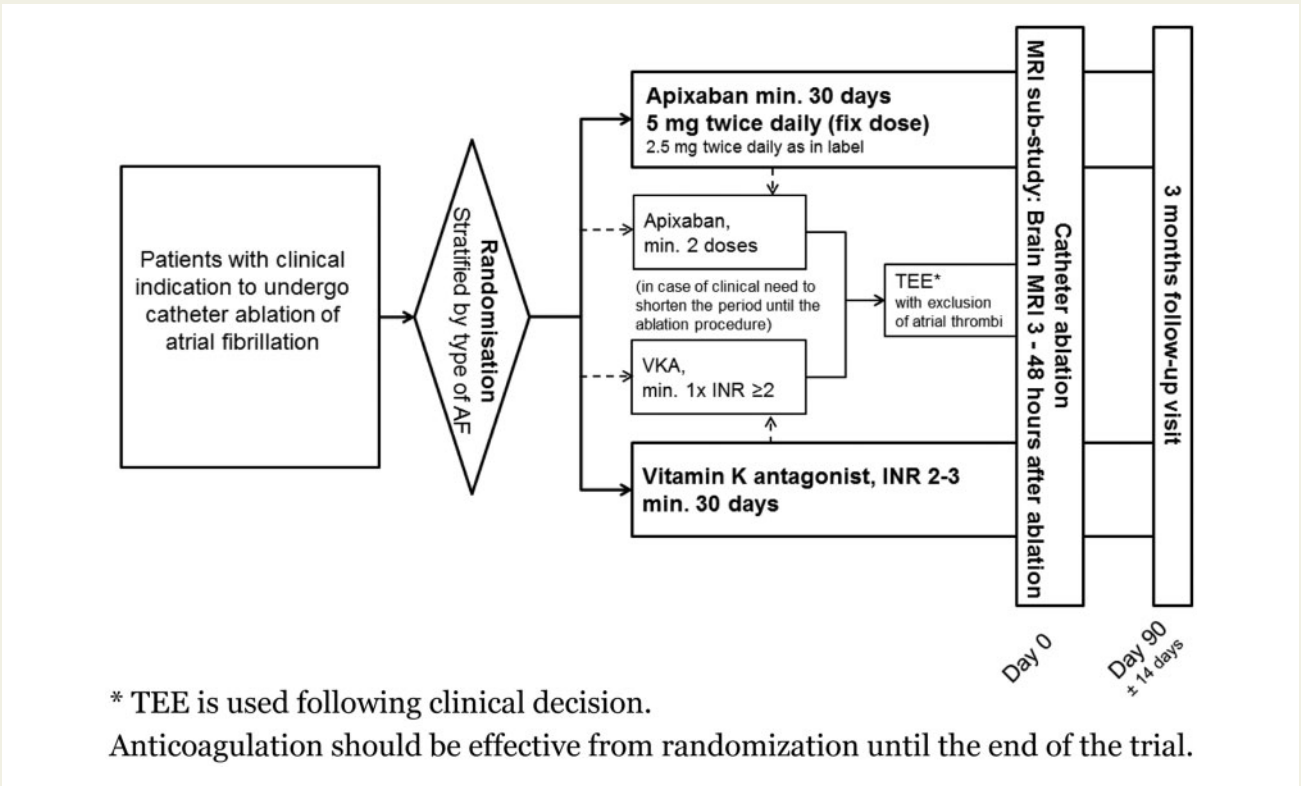

Figure 1 Flow chart of the AXAFA-AFNET 5 trial.
Anticoagulation should be effective from randomization until the end of the trial.

Xa inhibitor apixaban is a safe alternative to VKA therapy for patients undergoing catheter ablation of AF.

All patients will undergo the ablation procedure after pre-treatment with an anticoagulant (either apixaban in the 'Xa group' or a vitamin K antagonist in the 'VKA group'). Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by transoesophageal echocardiogram (TEE). Continuous effective anticoagulation must be ensured until the end of the trial in all patients.

Xa group

Patients randomized to the Xa group will receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure, including the morning dose, with twice daily dosing. The apixaban dose will be reduced to 2.5 mg twice daily in patients who fulfil at least two of the following criteria at the time of randomization: chronic kidney disease [defined as serum creatinine $\geq$ 1.5 mg/dl (133 mM)], $\leq$ 60 kg body weight, or age $\geq$ 80 years, consistent with the approved label of apixaban. All patients randomized to the Xa group must have received at least two doses of apixaban prior to the ablation procedure.

VKA group

Patients randomized to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. VKA therapy will be monitored by international normalized ratio (INR) measurements according to applicable medical guidelines and to local routine policy; a minimum of three INR measurements is mandatory. The frequency and values of INR measurements will be collected in the electronic case report form. Effective anticoagulation will be assessed by questioning the patient about medication intake and by INR measurements, which need to be therapeutic (INR $\geq$ 2.0) for at least 30 days prior to catheter ablation. Any INR value $<$1.8 resets this interval. In patients undergoing TEE, there must be at least one INR value $\geq$ 2 prior to catheter ablation. It is recommended that the ablation procedure is performed while the INR is between 2 and 2.5.

Patients undergoing TEE with exclusion of atrial thrombi prior to the ablation procedure will be handled according to local routine, which may include heparin or low-molecular weight heparins to achieve sufficient anticoagulation during initiation of VKA therapy.[27]

Concomitant Medications

The concomitant use of antiplatelet agents is discouraged in all study patients, because the concomitant use of an oral anticoagulant and antiplatelet agents increases the risk of bleeding without known benefits. All other concomitant medication is permitted.

Study population

AXAFA-AFNET 5 will be conducted in patients scheduled for catheter ablation of AF recruited in European and US American centres. The population will be enriched for patients at risk for stroke and bleeding. The main inclusion and exclusion criteria are given in *Table 1*.

Sample size estimation

Six hundred and thirty patients will be randomized and undergo the index therapy of catheter ablation for AF. However, to account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomized and have undergone the index therapy of catheter ablation) for the primary analysis using modified intention-to-treat (mITT) cohort. The sample size may be re-estimated once in a blinded manner as described in the statistics section. Randomization to Xa therapy or VKA therapy will be stratified by the pattern of AF (paroxysmal vs. persistent or long-lasting persistent).

Treatments relative to the procedure

Anticoagulation during the ablation procedure

All patients in AXAFA should undergo catheter ablation of AF while on continued oral anticoagulation as described above. Based on published recommendations,[3] a heparin bolus (100 IU/kg body weight) should be given either prior to or directly after transseptal puncture. Activated clotting time (ACT) $>$ 300s needs to be maintained and documented during the ablation procedure (assessed as mean, range, and number of ACT measurements within the target range). All other aspects of the ablation procedure and of peri-procedural management will follow local routine. The randomization merely defines the type of anticoagulation therapy used.

Ablation procedure

The aim of catheter ablation in AF patients is isolation of the pulmonary veins (PVI).[3,4] Some patients may require more extensive ablation procedures targeting additional structures e.g. by linear lesions, ablation of ganglionated plexus and fractionated electrograms, or others.[3,4] When sufficient local expertise and experience exists, such techniques can be used within AXAFA-AFNET 5. Local routine, informed by current professional society statements and guidelines should guide details of the procedure (e.g. the type of ablation and mapping system used, or the choice of ablation energy). We encourage the use of irrigated tip catheters and flushing of all left atrial sheaths. Information on the ablation technologies and approaches used in the trial will be documented and monitored. During the ablation procedure, the study team will collect the procedural information including ACT measurements, details of the ablation technology used, delivered energy, procedure time, rhythm at beginning and end of procedure, need for cardioversion during the procedure.

Endpoints

Primary outcome

The primary outcome parameter of AXAFA-AFNET 5 is a composite of all-cause death, stroke, and major bleeding events occurring during the trial period (from inclusion to 3 months after ablation). Stroke comprises ischemic strokes as defined by the Food and Drug

Table 1 Inclusion and exclusion criteria for the AXAFA-AFNET 5 trial

Inclusion	Exclusion
Atrial fibrillation (ECG-documented) with a clinical indication for catheter ablation	Any disease that limits life expectancy to less than 1 year
Clinical indication to undergo catheter ablation on continuous anticoagulant therapy	Participation in another clinical trial, either within the past 2 months or still ongoing
Presence of at least one of the $CHADS_2$ stroke risk factors[a]	Previous participation in AXAFA
Age $\geq$ 18 years	Pregnant women or women of childbearing potential not on adequate birth control: only women with a highly effective method of contraception (oral contraception or intra-uterine device) or sterile women can be randomized
Provision of signed informed consent	Breastfeeding women
	Drug abuse or clinically manifest alcohol abuse
	Any stroke within 14 days before randomization
	Concomitant treatment with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp
	Valvular AF (as defined by the focussed update of the ESC guidelines on AF, i.e. severe mitral valve stenosis, mechanical heart valve). Furthermore, patients who underwent mitral valve repair are not eligible for AXAFA
	Any previous ablation or surgical therapy for AF
	Cardiac ablation therapy for any indication (catheter-based or surgical) within 3 months prior to randomization
	Clinical need for 'triple therapy' (combination therapy of clopidogrel, acetylsalicylic acid, and oral anticoagulation)
	Other contraindications for use of VKA or apixaban
	Documented atrial thrombi less than 3 months prior to randomization
	Severe chronic kidney disease with an estimated GFR $<$ 15 ml/min or requirement for renal replacement therapy

[a]Stroke or TIA, age $\geq$ 75 years, hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure $>$ 145/90 mm Hg, diabetes mellitus, symptomatic heart failure (New York Heart Association $\geq$ II).
GFR, glomerular filtration rate.

Administration, including ischemic brain infarction on imaging with (transient) clinical symptoms that resolve completely within 24 h as well as ischemic brain infarction leading to death subarachnoid haemorrhage, and haemorrhagic stroke. Major bleeding events will be defined according to the Bleeding Academic Research Consortium (BARC) definition as BARC 2 or higher,[28] i.e. all bleeding events that require an action by a health care professional. This outcome parameter comprises all relevant bleeding events in a clinical setting and has been used to optimize arterial vascular procedures such as percutaneous coronary interventions.[28,29]

Secondary outcomes

The AXAFA-AFNET 5 data set collects information on a variety of pre-specified secondary outcomes. They include time from randomization to ablation, nights spent in hospital after ablation and healthcare related cost, ACT during ablation (assessed as mean, range, and number of ACT measurements within the target range), all bleeding events, tamponade, need for transfusion, rhythm outcomes during follow-up, and changes in quality-of-life and cognitive function compared to baseline. In patients participating in the MRI sub-study, the following additional outcomes will be compared between groups: prevalence of clinically 'silent' MRI-detected brain lesions, and impact of ablation-associated clinically overt strokes as well as MRI-detected clinically 'silent' acute brain lesions on cognitive function 3 months after ablation. All brain MRIs will be read in a blinded fashion by two independent neuroradiologists.[30]

Visits

After the baseline visit and randomization, every patient within AXAFA will undergo two scheduled in person follow-up visits, one at the time of the ablation procedure and another follow-up visit at the end of the study, 3 months after the ablation visit. Patients scheduled for ablation without exclusion of atrial thrombi by TEE will be treated for at least 30 days with the oral anticoagulant of their randomization group prior to the ablation visit. This period can be longer according to clinical needs (e.g. scheduling and waiting list requirements, or insufficient or insufficiently documented oral anticoagulation). Effective anticoagulation (i.e. continuous medication intake in patients randomized to Xa group, and INR between 2–3 in patients randomized to VKA group) needs to be present for 30 days prior to ablation. Ineffective anticoagulation (e.g. failure to take medication in Xa group

Table 2 Published event rates in patients undergoing catheter ablation of atrial fibrillation. AXAFA-AFNET 5 will only enrol patients with at least one stroke risk factor, thus enriching for patients at risk for events

	Ellis et al.[34]	Piccini JP, et al.[35]	Cappato R, et al.[19]	Lakkireddy D, et al.[10]	Lakkireddy D, et al.[20]	Average
Death	0.4	0.5				0.45
Stroke & TIA	0.6	0.8	0.8	1	1	0.8
Tamponade	3.1	1.7	1.2	3	1.2	2
Vascular access	5.7	2		4	5	4.2
Bleeding requiring medical attention		5				5
'Major' bleeding			1	3		2
'Minor' bleeding (e.g gastro-intestinal bleed) approximating BARC 3 bleeds				3	2	2.5
Combined event rate						17.0

BARC, Bleeding Academic Research Consortium.

or INR <1.8 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. A TEE can be performed to avoid rescheduling in patients with insufficient anticoagulation. At the ablation visit, INRs (VKA group patients) or pill count (Xa group patients) will be reviewed and a 12-lead ECG recorded. Procedural information will be collected and an echocardiogram will be done to exclude pericardial effusion. A brain MRI will be performed 3–48 h after the ablation procedure in all patients enrolled in centres who participate in the brain MRI substudy. A dedicated imaging centre defines the MRI workflow.

At the 3-month follow-up visit, rhythm will be assessed by 12 lead ECG and 24-h Holter ECG. Cognitive function will be assessed by Montreal Cognitive Assessment,[31] quality of life will be assessed by EQ-5D, SF-12 and by the Karnofsky scale,[32] and study medication will be returned. Thirty days after discontinuation of the study drug the investigator or designee will call the patient and assess for adverse events/serious adverse events that occurred since discontinuation of study drug.

Statistical methods

Patient selection for analyses

Under the mITT principle, all randomized patients who undergo an ablation procedure for AF will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up or on the day of last contact with the patient. This concept will be applied to both treatment arms. In addition, a sensitivity (robustness) analysis will be conducted using per-protocol population (i.e. among those without major protocol violations).

Sample size and power calculations

The sample size calculations were based on assumption that, at an overall event rate of the primary endpoint (composite of all-cause death, stroke or BARC 2–5 bleeding) at Day 90 of 17%, a total of 630 patients (315 per group) will be required to detect a pre-specified margin of 7.5% (absolute difference) with 80% power using upper one-sided 95% confidence interval (i.e. two-sided 90% CI,[33]). This event rate has been carefully estimated based on reports in the literature (*Table 2*). The steering committee will have the opportunity to adjust sample size blinded to random group based on the aggregated event rate during the planned interim analysis (see below). The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomized and having undergone the index therapy of catheter ablation, mITT population) for the primary analysis.

Analysis of the primary outcome

The primary endpoint analysis will be based on composite primary efficacy outcome in all randomized patients who undergo an ablation procedure for AF (i.e. mITT). The efficacy composite endpoint is measured (in days) from the randomization date to the day of the event (i.e. time-to-first event = event date - randomization date +1). As a secondary analysis, time-to-event analysis will be conducted for the components of the primary composite endpoint.

Kaplan–Meier (K–M) estimates of the survivor function and the log rank test statistic will be used to assess the statistical significance of observed treatment differences in the time-to-event distributions between the treatment groups. The log-rank test statistics, *P*-values, K–M estimates, and life table estimates will be obtained from the SAS V9.3 (or higher) procedure LIFETEST (SAS/STAT User's Guide, Version 9.3, Cary, NC: SAS Institute Inc. 2011).

Cox proportional hazards model will be used to obtain an estimate of the hazard ratio for Xa group to VKA therapy group. A 95% CI will be computed for the hazard ratio. Stratified Cox proportional hazards model will be conducted using the stratification factors at randomization as a strata statement in the model. In addition, the Cox proportional hazards model with clinically relevant baseline risk factors will be used to estimate the adjusted hazard ratio (95% CI).

As a sensitivity analysis, the per-protocol population will be used. Statistical models will be constructed to validate existing factors that predict outcome parameters, and to describe novel factors, e.g. blood- or ECG-based. Details of the statistical analysis will be defined in a separate statistical analysis plan.

Analysis of secondary outcomes

The secondary outcomes that are measured as time-to-event will be analysed using the same statistical methods used for the primary efficacy outcome. Quality-of-life and cognitive function outcomes will be summarized by treatment groups for each component of the questionnaires (EQ-5D, SF-12, Karnofsky scale, Montreal Cognitive Assessment). Total score quality of life outcomes from each assessment will be analysed as change from baseline at Month 3 using analysis of covariance with the baseline values as a covariate in the model. Details of the statistical analysis will be defined in a statistical analysis plan. The MRI sub-study will develop a separate specific analytic plan prior to locking the main study database. All the secondary endpoint analyses are exploratory in nature and will be tested at 0.05 significance level.

Safety analysis

Safety data include adverse events, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomized patients (i.e. ITT cohort) in this study. The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade, and major bleeding events, which will be analysed using time-to-event methodology. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint including MedDRA-coded adverse events adjudicated by an independent committee. Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. Serious adverse events will be summarized by severity and relation to study treatment received.

Interim analyses, reassessment of the sample size

There are two planned interim analyses to be conducted by the Data and Safety Monitoring Board (DSMB) after approximately one-third and two-third of patients underwent the catheter ablation procedure (i.e. roughly at 200 and 400 patients, respectively) who have completed 90 days (3 months) of study follow-up. In order to preserve the Type I error (alpha) for the final analysis, a conservative boundary such as Haybittle-Peto will be used as stopping rule guidance for the DSMB. The Steering Committee could decide on sample size re-estimation during the interim looks using the observed aggregated event rate of the primary endpoint. The re-estimation will be based on the current protocol assumptions (i.e. same study statistical power and the non-inferiority margin).

Study limitation

AXAFA-AFNET 5 is not powered to reliably detect differences in the component of the primary outcome parameter. TEE prior to the ablation procedure was not mandatory in this trial and this might be considered in centres who routinely perform TEE in all AF ablation patients.

Conclusions

Given the frequency of AF ablation in clinical practice and the paucity of randomized data comparing uninterrupted NOAC vs. uninterrupted VKA therapy, there is a need to test the peri-procedural use of NOACs in patients undergoing catheter ablation of AF in a randomized trial.

Therefore, AXAFA-AFNET 5 will explore the safety and efficacy of uninterrupted apixaban during AF ablation, AXAFA-AFNET 5 is an investigator-initiated, prospective, parallel-group, randomized, open, blinded outcome assessment interventional multi-centre study that will test whether peri-procedural anticoagulation therapy using apixaban is a safe alternative to VKA therapy for patients undergoing catheter ablation of AF. Moreover, the assessment of cognitive function and the brain MRI substudy will provide additional information on the safety and efficacy of NOACs compared to VKA in patients undergoing AF ablation on continued oral anticoagulation. Thus, the AXAFA-AFNET 5 results, especially when viewed in conjunction with the outcome of another, similarly sized study using dabigatran (RE-CIRCUIT), will provide evidence to inform the best peri-procedural anticoagulation management of AF patients undergoing ablation procedures.

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