Study Report - Synopsis

AXAFA - AFNET 5

Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

Investigational Medical Product (IMP): Apixaban

Indication:
Atrial Fibrillation

Phase of the clinical trial:
IV

EudraCT-Number:
2014-002442-45

Register-Number:
NCT number: NCT02227550
ISRCTN877110003

Date: 9.09.2018
Version: 1.0.

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Study Start: *27.02.2015 FPI*
Study Termination (regular): *12.09.2017 LPO*

SYNOPSIS ***ANNEX I***

Name of Sponsor: Kompetenznetz-Vorhofflimmern e.V. (Atrial Fibrillation NETwork;	Individual Study Table Referring to Part of the Dossier Volume: NA Page: NA	*(For National Authority Use only)*
Name of Finished Product: Eliquis ®		
Name of Active Ingredient: Apixaban		

Title of the Study:
AXAFA - AFNET 5 Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy.

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Study centre(s):

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Publication (reference):

Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation

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European Heart Journal (2018) 00, 1–14
https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehy176/4943979?guestAccessKey=f09ef6c0-eeb4-40b4-a860-467e86a55129

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

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Europace (2017) 19, 132–138
https://academic.oup.com/europace/article/19/1/132/2960817

Studied period (years):(date of first enrolment) (date of last completed)	Phase of development:
27.02.2015 – 12.09.2017	IV

Objectives:

The aim of the AXAFA-AFNET 5 trial was to demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular atrial fibrillation (AF) in the prevention of peri-procedural complications.

Methodology:

AXAFA was designed as an Investigator-initiated, prospective, parallel-group, randomised, open, blinded outcome assessment (PROBE) interventional multi-centre trial. The AXAFA trial compared periablational treatment with apixaban to periablational treatment with VKA in a randomized trial of patients undergoing catheter ablation of AF. This randomised trial clarified the clinical utility of apixaban in the periablational setting by systematically collecting data on clinically relevant ischemic and bleeding events in patients who were prospectively followed in the context of a clinical trial.

Continuous apixaban (5 mg b.i.d.) was compared to vitamin K antagonists (VKA, international normalized ratio 2–3) in atrial fibrillation patients at risk of stroke in a prospective, open, multi-centre study with blinded outcome assessment. Primary outcome was a composite of death, stroke, or bleeding (Bleeding Academic Research Consortium 2–5). A high-resolution brain magnetic resonance imaging (MRI) sub-study quantified acute brain lesions. Cognitive function was assessed by Montreal Cognitive Assessment (MoCA) at baseline and at end of follow-up.

Number of patients (planned and analysed):

It was planned to randomise 630 patients (315 per group) to undergo the index therapy of catheter ablation. However, to account for roughly 3% of patients who will not undergo the ablation procedure after randomisation, it was planned to enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.

In total 674 patients were randomised and constitute the ITT population (all patients randomised). The safety population which comprises all patients that received study drug consisted of 655 patients in total.

The mITT Population represented all 633 patients who started study drug and had the index catheter ablation procedure performed.

Diagnosis and main criteria for inclusion:

The intended population for this study were patients who were scheduled for catheter ablation of AF.

The main criteria for inclusion were:

1. Non-valvular atrial fibrillation (ECG-documented) with a clinical indication for catheter ablation.
2. Clinical indication to undergo catheter ablation on continuous anticoagulant therapy.
3. Presence of at least one of the $CHADS_2$ stroke risk factors

- Stroke or TIA,
- age >=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 (NYHA >= II).

4. Age: 18 years or above.
5. Provision of signed informed consent.

Test product, dose and mode of administration, batch number:

The test product was Apixaban.

Apixaban was administered at a dose of 5 mg twice daily orally. The apixaban dose was reduced to 2.5 mg twice daily at the time of randomisation in applicable patients according to the approved label.

Medication was labelled using the following batch numbers: 1G65165, 3D75747, AAB2726.

Duration of treatment:

Study medication was administered for at least 30 days prior to the planned catheter ablation procedure or during a shorter interval in patients undergoing a transesophageal echocardiogram (TEE) with exclusion of atrial thrombi. Study medication was continued for three months after the ablation procedure.

Reference therapy, dose and mode of administration, batch number:

Patients in the reference therapy group received oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione aiming for an international normalized ratio (INR) of 2.0-3.0.

No study medication was used but marketed goods that were prescribed to patients by the trial sites.

Name of Sponsor: Kompetenznetz-Vorhofflimmern e.V. (Atrial Fibrillation NETwork);	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Eliquis	Volume: NA	
Name of Active Ingredient: Apixaban	Page: NA	

Criteria for evaluation:

Efficacy:

The primary efficacy analysis was based on composite endpoints of all-cause death, stroke or major bleeding in all randomised patients who received study medication or VKA and underwent an ablation procedure for AF (i.e., modified intention-to treat). The efficacy composite endpoint was measured (in days) from the randomisation date to the day of the event. As a secondary analysis, time-to event analysis was conducted for the components of the primary composite endpoint.

The secondary endpoints were measured as time-to-event and were analysed using the same statistical methods used for the primary efficacy endpoint.

Stroke comprised ischemic strokes as defined by the FDA (including ischemic infarction with (transient) clinical symptoms that resolve completely within 24 hours, but have a matching lesion on brain imaging as well as ischemic infarction interrupted by death within 24 hours), subarachnoid haemorrhage and haemorrhagic stroke. Major bleeding events was defined according to the Bleeding Academic Research Consortium (BARC) definition as BARC 2 or higher, i.e. all bleeding events that require an action by a health care professional. This outcome parameter comprised all relevant bleeding events in a clinical setting and has been used to optimise arterial vascular procedures such as percutaneous coronary interventions.

The secondary outcome parameters are defined as

- any bleeding event,
- major bleeding events according to the ISTH and TIMI definitions,
- number of strokes, other systemic embolic events, and all-cause deaths,
- time from randomisation to ablation,
- nights spent in hospital after ablation,
- health-care related cost calculation estimated by quantification of interventions, nights spent in hospital, and the costs of outpatient treatment,
- number of hospitalisations (at least one over-night stay) for cardiovascular reasons,
- treatment duration prior to ablation and total time on oral anticoagulation,
- number of patients with clinically indicated TEE,
- ACT during ablation (assessed as mean, range, and number of ACT measurements within the target range),
- time to recurrent AF (determined clinically, and according to ECG and Holter ECG recording at the end of follow-up),
- rhythm status at the end of follow-up (assessed by Holter ECG),
- vascular access complications leading to prolongation of in-hospital stay or specific therapy,
- quality-of-life changes at month 3 compared to baseline (assessed by EQ-5D, SF-12 questionnaires, and by the Karnofsky Scale),
- change of cognitive function at month 3 compared to baseline (assessed by Montreal Cognitive Assessment Scale; MoCA)
- MRI sub-study, only: Prevalence of clinically "silent" MRI-detected brain lesions within 48 hours after the ablation procedure,
- MRI sub-study, only: Impact of ablation-associated clinically overt strokes or MRI-detected but clinically "silent" acute brain lesions on cognitive function after ablation.

Quality-of-life outcomes were summarized by treatment groups for each component of the questionnaires (assessed by EQ-5D, SF- 12 and by the Karnofsky Scale), Total score of quality of life outcomes from each assessment were analyses as change from baseline at month 3 using analysis of covariance with the baseline values as a covariate in the model.

The MRI sub-study developed a separate specific analytic plan prior to locking the main study database.

All the secondary endpoints analyses were tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

Safety:

Safety data included adverse events (AE) as defined in the study protocol, primary safety endpoints, and data for other safety evaluations. Safety data was collected on all randomised patients (i.e., ITT cohort) in this study. The primary safety outcome in this study was a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which were analysed using time-to-event methodology.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related Serious Adverse Events (SAEs) were summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups were made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs were summarized by severity and relation to study treatment received.

Statistical methods:

The statistical analysis was conducted following the described methods:

The primary efficacy analysis was based on composite endpoint of all-cause death, stroke or major bleeding in all randomised patients who underwent an ablation procedure for AF (i.e., modified intention-to-treat [mITT]). The efficacy composite endpoint was measured (in days) from the randomisation date to the day of the event (i.e., time-to-first event = event date - randomisation date +1). As a secondary analysis, time-to-event analysis was conducted for the components of the primary composite endpoint.

The Kaplan-Meier (K-M) estimates of the survivor function and the log rank test statistic were used to assess the statistical significance of observed treatment differences in the time-to-event distributions between the treatment groups.

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

Analysis of the secondary outcome

The secondary endpoints were measured as time-to-event and were analysed using the same statistical methods used for the primary efficacy endpoint. Quality-of-life outcomes were summarized by treatment groups for each component of the questionnaires (assessed by EQ-5D, SF- 12 and by the Karnofsky Scale), Total score of quality of life outcomes from each assessment was analysed as change from baseline at month 3 using analysis of covariance with the baseline values as a covariate in the model.

MRI sub-study developed a separate specific analytic plan prior to locking the main study database. All the secondary endpoints analyses were tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

Sample Size and Power Calculations

The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who did not undergo the ablation procedure, it was planned to include a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort to detect a pre-specified margin of 7.5% (absolute difference).

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

AXAFA – AFNET 5 randomized 674 patients across 49 sites in 9 countries from February 2015 to April 2017. Overall, 633 patients took study drug and underwent atrial fibrillation ablation. Demographic and clinical characteristics were well balanced between treatment groups. 633 patients took study drug and underwent atrial fibrillation ablation.

Primary outcome events (BARC 2–5 bleeding, stroke, or death) were observed in 22/318 (6.9%) patients randomised to apixaban, and in 23/315 (7.3%) patients randomized to VKA therapy in the ablation set.

Four events were classified as TIMI major bleeding, and 24 events are ISTH major bleeding.

Two patients died, one experienced a massive intracerebral haemorrhage, one died without an identifiable cause of death. Two patients randomised to apixaban had a stroke. Tamponade occurred in 2 apixaban- and 5 VKA- patients. Apixaban was non-inferior to VKA based on the non-inferiority margin of 7.5% (a difference of -0.38%, 90% CI -4.0%, -3.3%, noninferiority P = 0.0002) (Table1, Table 2).

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Secondary Outcome Parameters

There was no difference in time to ablation or nights spent in hospital after the ablation between the groups. As expected, the last INR prior to ablation and ACTs achieved during ablation were lower in the patients randomized to apixaban . Quality-of-life as assessed by the physical component of SF-12 and Karnofsky scale improved during the study without differences between study groups. At least mild cognitive dysfunction was found in 188/619 (30.4%) of the patients at baseline. At the end of follow-up, MoCA increased by a median of +1.0 (-1.0, 2.0) unit without differences between study groups, and only 141/607 patients (7.2% fewer than at baseline) had mild cognitive impairment.

Quality of Life

Quality-of-life as assessed by the physical component of SF-12 [+2.5 (-2.1, 8.1) units] and Karnofsky scale [+10 (0, 10)] improved during the study without differences between study groups . At least mild cognitive dysfunction was found in 188/619 (30.4%) of the patients at baseline (pre-defined as MoCA< 26,). At the end of follow-up, MoCA increased by a median of +1.0 (-1.0, 2.0) unit without differences between study groups, and only 141/607 patients (7.2% fewer than at baseline) had mild cognitive impairment (Table 3).

Magnetic resonance imaging sub-study

Acute brain MRI was performed in 335 patients across 25 centres. Clinical characteristics of the sub-study population were not different from the main study population, with the exception of a lower median weight in patients undergoing MRI [85.0 kg (74.5, 96.0)] compared to non-MRI patients [90.0 kg (80.0, 103.0)]. Clinical characteristics were well balanced between MRI sub-study treatment groups. There were 323 analysable MRIs. Acute brain MRI lesions were found in 44/162 (27.2%) patients randomised to apixaban, and in 40/161 (24.8%) patients randomised to VKA (P=0.635), with very similar distribution of lesions between random groups. Cognitive function at the end of follow-up was not different in patients with or without acute brain lesions (MoCA 27.1± 2.7 in 239 patients without MRI lesions, 27.1± 2.8 in 84 patients with MRI lesions, P=0.91) (Table 4).

SAFETY RESULTS:

All serious adverse events were collected, defined as adverse events that caused or prolonged hospitalization, caused disability or incapacity, were life-threatening, resulted in death or were important medical events. In addition, pregnancy, overdose, and cancer diagnosed after randomisation were defined as serious adverse events. As AXAFA – AFNET 5 compared approved anticoagulants within their indications, non-serious adverse events were generally not reported, but those of special interest were defined and assessed. These comprised ablation-related complications including non-serious bleeding. The protocol encouraged brain imaging in patients who developed neurological abnormalities after the ablation procedure. All events from randomisation to 3months after index ablation procedure or to premature study termination were analysed.

Within the safety population of 655 patients 341 SAEs were reported. 181 (27.6 %) patients had SAEs. 88 SAEs(26.8%) were reported in Apixaban and 93 (28.4%) in VKA.

SAEs are distributed to the following main sub-groups:

120 SAEs in the field of cardiac disorders occurred in 93 patients (14.2%). 47 SAEs in 42 (6.4%) patients were related to general disorders and administration site conditions. 54 SAEs in 42 (6.4%) patients were related to surgical and medical procedures. 24 SAEs in 22 (3.4%) patients were related to infections and infestations. 22 SAEs in 20 (3.1%) patients were related to injury, poisoning and procedural complications.

19 SAEs in 16 (2.4%) patients were related to nervous system disorders. 18 SAEs in 16 (2.4%) patients were related to vascular disorders. 10 SAEs in 9 (1.4%) patients were related to renal and urinary disorders. 7 SAEs in 6 (0.9%) patients were related to renal and gastrointestinal disorders. 5 SAEs in 5 (0.8%) patients were related to gastrointestinal disorders. 4 SAEs in 4 (0.6%) patients were related to respiratory, thoracic and mediastinal disorders. 3 SAEs in 3 (0.5%) patients were related to investigations. 3 SAEs in 3 (0.5%) patients were related to neoplasms benign, malignant and unspecified. 1 SAE in 1 (0.2%) patients was related to ear and labyrinths disorders. 2 SAEs in 1 (0.2%) patient were related to psychiatric disorders. 2 SAEs in 1 (0.2%) patient were related to skin and subcutaneous tissue disorders(Table 5).

CONCLUSION:

Continuous apixaban is safe and effective in patients undergoing atrial fibrillation ablation at risk of stroke with respect to bleeding, stroke, and cognitive function. Further research is needed to reduce ablation-related acute brain lesions.

Date of the report

09.09.2018

Funding

AXAFA – AFNET 5 is an investigator-initiated trial. Sponsor of the trial is AFNET. AXAFA – AFNET 5 was partially funded by BMS/Pfizer, the DZHK (German Centre for Cardiovascular Research) and by the BMBF (German Ministry of Education and Research) to AFNET.

Appendices

Appendix 1: Tables
Appendix 2: SAE listings and death narratives
Appendix 3: Protocol Versions

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)
OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: AXAFA-AFNET 5
Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy.

STUDY AUTHOR(S): Benjamin Blank, Heidi Oellers, Paulus Kirchhof

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: Prof. Dr. Paulus Kirchhof SIGNATURE(S): _____
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