

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

<b>Submission date</b> 16/06/2014	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 20/06/2014	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 13/05/2019	<b>Condition category</b> Circulatory System	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Atrial fibrillation (AF) is a common heart condition which causes an irregular and rapid heartbeat. People with AF can be of much greater risk of having a stroke than the general population, depending on the presence of additional risk factors (high blood pressure, for example). Reducing this risk has traditionally been via the use of vitamin K antagonists, anticoagulation drugs that reduce blood clotting and thrombosis (blood clots within a blood vessel). Factor Xa inhibitors and direct thrombin inhibitors are new, novel fixed dose oral anticoagulants (NOACS). These NOACS - apixaban, rivaroxaban and dabigatran have all been shown to prevent stroke in patients with AF and have now been approved for use in the USA, Canada and Europe. The use of NOACS are also recommended in the current guidelines for AF treatment. Between 5-15% of AF patients undergo a procedure to treat their condition called catheter ablation, where radiofrequency energy is used to destroy the area inside the heart that is causing the abnormal beating. While some of these patients are on long-term anticoagulation therapy due to their risk of stroke, all patients undergoing this procedure have to take them in a period just before and after the operation to reduce the risk of a stroke associated with the actual procedure. Some small observational studies have highlighted concerns with using NOACS in patients undergoing catheter ablation. One study investigating the use of dabigatran showed that 4.4% of patients treated with this drug during catheter ablation suffered severe complications such as fluid developing around the heart (pericardial tamponade), stroke and, in some cases, the patients died. This was compared with only 2.1% of patients suffering similar events when VKAs was used. Although it is likely that the results of this study occurred by chance (as since demonstrated by other observational studies), it does mean that the present data suggests that VKAs should be the treatment of choice during catheter ablation. The international consensus statement on AF catheter ablation was published before these reports on dabigatran. It suggests to perform AF catheter ablation on continuous anticoagulation using either a VKA or a NOAC. The focussed update of the European Society of Cardiology (ESC) guidelines on AF,

however, published after these reports on dabigatran became available, only mentions using a VKA. The aim of this study is to test whether NOACs can be safely and effectively used for catheter ablation of AF.

**Who can participate?**

Patients who have AF, are going to undergo catheter ablation and are at an increased risk of stroke (have, for example, had a previous stroke, are aged at least 75 years, have high blood pressure, diabetes mellitus or symptomatic heart failure)

**What does the study involve?**

Comparison of two therapies: NOACs and VKAs during the atrial fibrillation ablation procedure

**What are the possible benefits and risks of participating?**

The patient will receive a particularly thorough medical examination as part of the participation in the study. Beyond that, no further personal health benefits, besides the usual standard of care, are expected for the patient. In the AXAFA study, no investigational drugs or interventions not yet approved by health authorities will be applied. All study drugs are market approved and will be used within the approved indications, for AF only. All concomitant study procedures and therapies, e. g. the catheter ablation for AF, are standard care procedures according to applicable medical guidelines.

**Where is the study run from?**

8 EU countries: Austria, Germany, Italy, Spain, Belgium, Netherlands, UK, Denmark, USA

**When is the study starting and how long is it expected to run for?**

January 2015 – September 2017

**Who is funding the study?**

Kompetenznetz Vorhofflimmern e.V. (AFNET)  
[Atrial Fibrillation NETwork] (Germany)

**Who is the main contact?**

Elisabeth Freund  
e.freund@cri-muc.eu

## Contact information

**Type(s)**

Scientific

**Contact name**

Prof Paulus Kirchhof

**Contact details**

c/o Elisabeth Freund  
Head of Clinical Operations  
CRI - The Clinical Research Institute GmbH  
Arnulfstraße 19  
München  
Germany  
80335

# Additional identifiers

## Clinical Trials Information System (CTIS)

2014-002442-45

## ClinicalTrials.gov (NCT)

NCT02227550

## Protocol serial number

N/A

# Study information

## Scientific Title

Anticoagulation using the direct factor Xa inhibitor apixaban during atrial fibrillation catheter ablation and comparison to vitamin K antagonist therapy: A investigator-initiated, prospective, parallel-group, randomised, open, blinded outcome assessment (PROBE) interventional multi-centre trial.

## Acronym

AXAFA-AFNET5

## Study objectives

Anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Ethics Committee at the Medical Faculty of the University of Leipzig (Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig), 20/01/2015, ref: 341/14-ff

## Study design

Prospective phase IV parallel-group randomised open, blinded outcome assessment (PROBE) interventional multi-centre trial

## Primary study design

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

Non-valvular atrial fibrillation with a clinical indication for catheter ablation/bleeding + stroke risk/cardiology

## Interventions

Anticoagulation therapy with new oral anticoagulants and vitamin-k-antagonists during atrial fibrillation ablation

## **Intervention Type**

Drug

## **Phase**

Phase IV

## **Drug/device/biological/vaccine name(s)**

Test IMP: Apixaban, comparator IMP: locally used VKA

## **Primary outcome(s)**

A composite of

1. All-cause death
2. Stroke (ischemic stroke, subarachnoid hemorrhage and hemorrhagic stroke)
3. Major bleeding events, defined as BARC 2 or higher

## **Key secondary outcome(s)**

1. Any bleeding event
2. Major bleeding events according to the ISTH and TIMI definitions
3. Number of strokes, other systemic embolic events, and all-cause deaths
4. Time from randomisation to ablation
5. Nights spent in hospital after ablation
6. Health-care related cost calculation
7. Number of hospitalizations for cardiovascular reasons
8. Treatment duration prior to ablation and total time on oral anticoagulation
9. Number of patients with clinically indicated TEE
10. ACT during ablation
11. Time to recurrent AF
12. Rhythm status at the end of follow-up
13. Vascular access complications leading to prolongation of in-hospital stay or specific therapy
14. Quality-of-life changes at month 3 compared to baseline
15. Cognitive function change at month 3 compared to baseline

Updated 18/10/2017:

16. MRI sub-study, only: Prevalence of clinically "silent" MRI-detected brain lesions within 48 hours after the ablation procedure
17. 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

## **Completion date**

12/09/2017

## **Eligibility**

### **Key inclusion criteria**

1. Non-valvular AF (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 CHADS2 stroke risk factors
  - 3a. Stroke or TIA
  - 3b. Age  $\geq 75$  years

- 3c. Hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure >145/90 mm Hg
- 3d. Diabetes mellitus
- 3e. Symptomatic heart failure (NYHA  $\geq$ II)
- 4. Age  $\geq$ 18 years
- 5. Provision of signed informed consent

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Sex**

All

### **Total final enrolment**

674

### **Key exclusion criteria**

General exclusion criteria

- 1. Any disease that limits life expectancy to less than 1 year
- 2. Participation in another clinical trial, either within the past two months or still ongoing
- 3. Previous participation in AXAFA
- 4. 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 randomised.
- 5. Breastfeeding women
- 6. Drug abuse or clinically manifest alcohol abuse

Added 18/10/2017:

- 7. Any stroke within 14 days before randomisation
- 8. Coadministration 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 (Appendix VIII)

Exclusion criteria related to a cardiac condition

- 9. 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.
- 10. Any previous ablation or surgical therapy for AF
- 11. Cardiac ablation therapy for any indication (catheter-based or surgical) within 3 months prior to randomisation
- 12. Clinical need for triple therapy (combination therapy of clopidogrel, acetylsalicylic acid, and oral anticoagulation)
- 13. Other contraindications for use of VKA or apixaban

Exclusion criteria based on laboratory abnormalities

14. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) <15 ml/min

Added 18/10/2017: 15. Documented atrial thrombi less than 3 months prior to randomisation

**Date of first enrolment**

01/01/2015

**Date of final enrolment**

10/04/2017

## **Locations**

**Countries of recruitment**

United Kingdom

Austria

Belgium

Denmark

Germany

Italy

Netherlands

Spain

United States of America

**Study participating centre**

c/o Elisabeth Freund

München

Germany

80335

## **Sponsor information**

**Organisation**

Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]

**ROR**

<https://ror.org/01spm3d88>

# Funder(s)

## Funder type

Research organisation

## Funder Name

Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]

# Results and Publications

## Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

## IPD sharing plan summary

Data sharing statement to be made available at a later date

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	21/08/2018	13/05/2019	Yes	No
<a href="#">Protocol article</a>	protocol	01/01/2017		Yes	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes