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

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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 AF in the prevention of peri-procedural complications. The substudy involving...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON44975

Source
ToetsingOnline

Brief title
AXAFA

Condition

- Cardiac arrhythmias

Synonym
Atrial fibrillation, cardiac rhythm disturbance

Research involving
Human

Sponsors and support

Primary sponsor: Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]
Source(s) of monetary or material Support: non-commercial sponsor Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.) [German Atrial Fibrillation Competence NETwork]

Intervention

Keyword: Artrial Fibrilation, Catheter ablation, Continuous anticoagulation, Peri-procedural complications

Outcome measures

Primary outcome

A composite of

- all-cause death,

- stroke (ischemic stroke, subarachnoid haemorrhage and haemorrhagic stroke),

and

- major bleeding events, defined as BARC 2 or higher

Secondary outcome

- 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

- Number of hospitalisations for cardiovascular reasons

- Treatment duration prior to ablation and total time on oral anticoagulation

- Number of patients with clinically indicated TEE

- ACT during ablation

- Time to recurrent AF

- Rhythm status at the end of follow-up

- Vascular access complications leading to prolongation of in-hospital stay or specific therapy

- Quality-of-life changes at month 3 compared to baseline

- Cognitive function change at month 3 compared to baseline

- Prevalence of clinically *silent* MRI-detected brain lesions within 48 hours after the ablation procedure (MRI sub-study),

- Impact of ablation-associated clinically overt strokes or MRI-detected but clinically *silent* acute brain lesions on cognitive function after ablation (MRI sub-study)

Study description

Background summary

Factor Xa inhibitors and direct thrombin inhibitors are new, fixed dose oral anticoagulants that provide a much-needed alternative treatment to vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF). Their use has been evaluated in several large clinical trials enrolling patients with non-valvular AF at increased risk for stroke. Three non-inferiority trials comparing apixaban, rivaroxaban, or dabigatran to warfarin have been reported, as well as one additional trial demonstrating superiority of apixaban to aspirin. Based on the outcome of these large trials, these three novel oral anticoagulants (NOACs) have been approved in the USA, Canada, and in Europe for stroke prevention in patients with AF and at least one additional risk factor for stroke. Furthermore, NOACs are recommended in current AF guidelines. Approximately 5-15% of the non-valvular AF population undergoes catheter ablation in recent surveys. While some of these patients require long-term anticoagulation because of their individual stroke risk, all patients require anticoagulation during and after the ablation procedure to reduce the risk of procedure-associated stroke. The use of NOACs in patients undergoing catheter ablation for symptomatic AF has not been tested in randomised controlled trials. Rather, retrospective small observational case series raised concerns

about the peri-procedural use of NOACs in patients undergoing catheter ablation: The largest published experience exists with dabigatran, the NOAC which received approval first. Numerically, there were more severe events in patients undergoing catheter ablation with dabigatran than in those undergoing ablation while on VKAs, namely 18/409 patients with severe events on dabigatran (4.4%) compared to 8/371 patients with severe events on VKAs (2.1%). These numbers only represent serious events (such as pericardial tamponade, clinically overt stroke, death), as other major bleeding events were not collected. Although this observation is likely to reflect a play of chance rather than a biological difference, as suggested by more recent evidence from retrospective data, these data suggest to rather *choose the established treatment* of VKAs during ablation. In the absence of controlled trial data, this unequal distribution of serious complications is a cause of concern among ablationists.
The international consensus statement on AF ablation was published before these reports on dabigatran. It suggests to perform AF ablation on continuous anticoagulation using either a VKA or a NOAC, while the focussed update of the ESC guidelines on AF, published after these reports on dabigatran became available, only mentions continuous peri-procedural anticoagulation using a VKA. Hence, there is a need for a well-designed, adequately powered trial to test whether NOACs can be used in the setting of catheter ablation of AF.

Study objective

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 AF in the prevention of peri-procedural complications. The substudy involving MRI scans after the ablation procedure aims to identify invisible damage such as 'silent'strokes in the test versus the comparator group.

Study design

Investigator-initiated, prospective, parallel-group, randomised, open, blinded outcome assessment (PROBE) interventional multi-centre trial. Phase IV

Intervention

Investigational medicinal product: apixaban
Comparator: locally used, marketed VKA
Apixaban will be given 5 mg twice daily and compared to oral anticoagulation using the locally used VKA (aiming for an international normalized ratio (INR) of 2.0-3.0). The apixaban dose will be reduced to 2.5 mg twice daily at the time of randomisation according to the approved label. Study medication has to be administered effectively 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 has to be effectively continued for three months after the ablation procedure.
All patients will be treated following current guidelines (ESC focussed update of the AF guidelines, 2nd catheter ablation consensus statement) including continuous oral anticoagulation during ablation procedures (continuous apixaban, target INR 2.0-2.5 in the VKA group). All patients will receive peri-procedural heparin to assure an activated clotting time (ACT) >300 s.
MRI sub-study: A subgroup of maximal 300 study patients will undergo brain magnetic resonance imaging study (MRI, without contrast agents) within 3-48 hours after the ablation procedure.

Study burden and risks

General risk assessment of the AXAFA trial: All study drugs are market approved and will be used within the
approved indications, only. All concomitant study procedures, e. g. the catheter ablation for AF, are standard
care procedures according to applicable medical guidelines used within the recommended indications. All
participating study sites have to document sufficient experience in the management of patients with AF in
general and in catheter ablation of AF in detail. Thus, the overall risk level in this phase IV trial is expected to
be low.
The additional brain MRIs being performed in about 300 sub-study patients will not add radiation risk to
participating patients.
Assessment of the individual risk of study patients: The use of study drugs and concomitant procedures
within AXAFA does not deviate from standard care procedures. The tested modification of the most common
drug regime, treatment with a factor Xa inhibitor peri-ablation, is applying an approved medication within its
approved label and in the approved population. There are several single-center reports that suggest safety of
this approach, although a formal confirmation of its safety is lacking. Thus, the individual risk of study
patients in both treatment arms will not differ from the risk of therapy in clinical routine.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

I1. Non-valvular AF (ECG-documented) with a clinical indication for catheter ablation
I2. Clinical indication to undergo catheter ablation on continuous anticoagulant therapy
I3. Presence of at least one of the CHADS2 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).
I4. Age * 18 years
I5. Provision of signed informed consent

Exclusion criteria

General exclusion criteria

E1. Any disease that limits life expectancy to less than 1 year
E2. Participation in another clinical trial, either within the past two months or still ongoing
E3. Previous participation in AXAFA
E4. 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.
E5. Breastfeeding women
E6. Drug abuse or clinically manifest alcohol abuse
E7. Any stroke within 14 days before randomisation
E8. 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
Exclusion criteria related to a cardiac condition
E9. 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.
E10. Any previous ablation or surgical therapy for AF
E11. Cardiac ablation therapy for any indication (catheter-based or surgical) within 3 months prior to randomisation
E12. Clinical need for *triple therapy* (combination therapy of clopidogrel, acetylsalicylic acid, and oral anticoagulation)
E13. Other contraindications for use of VKA or apixaban
E14. Documented atrial thrombi less than 3 months prior to randomisation.
Exclusion criteria based on laboratory abnormalities
E15. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) < 15 ml/min

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-09-2015
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eliquis
Generic name:	Apixaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002442-45-NL
ISRCTN	ISRCTN87711003
CCMO	NL51728.042.15