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Non-vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes

Submission date 08/12/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data [_] Record updated in last year
Registration date 29/01/2016	**Overall study status** Stopped	
Last Edited 30/01/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Atrial fibrillation (AF) is a common heart condition, affecting millions of people worldwide. When a person is suffering from AF, the electrical signals that control the heartbeat fire chaotically, causing the heart to beat irregularly and often very fast (arrhythmia). Studies have shown that AF can increase a persons' risk of stroke, particularly ischaemic stroke (a condition in which the arteries that supply the brain with oxygen (carotid arteries) become narrowed or blocked, causing severely reduced blood flow). Many recent studies have shown that even very early stages of AF, so called "atrial high rate episodes" (AHRE), are linked with an increased risk of stroke. A large portion of these patients also develop AF over time. Stroke prevention from patients with AF is usually done using vitamin K antagonists (VKAs). These are anti-clotting medications which prevent blood clots from forming by interfering with the action of vitamin K (which plays a key role in blood clotting). These bear the risk of bleeding events and need to be dose-adjusted for each individual depending on blood values taken repetitively. Non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced into clinical practice in recent years as an alternative, appearing safer than VKAs and being administered in a fixed dose. The aim of this study is to find out whether long-term treatment with Edoxaban (a NOAC) is more effective than the current strategy of no oral anticoagulation treatment in AHRE patients who present with an additional risk factor for stroke but who do not have diagnosed AF.

Who can participate?
Adults aged 65 or over with an implanted pacemaker or defibrillator that can detect AHRE.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group are given 60mg Edoxaban tablets to take every day for at least 12 months (which can later be reduced to 30mg a day if appropriate). Participants are also given a placebo (dummy) tablet to take which looks the same as a 100mg aspirin tablet to take once a day for the same length of time. Those in the second group are given a placebo (dummy) tablet that looks the same as a 60mg Edoxaban tablet and are either given a 100mg aspirin tablet to take every day (if the doctor feels they could benefit from it) or a placebo (dummy) tablet to take which looks the same as a

100mg aspirin tablet to take every day for at least 12 months. All participants are monitored throughout the study in order to record the amount who have suffered from a stroke or have died.

What are the possible benefits and risks of participating?
There is not expected to be any direct benefits from taking part in the study. The risks involves with participating are expected to be low as edoxaban has a clinical licence for stroke prevention in patients with atrial fibrillation.

Where is the study run from?
The study is run from the Atrial Fibrillation Competence Network e . V. (Germany)

When is the study starting and how long is it expected to run for?
February 2016 to December 2022

Who is funding the study?
1. Daiichi Sankyo Europe GmbH (Germany)
2. German Centre for Cardiovascular Research (Germany)

Who is the main contact?
1. Dr Vincent Beuger, vincent.beuger@af-net.eu
2. Prof Paulus Kirchof, p.kirchhof@uke.de

Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02618577

Clinical Trials Information System (CTIS)
2015-003997-33

Protocol serial number
NOAH - AFNET 6

Study information

Scientific Title
Non-vitamin K Antagonist Oral Anticoagulants in patients with atrial high rate episodes - an investigator-driven, prospective, randomised, double-blind, multi-centre trial initiated by the European Society of Cardiology and AFNET

Acronym
NOAH

Study objectives
The aim of the trial is to demonstrate that oral anticoagulation using the NOAC edoxaban is superior to current therapy to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE and at least two stroke risk factors but without AF.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Technische Universität Dresden, Ethikkommission, 20/05/2016, Number: EK 144042016
Pilotprojekt-Nr. PB 0008
All other centres received ethics approval before recruitment of the first participant

Primary study design
Interventional

Study design

Prospective randomised double-blind multi-centre trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Atrial high rate episodes

Interventions
The investigational medicinal product being tested is the Non-vitamin K antagonist oral anticoagulant edoxaban. The IMP used as a comparator is acetylsalicylic acid or placebo. The patients will randomly be assigned to the “NOAC” or to the comparator group.

NOAC group: Participants will receive anticoagulation therapy with edoxaban. Edoxaban will be used at the therapeutic dose approved for stroke prevention in non-valvular AF, i.e. 60 mg OD or with a reduction of dose to 30 mg OD in patients.
In the “NOAC” group one edoxaban tablet plus one placebo tablet matching in colour, weight, form and size to ASA 100 mg will be administered per day irrespective of stratum according to indication for use of antiplatelet therapy. The use of edoxaban eliminates the necessity of parallel intake of ASA 100 mg in case of an indication for use of antiplatelet therapy.

Usual Care group: Participants will receive either acetylsalicylic acid (ASA) or no antithrombotic therapy depending on the indication for use of antiplatelet therapy (stratification at the time of randomisation). In the “Usual Care” group either one tablet of ASA 100 mg plus one placebo tablet matching in colour, form and size to edoxaban 60 mg or one placebo tablet matching in colour, weight, form and size to ASA 100 mg plus one placebo tablet matching in colour, form and size to edoxaban 60 mg will be administered per day depending on the indication for use of antiplatelet therapy as assessed by the responsible investigator. A documented change of indication for use of antiplatelet therapy in follow-up will lead to blinded exchange of double-dummy study drug according to actual indication.

Treatment is starting at baseline. Based on the sample size estimation, the expected mean follow-up time will be about 28 months per patient with a minimum follow-up time of 12 months and a maximum follow-up time of presumably 44 months until end of final visit after required number of endpoints has been reached. Every patient will be followed-up until global end of study. The exact duration of follow-up will be determined by the accrual of events (event-driven study).

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Edoxaban, acetylsalicylic acid (ASA, aspirin)

Primary outcome(s)
Time from randomisation to the first occurrence of stroke, systemic embolism, or cardiovascular death

Key secondary outcome(s)
Secondary outcome measures as of 27/09/2018:
1. Components of the primary outcome
2. Major Adverse Cardiac Events (MACEs: cardiac death, myocardial infarction, acute coronary syndrome (ACS))
3. All-cause death
4. Major bleeding event rate (according to the International Society on Thrombosis and Haemostasis (ISTH) definitions)
5. Quality of life assessed using the EQ-5D including its visual-analogue scale and the Karnofsky scale at baseline
6. Patient satisfaction is measured using the modified EHRA score and PACT-Q
7. Cost effectiveness and health resource utilisation is estimated using quantification of relevant events, interventions, nights spent in hospital and cardiovascular therapies
8. Patient autonomy
9. Cognitive function is measured using the Montreal Cognitive Assessment (MoCA)

Previous secondary outcome measures:
1. All cause death is determined at 24 months
2. Major bleeding event rate (according to the International Society on Thrombosis and Haemostasis (ISTH) definitions) is determined at 24 months
3. Quality of life assessed using the EQ-5D including its visual-analogue scale and the Karnofsky scale at baseline, 12 and 24 months
4. Patient satisfaction is measured using the modified EHRA score (36) and PACT-Q (43) at baseline, 12 and 24 months
5. Cost effectiveness and health resource utilisation is estimated using quantification of relevant events, interventions, nights spent in hospital and cardiovascular therapies is determined at 24 months
6. Patient autonomy is measured at baseline, 12 and 24 months
7. Cognitive function is measured using the Montreal Cognitive Assessment (MoCA) baseline, 12 and 24 months

Completion date
31/12/2022

Reason abandoned (if study stopped)
The reason for early termination is an observed trend towards futility for efficacy combined with expected safety concerns.

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 19/03/2020:
1. Implanted pacemaker, defibrillator or insertable cardiac monitor with feature of detection of AHRE, implanted at least 2 months prior to randomization
2. AHRE detection feature activated adequately according to "Suggestions for optimal programming of devices for adequate detection of AHRE"
3. AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration) documented by the implanted device via its atrial lead and stored digitally. AHRE episodes detected in the first 2 months after implantation of a new device involving placement or repositioning of electrodes are not counted. AHRE episodes recorded in the first two months after a simple "box change" operation, i.e. exchange of a pacemaker or defibrillator device without exchange or repositioning of electrodes, are

eligible.
4. Aged 65 years or over
5. In addition, at least one of the following cardiovascular conditions leading to a modified CHA2DS2VASc score of 2 or more:
a. Age ≥ 75 years
b. Heart failure (clinically overt or LVEF < 45%)
c. Arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mmHg)
d. Diabetes mellitus
e. Prior stroke or transient ischemic attack (TIA)
f. Vascular disease (previous myocardial infarction, peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram [TEE])
6. Provision of signed informed consent

Previous participant inclusion criteria as of 27/09/2018:
1. Implanted pacemaker or defibrillator with feature of detection of AHRE, implanted at least 2 months prior to randomisation
2. AHRE detection feature activated adequately according to "Suggestions for optimal programming of devices for adequate detection of AHRE"
3. AHRE (≥ 180 bpm atrial rate and ≥ 6 min duration) documented by the implanted device via its atrial lead and stored digitally. AHRE episodes detected in the first 2 months after implantation of a new device involving placement or repositioning of electrodes are not counted. AHRE episodes recorded in the first two months after a simple "box change" operation, i.e. exchange of a pacemaker or defibrillator device without exchange or repositioning of electrodes, are eligible.
4. Aged 65 years or over
5. In addition, at least one of the following cardiovascular conditions leading to a modified CHA2DS2VASc score of 2 or more:
5.1. Age ≥ 75 years;
5.2. Heart failure (clinically overt or LVEF < 45%);
5.3. Arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihyper-tensive therapy or resting blood pressure > 145/90 mmHg);
5.4. Diabetes mellitus;
5.5. Prior stroke or transient ischemic attack (TIA);
5.6. Vascular disease (previous myocardial infarction, peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram [TEE]).
6. Provision of signed informed consent

Previous participant inclusion criteria:
1. Implanted pacemaker or defibrillator with feature of detection of AHRE, implanted at least 2 months prior to randomisation
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4. Aged 65 years or over
5. In addition, at least one of the following cardiovascular conditions leading to a CHA2DS2VASc score of 2 or more:

5.1. Heart failure (clinically overt or LVEF < 45%)
5.2. Arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mmHg)
5.3. Diabetes mellitus
5.4. Prior stroke or transient ischemic attack (TIA)
5.5. Vascular disease (peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardio-gram [TEE])
6. Provision of signed informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Lower age limit
65 Years

Sex
All

Total final enrolment
2535

Key exclusion criteria
1. Any disease that limits life expectancy to less than 1 year
2. Participation in another controlled clinical trial, either within the past two months or still ongoing
3. Previous participation in the present trial NOAH
4. Drug abuse or clinically manifest alcohol abuse. Exclusion criteria related to a cardiac condition
5. Any history of overt AF or atrial flutter
6. Indication for oral anticoagulation (e.g. deep venous thrombosis)
7. Contraindication for oral anticoagulation in general
8. Contraindication for edoxaban as stated in the current SmPC
9. Indication for long-term antiplatelet therapy other than acetylsalicylic acid, especially dual antiplatelet therapy (DAPT) with acetylsalicylic acid and one of the following agents: clopidogrel, prasugrel, or ticagrelor. Patients with a transient requirement for DAPT (e.g. after receiving a stent) will be eligible when the need for DAPT is no longer present
10. Acute coronary syndrome, coronary revascularisation (PCI or bypass surgery), or overt stroke within 30 days prior to randomisation
11. End stage renal disease (creatinine clearance (CrCl) < 15 ml/min as calculated by the Cockcroft-Gault method)

Date of first enrolment
01/02/2016

Date of final enrolment
08/09/2022

Locations

Countries of recruitment
United Kingdom

Austria

Belgium

Bulgaria

Czech Republic

Denmark

France

Germany

Greece

Hungary

Italy

Netherlands

Poland

Portugal

Romania

Spain

Sweden

Ukraine

Study participating centre
Kompetenznetz Vorhofflimmern e. V.
Mendelstraße 11
Münster
Germany
48149

Sponsor information

Organisation
Kompetenznetz Vorhofflmmern e.V. (Atrial Fibrillation NETwork - AFNET)

Funder(s)

Funder type
Industry

Funder Name
Daiichi Sankyo Europe GmbH

Funder Name
Deutsches Zentrum für Herz-Kreislaufforschung

Alternative Name(s)
German Centre for Cardiovascular Research, DZHK Germany, Zentrum HerzKreislaufForschung, Deutsches Zentrum für Herz-Kreislauf-Forschung e.V., Deutsches Zentrum für Herz-Kreislaufforschung e.V., DZHK, DZHK e.V.

Funding Body Type
Government organisation

Funding Body Subtype
Research institutes and centers

Location
Germany

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Chief Investigator Prof Paulus Kirchhof, p.kirchhof@uke.de, and will be published as a supplement to the results publication.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		25/08/2023	29/08/2023	Yes	No

Protocol article	protocol	01/08/2017		Yes	No
Statistical Analysis Plan	version 4.0	21/03/2023	30/01/2024	No	No