Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes

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To demonstrate that oral anticoagulation with the NOAC edoxaban is superior to current therapy (antiplatelet therapy or no therapy depending on cardio-vascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52989

Source
ToetsingOnline

Brief title
NOAH * AFNET 6

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
atrial high rate episodes (AHRE), subclinical atrial fibrillation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Aminosalicylic Acid, Atrial High Rate Episodes (AHRE), Edoxban

Outcome measures

Primary outcome

Time from randomisation to the first occurrence of stroke, systemic embolism, or cardiovascular death. A detailed definition of these outcome events is provided in Appendix III.

Secondary outcome

-Components of the primary outcome

-Major Adverse Cardiac Events (MACEs: cardiovascular death, myocardial infarction, acute coronary syndrome (ACS), PCI, CABG)

- stroke or systemic arterial embolism

-All-cause death

-Major bleeding events according to the ISTH definitions

-Quality of life changes at 12 and 24 months compared to baseline

-Patient satisfaction at 12 and 24 months compared to baseline

-Cost effectiveness and health resource utilisation

-Patient autonomy changes at 12 and 24 months compared to baseline including chronic consequences of stroke (aphasia, hemianopia (*mild stroke*))

-Cognitive function at 12 and 24 months compared to baseline

Study description

Background summary

Atrial fibrillation (AF) is a common cause of stroke, especially ischemic stroke. So far, all available data that demonstrate a beneficial effect of oral anti-coagulation for stroke prevention have been collected in populations with AF documented by conventional ECG recordings. It is well established that a large proportion of AF episodes remain undiagnosed (*silent AF*), and many of these patients present with a stroke as the first clinical sign of AF. Earlier initiation of anticoagulation could prevent such events. Continuous monitoring of atrial rhythm by implanted devices could close this diagnostic gap. Pace-makers, defibrillators, and cardiac resynchronisation devices already provide automated algorithms alerting to the occurrence of highly organised atrial tachyarrhythmia episodes, also called *subclinical atrial fibrillation* or, more commonly, *atrial high rate episodes* (AHRE). Data from large prospectively followed patient cohorts demonstrated that stroke rate is increased in patients with AHRE. A sizeable portion of these patients develops clinically detected AF over time. In these patients, AHRE can be considered as an early manifestation of paroxysmal AF. A few AHRE patients do not develop clinically overt AF, and the absolute stroke rates are lower in patients with AHRE when compared to stroke rates in patients with clinically diagnosed AF. In light of the bleeding complications associated with oral anticoagulant therapy, there is thus uncertainty about the optimal antithrombotic therapy in patients with AHRE.
The Non-vitamin K antagonist Oral anticoagulants (NOACs) provide similar or slightly better stroke prevention, and appear slightly safer compared to vitamin K antagonists (VKAs). In addition, no individual therapy adjustment of NOACs has to be performed. Edoxaban, a newly introduced NOAC, at a dose regime of 60 mg once daily (OD) has a favourable profile compared to dose-adjusted VKA therapy: In the ENGAGE-TIMI 48 trial, edoxaban prevented strokes at least as effectively as VKA therapy but caused less major bleeding events than VKA therapy.

Study objective

To demonstrate that oral anticoagulation with the NOAC edoxaban is superior to current therapy (antiplatelet therapy or no therapy depending on cardio-vascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE but without overt AF and at least two stroke risk factors leading to a modified CHA2DS2VASc score of 2 or more.
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Study design

Investigator-initiated, prospective, parallel-group, randomised, double-blind, multi-centre trial. Although it can be argued that the indication tested is within the registered label of edoxaban, NOAH * AFNET 6 will be conducted as a phase IIIb study.

Intervention

not applicable

Study burden and risks

There are no additional risks in this study other than those which may occur with therapy in clinical routine treatment for prevention of stroke. Even simple procedures, e.g. blood sampling, may involve undesirable side effects. These may include bruising at the puncture site or infections. However, the overall risks in the study do not exceed the risks of adverse events in routine clinical care.

Treatment with edoxaban or ASA may increase the risk of visible or occult bleeding. However, the intensity and extent of bleeding may vary.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Elderly (65 years and older)

Inclusion criteria

-Pacemaker, defibrillator or insertable cardiac monitor implanted for any reason with feature of detection of AHRE, implanted at least 2 months prior to randomisation.
-AHRE detection feature activated for adequate detection of AHRE
-AHRE (* 170 bpm atrial rate and * 6 min duration) documented by the implanted device via its atrial lead and stored digitally.
Any AHRE episode recorded is potentially eligible, but AHRE episodes detected in the first 2 months after implantation of a new device involving placement or repositioning of atrial electrodes are not eligible. 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 atrial electrodes, are eligible.
-Age * 65 years
-In addition, at least one of the following cardiovascular conditions leading to a modified CHA2DS2VASc score of 2 or more:
--Age * 75 years,
--heart failure (clinically overt or LVEF < 45%),
--arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure 145/90 mmHg),
--diabetes mellitus,
--prior stroke or transient ischemic attack (TIA),
--vascular disease (previous myocardial infarction, peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram [TEE]).
-- Provision of signed informed consent

Exclusion criteria

- Patients with history of overt AF or atrial flutter
- patients with a clear contraindication for oral anticoagulation,
- patients with a clear need for oral anticoagulation,
- patients with indication for long-term antiplatelet therapy other than acetylsalicylic acid (ASA) or a need for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy (DAPT), are not suitable for NOAH - AFNET 6.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-07-2017
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspirin protect 100 mg
Generic name:	acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ASS Hexal protect 100mg
Generic name:	acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	lixiana
Generic name:	edoxaban
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-09-2016

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-003997-33-NL
ISRCTN	ISRCTN17309850
CCMO	NL58839.018.16