Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral aIntIcoagulation sTrategy (The RE-CIRCUIT Trial)

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

Summary

ID

NL-OMON42157

Source
ToetsingOnline

Brief title
RE-CIRCUIT

Condition

- Cardiac arrhythmias
- Vascular therapeutic procedures
- Vascular injuries

Synonym
non-valvular atrial fibrillation and pulmonary vein ablation

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim bv

Intervention

Keyword: Ablation, anticoagulation, Dabigatran

Outcome measures

Primary outcome

The primary endpoint for this trial is a safety endpoint:

* The incidence of Major Bleeding Events according to the ISTH definition

during the ablation procedure and up to 2 months post-ablation.

Secondary outcome

The secondary endpoints for this trial are the incidence of the following

efficacy and safety

endpoints:

*- Stroke/SE/TIA events during the ablation procedure and up to 2 months

post-ablation.

*- Minor bleeding events during the ablation procedure and up to 2 months

postablation.

*- A composite of major bleeding events and thromboembolic events (Stroke, SE

and TIA) during the ablation procedure and up to 2 months post-ablation.

Study description

Background summary

See section 1.1 of the protocol.
The current estimate of the prevalence of atrial fibrillation (AF) in the developed world is approximately 1.5*2% of the general population. The arrhythmia is associated with a fivefold increase in the risk of stroke and a three-fold increase in the incidence of congestive heart failure and higher mortality. Chronic anticoagulant treatment is mandatory in the great majority of patients with AF.
Catheter ablation is currently recommended in the guidelines as an interventional alternative for the treatment of patients with AF. During AF ablation, there is a measurable risk of thromboembolic complication (stroke, transient ischemic attack (TIA), peripheral embolism) due to the pro-thrombotic effects of AF itself, the instrumentation of the left atrium (transseptal access), due to restoration of sinus rhythm/ cardioversion, and the disruption of the atrial endocardium during application of radiofrequency (RF) energy. Minimizing these complications by optimal periprocedural anticoagulation with an appropriate balance between thrombosis and bleeding is critical to the efficacy and safety of the procedure.
The current standard of care is to anticoagulate patients with a vitamin K antagonist (VKA) (target international normalized ratio [INR] range 2.0-3.0) for at least 1 month pre-ablation and for 2-3 months post-ablation regardless of CHA2DS2-VASc score. In the past it was usual practice to stop VKA before the ablation to ensure a safe venous access during the procedure. Patients were bridged with low molecular weight heparin (LMWH) or unfractionated heparin.(UFH) during the time off VKA pre-procedure and also for a few days post-ablation until the VKA therapy returned to the target therapeutic range (INR 2.0-3.0). There is evidence for the superiority of uninterrupted VKA therapy, with a target INR between 2.0 and 3.0, as a periprocedural anticoagulant over other interrupted anticoagulation strategies. The current guidelines state that the
performance of catheter ablation of AF in patients who are therapeutically anticoagulated with VKA should be considered. In recent years, increasingly more AF patients are maintained on non-vitamin K oral anticoagulants (NOACs), posing a management challenge for periprocedural anticoagulation when patients are scheduled for AF ablation.

Study objective

See section 2.2. of the protocol.
The primary objective of this trial is to assess the safety of an uninterrupted dabigatran etexilate periprocedural anticoagulant regimen compared to an uninterrupted warfarin regimen in NVAF patients undergoing AF ablation in a PROBE (Prospective, randomized, open label, blinded end point) active controlled study.

Study design

See section 3.1 of the protocol.
This study is a prospective, randomised, open label, blinded endpoint (PROBE), multicentre, active controlled trial and the primary clinical endpoint is being adjudicated by an IAC in a blinded fashion.
Patients will be randomly assigned to 150 mg dabigatran etexilate b.i.d. or warfarin in a 1:1 ratio and remain on this treatment for the duration of the trial.
The screening period will consist of one visit (Visit 1). The patients will be randomised at Visit 2. Screening and randomisation can be conducted on the same day.
Pre-ablation period
There will be a pre-ablation period of 4 to 8 weeks.
Ablation procedure
The ablation procedure will be performed after at least 4 weeks of anticoagulation.
Post-ablation period
Systemic anticoagulation with dabigatran etexilate 150 mg b.i.d. or with adjusted warfarin (target INR 2.0-3.0) will be continued for 60 days post-ablation. Patients will be assessed at the time of randomisation, on the day of the AF ablation procedure and just before discharge (next day or 48 hours after the ablation procedure at the latest) and also on Day 30 and Day 60, which is the end of treatment (EOT) with trial medication. All patients will have a follow-up visit one week after the EOT visit.

Intervention

Treatment with dabigatran etexilate instead of VKA.

Study burden and risks

The burden for the study is mainly undergoing a TEE, which in most cases is a standard procedure when a patient needs to undergo an ablation.

The to be expected risks are low, as described in the patient information sheet. This consist of risks with adverse events like bleeding events. And the risks during blood draws, ECG, and unforeseen risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patients aged ><=18 years.
- Patients eligible for treatment with dabigatran etexilate 150 mg b.i.d. according to local label.
- Treatment naïve patients or patients on oral anticoagulant treatment with a VKA, dabigatran etexilate, rivaroxaban, apixaban or edoxaban.
- Patients with paroxysmal or persistent NVAF with a planned catheter ablation for AF unless it is performed an investigational ablation technique.
- AF must have been documented at least once within 24 months prior to screening (Visit 1).
- The patient must be able to give informed consent in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

Exclusion criteria

- Patients with permanent AF.
- Patients with AF felt to be secondary to an obvious reversible cause.
- Patients with LA size >= 60 mm

- Patients with contraindications to systemic anticoagulation with heparin, warfarin or dabigatran etexilate
- Patients with a known allergy to warfarin tablets and it excipients or to dabigatran etexilate or its excipients
- Mechanical or biological heart valve prosthesis
- Severe renal impairment
- Stroke within 1 month prior to screening visit
- Major surgery per investigator judgement within the previous month prior to screening.
- Patient has received an organ transplant or is on a waiting list for an organ transplant
- History of intracranial haemorrhage, intraocular, spinal, retroperitoneal or non-traumatic intra-articular bleeding
- Gastrointestinal haemorrhage within one month prior to screening, unless, in the opinion of the investigator, the cause has been permanently eliminated (e.g. by surgery).
- Major bleeding episode (ISTH definition) one month prior to the screening visit.
- Haemorrhagic disorder or bleeding diathesis
- Anaemia or thrombocytopenia including heparin-induced thrombocytopenia at screening
- Recent malignancy or radiation therapy (<=6 months prior to screening) unless, in the opinion of the Investigator, the estimated life expectancy is greater than 36 months
- Active liver disease
- Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John*s Wort or any cytotoxic/myelosuppressive therapy.

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):	28-07-2015

Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Coumadin
Generic name:	warfarin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pradaxa
Generic name:	dabigatran etexilate

Ethics review

Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-04-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-01-2016

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2014-003890-40-NL
ClinicalTrials.gov	NCT02348723
CCMO	NL51969.060.15