# Vitamin K antagonist (VKA) therapy versus New Oral Anticoagulants (NOACs) therapy in patients with currently well controlled VKA therapy for non-valvular atrial fibrillation: a pilot study

Published: 09-04-2014
Last updated: 23-04-2024

Objectives:To collect data on effect size for, and determine the feasibility of, a full scale multicentre RCT(Randomized Controlled Trial) that1. compares the efficacy and safety of NOACs with VKA treatment according to Dutchstandards, in VKA-...

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

## Summary

### ID

NL-OMON41389

**Source**
ToetsingOnline

**Brief title**
GAInN

### Condition

- Cardiac arrhythmias

**Synonym**
atrial fibrillation, cardiac arrhythmia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** stichting SBOHTR (Stichting ter Bevordering van Onderzoek/Onderwijs op het gebied van Hemostase;Trombose en Reologie

## Intervention

**Keyword:** NOACs, non-valvulalar atrial fibrillation, VKA

## Outcome measures

### Primary outcome

Main study parameters/endpoints:

· Primary: net clinical benefit (stroke, major bleeds, systemic embolism,

myocardial infarction, vascular death)

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### Secondary outcome

Secondary: safety (major bleeds, clinically relevant non-major bleeds,

all-cause mortality), efficacy (ischemic/unspecified stroke, systemic embolism,

myocardial infarction, vascular death), burden of complications,

# Study description

### Background summary

Rationale:
Life-long anticoagulation is indicated for many patients with atrial fibrillation (AF) to prevent embolic stroke. In the Netherlands in 2010, 225,000 patients received vitamin K antagonists (VKA) for this indication. This number has been increasing by about 5% per year for the last view years.
Yet, VKA therapy is challenging due to inter- and intra-individual variations, which require frequent monitoring and dose adjustments. The efficacy and safety of VKA therapy are strongly dependent on the achieved quality of anticoagulation (i.e. the proportion of time that

a given patient is within the predefined therapeutic range, or *individual Time in Therapeutic Range* (iTTR).
Recently, anticoagulant treatments have become available that are easier to use. These NewOral Anticoagulants (NOACs; dabigatran and rivaroxaban) showed non-inferiority for prevention of embolic stroke or systemic embolism and major bleeding compared to warfarin.
A disadvantage of the NOACs is the higher costs. Introduction for all patients would result in an increase of 78-156 million Euro in the Dutch pharmaceutical budget annually. Before the general introduction of the NOACs, the advantages must be weighed against the limitations.
This balance might be different for different categories of patients.
In the large registration trials, concerns were raised focusing on a low achieved quality of anticoagulation in the control VKA group, and a possible heterogeneity of the risk-benefit ratio in patients with different VKA control. This means that the observed non-inferiority of
NOACs versus VKA might not be applicable to patients whom VKA is well controlled. This has triggered concerns, as expressed in reports from the Health Care Council and the Health Care Insurance Board of the Netherlands (1,2). This is in particular relevant for the Dutch setting, in which VKA treatment is managed by a well organized nation-wide network of Thrombosis Services. As a result, in a large cohort of
Dutch patients, three quarter of AF patients achieved an iTTR that was associated with good clinical outcome, both in terms of efficacy and safety. Bad quality of VKA treatment was restricted to a subgroup of patients and not randomly distributed over time. Presently, the relevant guidelines do not endorse switching patients who are already on anticoagulants from VKA to NOACs. However, it is anticipated that many providers and patients will switch to a NOACs because of the ease of use, without taking quality of VKA treatment into account. The three quarters of patients with adequate controlled VKA might not benefit from such a switch to NOACs. We hypothesize that, in patients in whom adequate quality of anticoagulation is achieved, VKA therapy is superior to NOACs, in terms of net clinical benefit as well as cost-effectiveness

**Study objective**

Objectives:
To collect data on effect size for, and determine the feasibility of, a full scale multicentre RCT
(Randomized Controlled Trial) that
1. compares the efficacy and safety of NOACs with VKA treatment according to Dutch
standards, in VKA-experienced patients with currently well controlled VKA therapy, in
the Dutch real-life setting
2. compares differences in treatment satisfaction, compliance and quality of life between

NOACs and VKA treatment.

### Study design

A randomized (1:1) controlled open-label two-center study comparing VKA versus NOACs in 240 patients with currently well controlled VKA therapy for non-valvular AF.

### Intervention

Intervention:
Patients randomized to receive VKA will continue their treatment according to usual care, managed by the Thrombosis Service using a therapeutic range of INR 2.0-3.5. Patients randomized to NOACs will be instructed on the use of NOACs, and followed as per usual care

### Study burden and risks

We will compare two registered treatment modalities; therefore we expect no extra risks associated with participation in this study compared to regular treatment. A data safety monitoring board will review the study after every 20 clinical events that qualify as study endpoints. The study will include 3 extra visits (randomization, 6 months and 12 months). During these visits patients will be asked to report on events and other
relevant medical information and to fill in 2 questionnaires. Patients will be asked to keep a diary during the whole study period.

## 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

Men or women aged >18 years who are currentlly treated with VKA for non-valvular AF, managed by participating Thrombosis Service;-A minimum duration of 6 months of VKA treatment prior to the screening visit.;- An ITTR> 60% over the 4 months of VKA treatment before selection by the Thromobosis Service;D4b. In het Nederlands

## Exclusion criteria

-thrombo-embolic event or major bleeding ever while on VKA;-Indication for anticoagulation other then AF;-contra-indication to receive NOACs, i.e. reduced renal clearance defined as <30ml/min (Cockroft-Gault formula)

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 13-01-2015 |
| Enrollment: | 240 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | acenocoumarol |
| Generic name: | acenocoumarol |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Eliquis |
| Generic name: | apixaban |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Pradaxa |
| Generic name: | dabigatran etexilate mesilate |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Xarelto |
| Generic name: | rivaroxaban |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 09-04-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 14-08-2014 |
| Application type: | First submission |

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| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 03-12-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 28-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 21-12-2015 |
| 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 | EUCTR2013-004805-14-NL |
| CCMO | NL47130.042.13 |