Anticoagulation in frail elderly patients with atrial fibrillation.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22182

Source
NTR

Brief title
FRAIL-AF study

Health condition

Frail elderly, atrial fibrillation, oral anticoagulants (vitamin K antagonists, NOACs), bleeding complications.

Kwetsbare ouderen, atriumfibrilleren, orale antistolling (VKA's, NOAC's), bloedingscomplicaties.

Sponsors and support

Primary sponsor: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.
Source(s) of monetary or material Support: 1. ZonMw;
2. Unrestricted educational grants of 3 NOAC-firms (Boehringer Ingelheim, Bayer, BMS Pfizer) for the organisation of symposia and the development of an e-learning. Positive advise from 'de Codecommissie Geneesmiddelen Reclame' (i.e. the Codecommittee on Drug Advertising).

Intervention

Outcome measures

Primary outcome

The primary outcome is the first occurrence of the composite of at least one major or one clinically relevant non-major bleeding complication during the one-year follow-up period, following definitions from the International Society of Thrombosis and Haemostasis (ISTH).

A major bleeding is defined as:

1. A fatal bleeding;

2. Any bleeding in a critical area or organ (i.e. intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular, pericardial, or intramuscular leading to a compartment syndrome);

3. Bleeding leading to a fall in haemoglobin levels of 1.25 mmol/L or more;

4. Bleeding leading to a transfusion of 2 or more units of whole blood or red cells.

A clinically relevant non-major bleeding complication is defined as any bleeding not being major, but includes at least one of the following items:

1. Prompting a face-to-face consultation;

2. Requiring a medical intervention by healthcare professionals;

3. Leading to hospitalization or increased level of care.

Secondary outcome

Secondary outcomes include the endpoints of:

1. major or clinically relevant non-major bleeding complications separately;

2. thrombo-embolic events;

3. the occurrence of the composite of ischaemic and haemorrhagic stroke;

4. quality of life;

5. cost-effectiveness;

6. risk factors for bleeding.

Thrombo-embolic events are defined as:

1. Ischemic stroke;

2. Transient ischemic attack (TIA);

3. Peripheral arterial thrombo-embolism;

4. Pulmonary embolism.

Study description

Background summary

Rationale:

For long, vitamin K antagonists (VKAs) were the only therapeutic strategy to reduce stroke risk in patients with atrial fibrillation (AF). Recently, an alternative has entered the clinical domain: non-VKA oral anticoagulants (NOACs). Large randomized controlled trials (RCTs) demonstrated that NOACs are at least as effective as VKAs to reduce the risk of ischaemic stroke, yet with a better safety profile (notably fewer intracranial bleeds). Based upon these trial results, the recent guidelines from the European Society of Cardiology (ESC) has a preference of NOACs over VKAs when initiating oral anticoagulant treatment in new AF patients. Moreover, the ESC guideline considers switching VKA-treatment to a NOAC appropriate, in particular when the time in therapeutic INR range is low while on a VKA, although this latter recommendation is less strong than the preference of NOACs over VKAs when newly initiating oral anticoagulant treatment. However, frail elderly patients were under-represented in the landmark NOAC RCTs, leaving a knowledge gap on the optimal anticoagulant treatment strategy (VKA or NOAC) in the increasing group of frail AF patients. Both may have advantages as well as risks, and it is yet unknown which type of oral anticoagulant (VKAs or NOACs) should be preferred in this specific population. In particular, it is unknown if switching (chronic) VKA treatment to a NOAC yields fewer bleeding complications in frail elderly AF patients, as may be expected given the current results from RCTs and observational studies that were performed with non-frail AF patients.

Objective:

The primary objective is to evaluate whether the impact of a strategy aimed at switching INR-

guided VKA management to a NOAC-based treatment strategy reduces the occurrence of major or clinically relevant non-major bleeding complications in frail elderly patients with AF. Hereto we will assess the relative risk (hazard ratio) of the randomised groups with respect to the time to first occurrence of a major or clinically relevant non-major bleeding complication (whichever comes first). The two components of this composite outcome, major or clinically relevant non-major bleeding complications, will also be analysed as separate outcomes secondarily.

Other secondary objectives include a comparison of both treatment strategies on the occurrence of all-cause thrombo-embolic events, the composite of ischaemic and haemorrhagic stroke, quality of life and cost-effectiveness, as well as an identification of risk factors for bleeding in frail elderly AF patients treated with either a VKA or a NOAC.

Study design:

Multi-centre pragmatic open label registry-based randomized controlled clinical trial. The FRAIL-AF study will only take place in The Netherlands.

Study population:

This study will include frail elderly patients (age >75 years) diagnosed with non-valvular AF, currently managed on VKA treatment and monitored by one of the participating thrombosis services. Frailty will be defined using the Groningen Frailty Indicator (with frailty being a GFI score of 4 or higher). Patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) 30 ml/min/1.73 m2) will not be randomized but will be followed-up observationally (thus remain on VKA treatment).

Intervention:

In the index group we will switch oral anticoagulant management from INR-guided VKA-management to a NOAC-based management with prescription of one of the available NOACs (dabigatran 150mg twice a day, rivaroxaban 20mg once daily, apixaban 5mg twice a day or edoxaban 60mg once daily) based upon patient‘s personal preference and current guidelines. The intervention itself (switching oral anticoagulant management form INR-guided VKA-management to a NOAC-based management) will last one month. After one month, there will be a follow-up period of eleven months. Dose adjustments for NOAC treatment will also be conform guidelines. The control group continues with current routine-care VKA treatment (either acenocoumarol 1mg or fenprocoumon 3mg), with dose tailoring based upon regular INR measurements.

Main study parameters/endpoints:

Primary outcome: the first occurrence of the composite of at least one major or one clinically relevant non-major bleeding complication during the one-year follow-up period, following definitions from the International Society of Thrombosis and Haemostasis (ISTH).

Secondary outcomes include the endpoints of major or clinically relevant non-major bleeding complications separately, thrombo-embolic events, the occurrence of the composite of ischaemic and haemorrhagic stroke, quality of life, cost-effectiveness, and risk factors for bleeding.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Both VKAs and NOACs are guideline-recommended treatment options for stroke prevention in AF, and inherently carry a risk of bleeding with possibly an overall lower risk of (notably intracranial) bleeding on NOACs. Nevertheless, the risk of these bleeding complications is not directly related to study participation or study procedures, yet part of routine practice as current guidelines clearly indicates the need to prescribe anticoagulants for stroke prevention in (elderly) AF patients. Patients in the index group are not being visited at home anymore by the thrombosis service for regular INR measurements and dismissal of these regular home visits could lead to change in quality of life, both in a positive and negative way. Patients in both the index group and the control group are asked baseline characteristics and follow-up questions at respectively 0 and 1, 3, 6, 9 and 12 months. Moreover, patients are asked to fill in quality of life questionnaires at 0, 6 and 12 months.

Study objective

A strategy aimed to switch from INR-guided VKA therapy to a NOAC-based treatment strategy is superior to continuation of INR-guided VKA therapy with regard to the occurrence of major or clinically relevant non-major bleeding complications in frail elderly patients with non-valvular atrial fibrillation.

Study design

All outcomes will be assessed at 1, 3, 6, 9 and 12 months after t=0 (randomization).

Intervention

There are three different groups within the FRAIL-AF study:

1. an index group (i.e. switching to a NOAC-based treatment strategy);

2. a control group (i.e. continuation of VKA-management);

3. an observational group (i.e. patients with severe renal impairment: eGFR < 30 ml/min/1.73m2).

Patients in the index group will be switched from VKA to a NOAC-based treatment regime. Treating physicians of patients in the index group will make an informed decision for one particular NOAC (dabigatran, rivaroxaban, apixaban or edoxaban), where needed in collaboration with expertise of the thrombosis service, the research group or local cardiologists and guidelines. Researchers of the UMC Utrecht who also work as medical physicians will take care of the switching process (in collaboration with the thrombosis services), and prescribe the specific NOAC for patients in the index group in dosages according to the SPCs and current guidelines of the Dutch co-operation of anticoagulation and thrombosis services (CAT, see www.hetcat.nl). Treatment will be taken over by the treating physician after the intervention (switching treatment from VKA to a NOAC) which will last one month.

Patients randomized to the control group and patients in the observational arm (severe renal impairment: i.e. eGFR<30ml/min/1.73m2) will continue INR-guided VKA management (i.e. either 1 mg acenocoumarol or 3 mg fenprocoumon) and will be controlled by one of the participating thrombosis services for regular INR measurements and subsequent dose adjustments (INR between 2.0 and 3.0, following usual care).

Contacts

Public
Linda P.T. Joosten
P.O. Box 85500

Utrecht 3508 GA
The Netherlands
+31 88 75 692 38
Scientific
Linda P.T. Joosten
P.O. Box 85500

Utrecht 3508 GA
The Netherlands
+31 88 75 692 38

Eligibility criteria

Inclusion criteria

1. Age > 75 years;

2. Currently managed on VKA treatment for AF by one of the participating thrombosis services;

3. Groningen Frailty Indicator (GFI) ≥ 4;

4. Willingness to switch from VKA management to a NOAC-based treatment strategy.

Exclusion criteria

1. Renal impairment, i.e. an eGFR below 30 ml/min/1.73m2. These patients will not be randomized for our main objective, but will be followed-up observationally in order to evaluate one of our secondary objectives (risk factors for bleeding);

2. Valvular AF: AF in the presence of a mechanical heart valve, and/or severe mitral valve stenosis;

3. Taking part in other medical scientific research;

4. Unwilling or unable to provide written informed consent by the patient.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-01-2018
Enrollment:	2750
Type:	Anticipated

Ethics review

Positive opinion

Date:	11-10-2017
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 55760
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL6533
NTR-old	NTR6721
CCMO	NL60426.041.17
OMON	NL-OMON55760

Study results

Summary results

Follows.