Prospective registry of management and outcome of bleeding complications in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs)

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Primary objectiveTo assess the outcome of NOAC associated bleeds and emergency invasive surgery or procedures. Secondary objectives1) To describe the treatment of patients presenting with NOAC associated bleeding2) To evaluate the current...

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

Summary

ID

NL-OMON44969

Source
ToetsingOnline

Brief title
NOAC bleeding registry

Condition

- Cardiac arrhythmias
- Embolism and thrombosis

Synonym
atrial arrythmia; deep vein thrombosis, atrial fibrillation, pulmonary embolism

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW beurs 'Goed gebruik geneesmiddelen' en beurs van Sanguin aan prof. dr. S. Middeldorp

Intervention

Keyword: Bleeding, Management, Non-vitamin K antagonist oral anticoagulants, Outcomes

Outcome measures

Primary outcome

The primary outcome variable will be a successful clinical outcome of bleeding defined as excellent or good haemostatic efficacy. For the exact definition of excellent or good haemostatic efficacy see the table in paragraph 6.1.1 of the protocol.

The primary outcome for patients who require an emergency invasive procedure, will be the occurrence of a major bleeding within 30 days follow-up. For the definition of major bleeding, see paragraph 6.1.1 of the protocol.

Secondary outcome

- Thromboembolic complications: ischemic stroke, transient ischemic attack, myocardial infarction, DVT or PE
- Bleeding complications: intracranial haemorrhage, extracranial haemorrhage, gastro-intestinal haemorrhage, all other haemorrhages
- Length of stay in hospital
- Admission in and length of stay in high care unit
- Mortality at 30 days
- Drop in haemoglobin (Hb) over 24 hours

- Management of bleeding: transfusion, surgical, endoscopic or radiologic interventions to control bleeding

- NOAC blood levels estimated by chromogenic anti-Xa for rivaroxaban, apixaban or edoxaban and diluted thrombin time (dTT) for dabigatran) at entry emergency department and decrease after 24 hours (in %)

- Complete blood count, PT, aPTT, and other laboratory tests of interest including thrombin generation

- Comparison of outcome of NOAC bleeding in the subgroup of patients treated with PCC with a historical cohort of patients treated with PCC for VKA associated bleeding.

Study description

Background summary

Oral anticoagulants (OAC) are indicated for patients with atrial fibrillation (AF) and for treatment and prevention of venous thromboembolism (VTE). For six decades vitamin K antagonists (VKA) were the only available OAC. Although VKA are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index and huge inter- and intra-individual variability that necessitates frequent monitoring and dose adjustments. An important side effect of VKA is an increased risk of bleeding. The incidence of VKA associated bleeding is estimated at 16.5% per year and the incidence of major bleeding is 2.7% per year.
Recently a new class of oral anticoagulants has been developed. These non-vitamin K antagonist oral anticoagulants (NOACs) have a predictable pharmacokinetic and -dynamic profile allowing a fixed dose regimen. This offers major simplification of coagulant treatment. Currently three NOACs are registered, namely rivaroxaban, apixaban and dabigatran etexilate (after here referred to as dabigatran). Procedures for registration of edoxaban are ongoing with the European Medicine Agency. Approval is expected in 2014.
As with VKA, the most important adverse event of NOACs is the occurrence of bleeding. NOACs are evaluated in large phase III clinical trials. These studies showed that NOACs reduced the risk of major bleeding in comparison to VKA. Also the risk of intracranial bleeding was reduced with 30-70% in patients on NOACs.

No data on post-marketing surveillance in patients with long-term exposure are available yet.

A potential drawback of NOACs is the lack of a (specific) antidote that neutralizes the anticoagulant effect. Such an antidote can be useful in patients that need to undergo emergency invasive surgery or in case of bleeding complications. For VKA reversal can be reached through administration of vitamin K or prothrombin complex concentrate (PCC). Studies in animals and healthy volunteers have indicated that PCC may have a role in reversing the anticoagulant effect of NOACs and can reduce the bleeding. Based on these studies, the Dutch Leidraad Begeleide Introductie Nieuwe Orale Antistollingsmiddelen advises treatment with PCC in case of a severe NOAC associated bleeding. However, the efficacy of PCC for immediate reversal of NOACs has not been tested in patients on NOACs.

Study objective

Primary objective
To assess the outcome of NOAC associated bleeds and emergency invasive surgery or procedures.

Secondary objectives
1) To describe the treatment of patients presenting with NOAC associated bleeding
2) To evaluate the current perioperative strategies for patients on NOAC*s who require emergency invasive procedures
3) In the subgroup of patients who receive PCC as a prohaemostatic agent (as indicated by the treating physician), the goal is to determine the effect of administration of PCC on 1) the outcome of the bleed (or invasive procedure) and 2) coagulation assays.

Study design

This is an investigator initiated prospective multi-center cohort study. The currently participating hospitals are the academic hospitals of the Universities of Amsterdam, Rotterdam, Maastricht and Groningen. Further participation with community hospitals around Amsterdam will be sought.

Main study
Patients will be eligible for participation in this study if they are treated with a NOAC and present themselves with a NOAC associated bleed or the need to undergo an immediate invasive surgery or procedure within 8 hours. The treatment of a NOAC related emergency situation is the responsibility of the treating physician. The interventions to control bleeding and the perioperative strategies are not part of the study protocol.
Information about history, concomitant medication, laboratory assays, applied

treatment regimens and outcomes will be collected from patient charts and letters. In addition, we will collect citrated blood at two different time points, at presentation and 4-8 hours after presentation (total 2x 9.0 mL).

Substudy
In the subgroup of patients that are treated with PCC, two additional blood draws (9 mL each) will be performed in the first 24 hours (just after PCC administration and 24 hours after administration).

The tubes of all patients will be double spun to produce platelet poor plasma and will be stored to later on assess the effect of PCC on coagulation assays.

Historic control group
The subgroup of patients receiving PCC for a NOAC related emergency will be compared to a historical control cohort of age-matched patients treated with PCC because of VKA associated bleeding or the need for immediate invasive procedures whilst on VKA treatment. The patients for this retrospective group will be identified through PCC distribution and administration files from the blood bank in the AMC. Clinical data from the patients will be retrieved form charts and letters.

Study burden and risks

Because this is not an intervention study, we will not administer a specific investigational product or treatment. Patient management is left to the treating physician, including the decision to administer PCC.
The only executed intervention is the collection of additional blood. We will collect citrated blood at two times in the first 24 hours in all patients (total 2x 9.0 mL). In the subgroup of patients treated with PCC, citrated blood will be collected at two additional time points in the first 24 hours (total 2x 9.0 mL). The extra samples will be drawn adjacent to regular blood drawings or additional venepunctures will be performed when this is not attainable (maximum of four drawings). The risks of a venepuncture are hematoma formation or tromboflebitis.
This study does not include additional visits to the hospital, nor will patients be asked to fill out questionnaires.
Based on the small risks of venepunctures and the fact that we will not impose an intervention or change a patients behaviour, we think the burden for patients participating in this study is minimal.

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

- Age * 18 years
- Treatment with dabigatran, rivaroxaban or apixaban (and after approval also edoxaban)
- Presentation with NOAC bleeding or the need for an emergent invasive surgery or procedure within 8 hours.

Exclusion criteria

None

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-01-2015
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	17-12-2014
Application type:	First submission
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
CCMO	NL49329.018.14