

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

[This protocol contains the originally accepted protocol \(version 1.1\) and tracked changes made in the only significant amendment \(version 1.2\).](#)

PROTOCOL TITLE '*Vitamin K antagonist (VKA) therapy versus New Oral Anticoagulant (NOAC) therapy in patients with currently well controlled VKA therapy for non-valvular atrial fibrillation: a pilot study.*'

Protocol ID	
Short title	GAIN-pilot
EudraCT number	2013-004805-14
Version	1.2
Date	26-10-2015
Project leaders	<p><b>N.J.G.M. Veeger PhD</b>  <i>Clinical epidemiologist, UMCG</i>  <i>T: 050 3618064 E: <a href="mailto:n.veeger@umcg.nl">n.veeger@umcg.nl</a></i></p> <p><b>K. Meijer MD PhD,</b>  <i>Hematologist, UMCG</i>  <i>T. 050 3610225 E: <a href="mailto:k.meijer@umcg.nl">k.meijer@umcg.nl</a></i></p>
Coordinating investigator	<p><b>J.H.A. van Miert, MD</b>  <i>Research physician, Hematology UMCG and Thrombosis Service Groningen</i>  <i>T: 050 3610225 E: <a href="mailto:j.h.a.van.miert@umcg.nl">j.h.a.van.miert@umcg.nl</a></i></p>
Principal investigator(s)	<p><b>G. Piersma-Wichers, MD</b>  <i>Internist, medical director Thrombosis Service Groningen</i></p>
Sponsor (in Dutch: verrichter/opdrachtgever)	<p><b>Universitair Medisch Centrum Groningen</b>  <i>Afdeling Hematologie,</i>  <i>Hanzeplein 1</i>  <i>9713 GZ Groningen</i></p>
Subsidising party	<p><b>Stichting ter Bevordering van Onderzoek/Onderwijs op het gebied van Hemostase, Trombose en Reologie</b></p>
Independent expert (s)	<p><b>A.B.U. Makelburg</b>  <i>Hematologist, UMCG</i>  <i>T. 050 3612354 E: <a href="mailto:a.b.u.makelburg@umcg.nl">a.b.u.makelburg@umcg.nl</a></i></p>
Laboratory sites	NA
Pharmacy	NA

Deleted: 1

Deleted: 01-05-2014

Formatted: Dutch

## PROTOCOL SIGNATURE SHEET

Name	Signature	Date
<b>Head of Department:</b> <b>G. Huls MD PhD,</b> <b>head of Department of Haematology</b>		
<b>[Coordinating Investigator/Project leader/Principal Investigator]:</b>  <b>N.J.G.M. Veeger PhD</b> <b>K. Meijer MD PhD</b>		

## TABLE OF CONTENTS

1. OBJECTIVES	11
2. STUDY DESIGN	12
2.1 Study population	14
2.2 Inclusion criteria	14
2.3 Exclusion criteria	14
2.4 Sample size calculation	14
3. TREATMENT OF SUBJECTS	16
3.1 Investigational product/treatment	16
3.2 Use of co-intervention	16
4. INVESTIGATIONAL PRODUCT	16
5. NON-INVESTIGATIONAL PRODUCT	16
5.1 Name and description of non-investigational product(s)	16
6. METHODS	21
6.1 Study parameters/endpoints	21
6.1.1 Main study parameter/endpoint	21
6.1.2 Secondary study parameters/endpoints	22
6.1.3 Other study parameters	22
6.2 Specific criteria for discontinuation of any study treatment (VKA, NOACs).	25
6.3 Premature termination of the study	25
7. AEs, SAEs and SUSARs	26
7.1 Adverse events (AEs)	26
7.2 Serious adverse events (SAEs)	26
7.3 Suspected unexpected serious adverse reactions (SUSARs)	27
8. DATA SAFETY MONITORING BOARD (DSMB) / SAFETY COMMITTEE	27
9. STATISTICAL ANALYSIS	28
10. ETHICAL CONSIDERATIONS	30
10.1 Regulation statement	30
10.2 Recruitment and consent	30
10.3 Benefits and risks assessment, group relatedness	30
11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION	32
12. STRUCTURED RISK ANALYSIS	33
12.1 Potential issues of concern	33
12.2 Synthesis	33
13. REFERENCES	33

Deleted: 23

Field Code Changed

Field Code Changed

## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AF	Atrial Fibrillation
CABG	Coronary Artery Bypass Surgery
CNS	Central Nervous System
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
FXa	Factor X
HR	Hazard Ratio
ITT	Intention To Treat
iTTR	Individual Time in Therapeutic Range
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NOACs	New Oral AntiCoagulants
PCI	Percutaneous Coronary Intervention
RCT	Randomized Controlled Trial
RR	Relative Risk
(S)AE	(Serious) Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
VKA	Vitamin K Antagonist
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

Deleted: 28-9

**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 few 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 New Oral Anticoagulants (NOACs; dabigatran, rivaroxaban and apixaban) showed at least 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 NOAC therapy 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 NOAC therapy, in terms of net clinical benefit as well as cost-effectiveness.

Assumptions on the relative efficacy and safety of VKA therapy versus NOAC therapy in patients with adequately controlled VKA can be derived from previous studies. However, the experimental nature of these studies, as non-registered drugs were analyzed, resulted in

Deleted: 28-9

highly selective enrollment of patients. This makes these data less generalizable to the total group of AF patients. Moreover, patients from countries with different standards of VKA treatment were included. Subanalyses for the countries with high standard of care, like the Netherlands, were possible but only on group's level and not for the individual patient. Even with the high standard of Dutch care, we don't expect VKA therapy to be superior to NOACs in all patients, but only in the patients with good quality of VKA therapy. The optimal method to identify the best treatment for patients with well controlled VKA therapy, is to randomize these patients and treat them according to the usual care. In this way, patients with VKA will have the same characteristics as patients on NOACs and differences will be solely based on differences in real-life treatment strategy.

Sample size calculations showed that the number needed for such a study heavily depends on the actual assumption chosen. We will therefore first perform this pilot study to determine the effect size (net clinical benefit) and the feasibility of randomization in this new context.

We do not aim to compare two different drugs, but rather two strategies: either VKA (acenocoumarol or phenprocoumon) with the routine care provided by the Thrombosis Service or NOAC (dabigatran, rivaroxaban, apixaban or any drug in this class that becomes available) with the routine care as described in the relevant guidelines. In this protocol, these two strategies are called 'VKA therapy' and 'NOAC therapy'.

**Objectives:**

To collect data on effect size for, and determine the feasibility of, a full scale RCT (Randomized Controlled Trial) that

1. compares the efficacy and safety of NOAC therapy according to Dutch standards with VKA therapy 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 therapy and VKA therapy.

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

**Study population:** Eligible patients are currently treated by the Groningen Thrombosis Service for non-valvular atrial fibrillation and have had an iTTR  $\geq 70\%$  during the 4 months before the study, without ever a thrombotic or major bleeding complication while on VKA.

**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 NOAC therapy will be instructed on the use of NOACs, and followed as per usual care.

**Main study parameters/endpoints:**

Deleted: 28-9

- Primary: net clinical benefit (stroke, major bleeds, systemic embolism, myocardial infarction, vascular death)
- 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, treatment satisfaction, quality of life, compliance
- Feasibility: proportion of eligible patients that the referring physician opts out for.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** We will compare two registered treatment strategies; 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 10 clinical events that qualify as primary study endpoints. The study will include 4 extra visits (screening, randomization, 6 months and 12 months). (During screening visit a blood sample is drawn (4.5 ml ) to monitor the renal function). 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.

Deleted: 28-9

## INTRODUCTION AND RATIONALE

Atrial fibrillation (AF) is a very common cardiac arrhythmia with an increasing prevalence due to the ageing society. AF increases the risk of embolic stroke 4 to 5 times (3), therefore life-long anticoagulation is indicated for patients with additional risk factors (CHA2DS2-VASc  $\geq$  1) (4). For this, VKA are used world-wide. In the Netherlands in 2010, 225,000 patients with AF received VKA under supervision of dedicated Thrombosis Services. This number has been increasing by about 5% per year for the last few years.

Although VKA have proven to lower the risk of stroke vastly, their use is challenging due to both inter- and intra-individual variation (5). Frequent monitoring of the INR and dose-adjustments are required. For that reason, alternatives are sought that are as effective and safe as VKA but with a more predictable dose-response relationship.

Recently, less complicated treatments have become available. These New Oral Anticoagulants (NOACs; dabigatran, rivaroxaban and apixaban) showed at least non-inferiority for prevention of stroke or systemic embolism and major bleeding with a decrease in intra-cerebral bleeding in phase III studies (6,7). 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.

Concerns were raised about the quality of VKA management in two pivotal studies. In RE-LY, overall time within therapeutic range was only 64%, and in ROCKET-AF 58% (with target range 2-3), both complicating the interpretation of the non-inferiority finding. Moreover, it was not clear whether non-inferiority was consistent over different levels of achieved quality of VKA management. As the majority of events occur in those patients with the poorest quality of VKA management (8,9), the overall non-inferiority may be the net result from superiority in those with bad VKA control, and inferiority in those with good control. The Health Care Council and the Health Care Insurance Board of the Netherlands endorse these issues (Health Council 2012, Health Care Insurance Board 2012).

We know from previous work that adequate VKA treatment is the result of the local standard of care in combination with a specific patient profile and not randomly distributed over time in all patients (8). Therefore, the possible heterogeneity of the risk-benefit ratio is in particular relevant for the Dutch setting where VKA treatment is managed by a well organized nationwide network of Thrombosis Services. As a result, in our large cohort of Dutch patients, three quarter of AF patients achieved an individual time in the therapeutic range (iTTR; the measure for quality of VKA treatment) that was associated with good clinical outcome, both in terms of efficacy and safety. In comparison to the 75% of patients with the best iTTR, the other 25% of patients had a relative risk of thrombotic and bleeding complications of 2-3.

Deleted: 28-9

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 and without taking quality of VKA treatment into account. We hypothesize that in patients in whom adequate quality of anticoagulation is achieved VKA therapy is superior to NOAC therapy, in terms of net clinical benefit as well as cost-effectiveness.

This research question is relevant because it affects treatment decisions in large and growing numbers of patients and has the potential to prevent major unnecessary increases in pharmaceutical costs.

Assumptions on the relative efficacy and safety of VKA therapy versus NOAC therapy in patients with adequately controlled VKA can be derived from previous studies. However, the experimental nature of these studies, as non-registered drugs were analyzed, resulted in highly selective enrollment of patients. This makes these data less generalizable to the total group of AF patients. Moreover, patients from countries with different standards of VKA treatment were included. Subanalyses for the countries with high standard of care, like the Netherlands, were possible but only on group's level and not for the individual patient. Even with the high standard of Dutch care, we don't expect VKA therapy to be superior to NOACs in all patients, but only in the patients with good quality of VKA therapy. The optimal method to identify the best treatment for patients with well controlled VKA therapy, is to randomize these patients and treat them according to the usual care. In this way, patients with VKA will have the same characteristics as patients on NOACs and differences will be solely based on differences in real-life treatment strategy.

Sample size calculations shown that the number needed for the study heavily depends on the actual assumption chosen. We will therefore first perform a pilot study to determine the effect size (net clinical benefit) and the feasibility of randomization in this new context.

Deleted: 28-9

## 1. OBJECTIVES

To collect data on effect size for, and determine the feasibility of, a full scale RCT with the aim

1. To compare the efficacy and safety of NOAC therapy with VKA therapy according to Dutch standards, in VKA-experienced patients with currently well controlled VKA therapy in the Dutch real-life setting.

The primary endpoint is net clinical benefit, secondary endpoints are efficacy, safety and burden of complications.

Net clinical benefit: composite of stroke, major bleeds, systemic embolism, myocardial infarction and vascular death. All components will also individually be assessed.

Efficacy: composite of ischemic or unspecified stroke, systemic embolism, myocardial infarction and vascular death. All efficacy components will also individually be assessed.

Safety: composite of major bleeds (including haemorrhagic stroke) and non-major clinically relevant bleeds and all- cause mortality. All safety components will also individually be assessed. In addition, differences in adverse events will be evaluated.

Burden of complications: The severity of a clinical endpoint event and the cumulative number of days after a clinical endpoint during which the patient is hospitalized or needs unplanned professional care for activities of daily living. This is followed until the need for extra professional care is ceased, until one month after end of study or until death, whatever comes first.

2. To compare differences in treatment satisfaction, compliance and quality of life between NOAC therapy and VKA therapy.

Treatment expectations and satisfaction: scores on PACT-Q questionnaires.

Compliance: based on information from the pharmacy registry whether patients appropriately collected their anticoagulant drugs.

Quality of life: scores on SF-36 questionnaires.

Deleted: 28-9

## 2. STUDY DESIGN

### Overview

This is a prospective, randomized, open-label, controlled, pilot study comparing the efficacy and safety of NOAC therapy with VKA therapy for the prevention of stroke and systemic embolism in subjects with currently well controlled VKA therapy for non-valvular AF.

### Study design

This pilot trial will be conducted within the setting of care provided by the specialized Thrombosis Service in Groningen. The cardiologists of the referring hospital are informed about the content of this study. Representatives of the cardiologists and Thrombosis Service are members of the steering committee, in addition to the principal investigators.

The study will be divided into a screening period and an open-label treatment period closing with an end-of-study visit. As VKA and NOACs are both registered treatment options, patients allocated to NOACs will not standard be switched back to VKA at the end of study, but choice of treatment will be made in agreement with the patient and his/her referring physician.

The Thrombosis Service selects from its files those patients who, based on their quality of anticoagulation, would be candidates for the study. The referring physician is informed about the study, and patients are only invited for the study if he/she does not object. After informed consent, there is a screening period of 1-3 weeks during which in- and exclusion criteria are checked (including indication for VKA is solely non-valvular AF, VKA-related bleeds and thrombotic events and contra-indications to receive any kind of NOAC) and renal function measured. The recruitment of patients and collection of screening data is performed by research nurses, physicians are available, if necessary. Finally, at the Thrombosis Service the principal investigator (i.e. a medical doctor) will judge whether patients fulfill all inclusion criteria and none of the exclusion criteria and are eligible for inclusion.

The treatment period starts at the randomization visit and takes 1 year. During the randomization visit eligible patients will be randomly allocated to either VKA therapy or NOAC therapy using a central computerized voice-response system. Patients randomized to receive VKA therapy 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 NOAC therapy will be instructed on the use of NOACs, and followed as per usual care for these drugs, based on national and local guidelines. The type of NOAC will be determined upon according to local standards and guidelines prior to the start of the study. The switch from VKA to NOACs according to protocol will be supervised by the Thrombosis Service. Frequent visits, as in VKA-treated patients, will not be performed as they are not part of the routine care for these patients. Referring physicians will be notified. Further details on VKA and NOACs are provided in appendix 1.

During the treatment period mandatory study visits will take place at 6 months and at 12 months (end-of-study visit). During these visits data will be collected by standardized questionnaires filled in by the patient (appendix 2). Patients will also be questioned about

Deleted: 28-9

changes in concomitant medication and treatment complications, and their study diaries will be reviewed. If an outcome event has been reported by the patient or is suspected, patients will be asked for information on the date, severity, treatment, burden, and treating physician. Thereafter, as permitted in the informed consent form, a request for additional information on the event is sent to the treating physician and/or the general practitioner. During the full conduct of the study, a dedicated physician at the Thrombosis Services will be available for consultation.

**Deleted:** 28-9

## 2.1 Study population

### Population (base)

## 2.2 Inclusion criteria

Inclusion criteria:

- Men or women aged  $\geq 18$  years who are currently treated with VKA for non-valvular AF, managed by the Groningen Thrombosis Service.
- A minimum duration of 6 months of VKA treatment at the time of selection by the Thrombosis Service.
- An iTTR  $\geq 70\%$  over the 4 months of VKA treatment before selection by the Thrombosis Service.

## 2.3 Exclusion criteria

Exclusion criteria:

- A thrombo-embolic event or major bleeding ever while on VKA.
- Indication for anticoagulation other than AF.
- Contra-indication to receive any kind of NOAC.
- Life expectancy  $<1$  year.

## 2.4 Sample size calculation

In the ROCKET-AF, the estimated rate of the composite of net clinical benefit events was 8.5% and 8.4% per year in rivaroxaban and VKA, respectively. Between the different types of NOACs, the event rates are highly comparable (6,7). The event rates in patients on VKA depend on the achieved quality of VKA treatment (8,9).

Patients on stable VKA treatment tend to stay stable over time (10). Therefore, the patients in our study will have relative good quality of VKA treatment. Based on previous data from our group, we expect the 75% of patients with best controlled VKA to have a RR of 0.73 for the net clinical benefit events (8). This is the group of patients that we aim to select for this study.

Furthermore, the event rates on a NOAC could be higher in a real life setting than in the studies, because of lower treatment adherence, less favorable patient characteristics and/or other unknown factors. However, the cumulative effect of these factors on the event rate is unknown.

In case of an event rate of 6.1% ( $0.73 \times 8.4$ ) per year for VKA-users versus 8.5% per year in patients treated with NOACs, a sample of 1494 patients with a follow-up of 2.0 years would be needed to achieve 80% power at a 0.05 significance level (one-sided). Such a difference of 2.4% per year would be considered the lower limit of a clinically relevant difference, because the NOACs have other advantages.

The uncertainty which proportion of patients remains to have good quality of VKA treatment over time, combined with the unknown real life event rate on NOACs, makes it impossible to make reliable assumptions on the rate difference and the needed sample size. Even more

Deleted: 28-9

important, there is a chance that a clinically relevant difference cannot be expected and in that case we don't want to expose al large group of patients to the burden of a trial. For these reasons, we plan to perform the current pilot study. For this pilot, we limited the duration of the study to 1 year, with a relatively large number of 240 patients, to optimize precision of the point estimate. The number of 240 patients is feasible, the prevalence of VKA use for atrial fibrillation is high. So accrual time is short and the pilot study can be completed within 15 months (3 months inclusion, 1 year duration).

### 3. TREATMENT OF SUBJECTS

#### 3.1 Investigational product/treatment

Vitamin K antagonists (acenocoumarol and phenprocoumon are currently available), new oral anticoagulants (NOACs, dabigatran, rivaroxaban and apixaban are currently available, this number might increase over the next years).

#### 3.2 Use of co-intervention

For the NOACs adequate contraception is indicated for women of childbearing potential and caution is advised when concomitant medication is changed as this could influence the plasma levels of the study drug. However these are not co-interventions as these also apply to VKA therapy. The anticipated proportion of eligible patients being women below the age of 45 years is small (<1%).

### 4. INVESTIGATIONAL PRODUCT

Not applicable

### 5. NON-INVESTIGATIONAL PRODUCT

#### 5.1 Name and description of non-investigational product(s)

##### VITAMIN K ANTAGONISTS

VKA have an anticoagulant effect by interfering with the cyclic interconversion of vitamin K. This leads into a vitamin K depletion which lowers the production of vitamin K-dependent proteins including coagulant factors II, VII, IX and X. This results in less formation of thrombin and fibrin.

The half-life of VKA varies from 8 to 160 hours depending on the choice of drug. The liver inactivates the active substances followed by renal and fecal excretion. VKA do not inactivate the present coagulant factors. Therefore, due to the relative long half-life of factor II, the antithrombotic effect needs at least five days to reach full potential.

The total price of VKA treatment is mainly determined by the costs of INR monitoring as the drugs themselves are very cheap. In the Netherlands, the yearly costs per person are approximately 200 euro.

##### NOACs

Rivaroxaban is a competitive reversible antagonist of activated factor X (FXa). It lowers the thrombin generation because FXa is needed to catalyse the conversion of prothrombin to thrombin. The half-life of rivaroxaban is generally 5-9 hours but can increase to 11-13 hours in elderly. It is renally cleared for 67% and by feces for 33%. The antithrombotic effect starts immediately after intake (30 minutes), as rivaroxaban directly inactivates FXa. It can be used once daily in a fixed dose that depends on the creatinine clearance.

In January 2012, rivaroxaban has been approved for prevention of embolic stroke in patients with non-valvular AF in Europe.

Deleted: 28-9

Dabigatran is a competitive reversible non-peptide antagonist of thrombin. As thrombin converts fibrinogen to fibrin, antagonizing thrombin results directly in less fibrin generation. Therefore, also dabigatran has a rapid onset of anticoagulant effect. The half-life is 12-14 hours and dabigatran is mainly renally cleared. It is prescribed twice daily in fixed dose without the need for laboratory monitoring.

In Europe, dabigatran has been approved since August 2011 for prevention of stroke and systemic embolism in patients with non-valvular AF.

Apixaban is a direct and competitive inhibitor of factor Xa. Its half-life is around 12 hours and it is mainly fecally cleared. The renal clearance is 25%. As with dabigatran and rivaroxaban, the onset of the anticoagulant effect is rapid. It is used twice daily in a fixed dose and there is no need for laboratory monitoring of the anticoagulant effect. Since December 2012, Apixaban has been approved for the prevention of embolic stroke in patients with non-valvular atrial fibrillation.

The actual price of the NOACs is the result of negotiations by the Ministry and is not in the public domain. A conservative estimate would be that the costs of a NOAC are at least 2.5 x that of VKA with the associated monitoring (i.e, 700-800 euro per year).

Deleted: 28-9

#### Summary of findings from non-clinical studies

This is not relevant anymore for these products, as there are already clinical data available.

#### Summary of findings from clinical studies

##### Vitamin K antagonists

A meta-analysis of 6 randomized trials, published in 1999, demonstrated that warfarin highly effectively lowers the incidence of total stroke (ischemic and hemorrhagic) compared to placebo in patients with non-valvular AF (11,12). The relative risk (RR) was, with 64%, equally reduced in patients with and without recent stroke or transient ischemic attack. This risk reduction was consistent over a wide range of absolute risks. The absolute risk reductions were 2.7% per year for primary prevention and 8.4% per year for secondary prevention.

Adjusted dose warfarin also proved more effective than aspirin and antiplatelet therapy in general in a meta-analysis of 8 trials and 11 trials (12). The ACTIVE W-trial comparing VKA with a combination of aspirin and clopidogrel was prematurely terminated as VKA performed significantly better (13). The AMADEUS-trial showed that idraparinix was as effective as warfarin, but the trial was stopped early because of excess clinically relevant bleeding with idraparinix (14). Ximelagatran showed to be equally effective but was found to be hepatotoxic (15)..

One meta-analysis showed a 1.7-fold increased risk of major bleeding for patients treated with VKA compared with aspirin-treated patients (16). Another meta-analysis found a doubled risk for intracranial bleeding during warfarin use compared to aspirin use, though the absolute risk increase was only 0.2% per year (12). The same applies to the risk of major extracranial bleeding which is also just 0.2% per year higher during acenocoumarol usage as compared to aspirin.

Summarized, VKA have been proven to be more effective than no therapy or any kind of antiplatelet therapy for the prevention of stroke, at the expense of a relative small increase in intra- and extracranial bleeding.

##### NOACs

For rivaroxaban, the pivotal phase III study for the indication of AF was the ROCKET-AF (7). This double-blind, double-dummy randomized controlled clinical trial treated 14,264 AF patients with 20 mg rivaroxaban once daily (15 mg daily for patients with moderate renal impairment at screening, i.e. creatine clearance 30-45 ml/min) or with INR-adjusted warfarin (INR target range 2.0–3.0).

In the ROCKET-AF, rivaroxaban was non-inferior but not superior to warfarin for the primary endpoint: prevention of stroke or systemic embolism (HR = 0.88; 95% CI 0.74 to 1.03, P < 0.001 for non-inferiority). The rivaroxaban group had slightly but insignificantly more total major bleeding (HR = 1.04; 95% VI 0.90 to 1.20, P=0.58), but significantly less intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003).

Summarized, rivaroxaban seems to be as effective as warfarin to prevent stroke or systemic embolism. Its use results in insignificantly more major bleeding and significantly less

Deleted: 28-9

intracranial hemorrhage. Compared to acenocoumarol it has the advantage of a fixed dose without the need for regular laboratory tests.

For dabigatran, the pivotal phase III study for the indication of AF was the RE-LY study which included 18,113 patients (6). This randomized non-inferiority trial compared two fixed doses of dabigatran (in a blinded fashion, 110 mg or 150 mg twice daily) with unblinded INR-adjusted warfarin (INR target range 2.0–3.0). The primary outcome was stroke or systemic embolism.

In the RE-LY study, dabigatran 110 mg (relative risk (RR) = 0.91; 95% CI 0.74 to 1.11) and 150 mg (RR = 0.66; 0.53 to 0.82) were both non-inferior and the latter also superior ( $P < 0.001$ ) for the primary outcome compared to warfarin. The rate of major bleeding per year was significantly lower during use of low dose dabigatran (2.71%) and similar for high dose dabigatran (3.11%) compared to warfarin (3.36%). The rate of hemorrhagic stroke was with 0.38% per year significantly higher in the warfarin group, as compared with 0.12% per year during use of dabigatran 110 mg ( $P < 0.001$ ) and 0.10% per year during use of dabigatran 150 mg ( $P < 0.001$ ). The incidence of myocardial infarction was higher with dabigatran than with warfarin, which could not be explained. The overall mortality rate did not significantly differ between the 3 treatment groups. The net clinical benefit outcome showed a significant benefit for dabigatran 150 mg but not for dabigatran 110 mg.

Summarized, dabigatran 110 mg appears to be as effective as warfarin, but with lower rates of major hemorrhage. Dabigatran 150 mg seems even more effective than warfarin, without the expense of more major hemorrhages. Both can be given in fixed dose, without the requirement of regular monitoring.

For Apixaban, the pivotal phase III study for the indication of non-valvular AF was the ARISTOTLE ((17)). This was, like the ROCKET-AF, a double-blind and double-dummy randomized controlled trial and included 18,201 patients. Apixaban was given twice daily in doses of 5mg. Doses were lowered to 2.5mg if patients had 2 or more of the following characteristics: age  $\geq 80$  years, body weight  $\leq 60$  kg or a serum creatinine level of  $\geq 133 \mu\text{mol}$  per liter. Treatment with Apixaban was compared with dose-adjusted warfarin. The primary outcome was stroke or systemic embolism.

In the ARISTOTLE trial, the risk to develop a primary outcome was significantly lower in the Apixaban group (HR = 0,79; 95%CI 0,66 - 0,95;  $p = 0,01$  for superiority). The risk of major bleeding was also lower (HR = 0.69, 95%CI 0,60 – 0,80), especially for hemorrhagic stroke (HR = 0,51; 95%CI 0.35 – 0.75). The rate of ischemic or uncertain type of stroke was comparable (HR = 0.92; 95% CI 0.74 – 1.13).

Summarized, Apixaban was superior to warfarin in preventing stroke or systemic embolism and caused less bleeding.

#### Description and justification of route of administration and dosage

Dose-adjusted VKA p.o. once daily, titrated to a target INR of 3.0 (range 2.5-3.5), therapeutic rang INR 2.0-3.5.

Deleted: 28-9

As mentioned before, the sensitivity for VKA can differ between patients and also over time within patients. Frequent INR-measurements are required to achieve an anticoagulant effect within the target range of INR 2.5-3.5. The frequency of monitoring depends on the stability of INRs, but can also be intensified due to changes in health status such as the need for invasive procedures or changes in co-medication. In case of under- and over-anticoagulation the dosage can be adjusted, for extreme over-anticoagulation vitamin K suppletion can be used. The procedures for this are laid down in protocols by the Thrombosis Services, and will not differ from regular care.

- Rivaroxaban, 20 mg p.o., once daily. Dose modifications are made per the most recent UMCG NOAC protocol (appendix 1).

Dabigatran 150 mg p.o., twice daily. Dose modifications are made per the most recent UMCG NOAC protocol (appendix 1).

Apixaban 5 mg p.o., twice daily. Dose modifications are made per the most recent UMCG NOAC protocol (appendix 1).

#### Preparation and labelling of Non-Investigational Medicinal Product

All medication used by participants in this study will be provided by their usual out-patient pharmacies with regular labelling, according to usual care.

Deleted: 28-9

#### Drug accountability

The investigators will contact the pharmacies to obtain information on how many pills they have provided to the individual patient and at which date the drugs were given to the patient. No further attempts towards drug accountability are made, in keeping with comparing two strategies of routine care.

## 6. METHODS

### 6.1 Study parameters/endpoints

#### 6.1.1 Main study parameter/endpoint

Net clinical benefit: composite of stroke, systemic embolism, myocardial infarction, vascular death and major bleeds. All components will also individually be assessed.

#### Definitions (7):

- Stroke: a sudden focal neurological deficit of presumed cerebrovascular etiology that persisted beyond 24 hours, [or was treated \(e.g. by thrombolysis or thrombectomy\) to avoid persistence beyond 24 hours](#), and was not due to another identifiable cause.  
Brain imaging (computer tomography or magnetic resonance imaging) is recommended for all suspected strokes.
- Systemic embolism: an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (e.g. atherosclerosis, instrumentation, or trauma).
- Myocardial infarction: the occurrence of a percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). In the absence of PCI or CABG, myocardial infarction is defined by typical symptoms and cardiac biomarker elevation (troponin I or T, creatine kinase-MB) above the upper limit of normal, new pathological Q waves in at least 2 contiguous electrocardiogram leads, or confirmed by autopsy.
- Vascular death: death due to vascular causes e.g. stroke, systemic embolism or acute myocardial infarction.
- Major bleeding: a clinically overt bleeding with fatal outcome, a fall in hemoglobin of at least 2 g/dL, leading to transfusion  $\geq 2$  units of packed red blood cells or occurring at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal).

**Commented [JvM1]:** To bring it more in line with the definition for myocardial infarction (see below). This amendment was made before any potential stroke had happened.

**Deleted:** 28-9

### 6.1.2 Secondary study parameters/endpoints

**Efficacy:** composite of ischemic or unspecified stroke, systemic embolism, myocardial infarction and vascular death. All efficacy components will also individually be assessed.

Definitions (7): For definitions: see 'main study endpoint',

**Safety:** composite of major bleeds (including haemorrhagic stroke) and non-major clinically relevant bleeds and all-cause mortality. All safety components will also individually be assessed. In addition, differences in serious adverse events (SAE) and treatment complications will be evaluated.

Definitions (7):

- For definition of major bleeds: see 'main study endpoint',
- Non-major clinically relevant bleeding: overt bleeding not meeting the above mentioned criteria for major bleeding, but resulting in a medical intervention, unscheduled contact with health care provider (visit or phone) and/or temporary interruption of study treatment.
- A SAE is any untoward medical occurrence or effect that at any dose:
  - o results in death;
  - o is life threatening (at the time of the event);
  - o requires hospitalisation or prolongation of existing inpatients' hospitalisation;
  - o results in persistent or significant disability or incapacity;
  - o is a congenital anomaly or birth defect;
  - o any other important medical event may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

**Burden of complications:** The severity of a clinical endpoint event and the cumulative number of days after a clinical endpoint, during which the patients is hospitalized or needs unplanned professional care for activities of daily living, until one month after end of study or until death, whatever comes first.

Defintions:

Severity:

- Stroke: according to the modified Rankin scale.
- Myocardial infarction: fatal versus non-fatal.
- Systemic embolism: fatal versus non-fatal.
- Bleeding: major versus non-major.

### 6.1.3 Other study parameters

Deleted: 28-9

Treatment expectations and satisfaction: scores on PACT-Q questionnaires.

Compliance: based on information from the pharmacy registry whether patients appropriately collected their anticoagulant medication.

Quality of life: scores on SF-36 questionnaires.

Feasibility: proportion of eligible patients that the referring physician opts out for, proportion of invited eligible patients who give informed consent, drop-out rate.

Randomization, blinding and treatment allocation

Patient and caregivers will know to which strategy the patient is allocated.

All endpoint events will be adjudicated by an independent clinical endpoint committee which will be blinded for received treatment. In this, all death will be classified as either vascular (e.g. due to stroke, systemic embolism or acute myocardial infarction) or non-vascular (e.g. trauma, malignancy, infection). Also, the classification of the type of stroke in hemorrhagic, ischemic or unspecified is the exclusive responsibility of the clinical endpoint committee.

Deleted: 28-9

## Study procedures

Visit	-1	0	1	2
	Screening -2 weeks +/- 1 week	Randomization	6 months +/- 4 weeks	12 months/ end-of-study +/- 4 weeks
Informed consent	X			
Medical history including thrombotic and major bleeding complications	X			
Concomitant medication	X			
CHA2DS2-VASc-score	X			
VKA treatment related history	X			
Inclusion/exclusion		X		
Randomization		X		
Net clinical benefit outcome			X	X
Additional information in case of primary endpoint			X	X
Changes in comedication (charts)			X	X
Adherence to study medication (diary)			X	X
Questionnaire on quality of life (SF-36)		X	X	X
Questionnaire on satisfaction (PACT-Q)		X	X	X
Clinical examination				
Weight, length, vital signs	X			
Biochemistry (renal clearance)	X			
Serious Adverse Events, treatment complications			X	X

Deleted: 28-9

**Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

**6.2 Specific criteria for discontinuation of any study treatment (VKA, NOACs).**

A subject could be discontinued from study treatment for any of the following reasons:

- The investigator or treating physician believes that for safety reasons (e.g. adverse events) it is in the best interest of the subject to stop treatment.
- If at any time, in the investigator's or treating physician's opinion, the subject no longer requires anticoagulation treatment.
- Pregnancy
- If contraindications develop to the allotted treatment (i.e., for NOAC: decrease of creatinine clearance <30 ml/min on repeated measurements).
- The development of an indication for anticoagulation therapy other than atrial fibrillation.

**Replacement of individual subjects after withdrawal**

We will not replace individual subjects. Patients who want to withdraw consent will be asked to attend an end-of-study visit. If they refuse, the study time of that specific patient will end retrospectively at the last attended study-visit.

Another situation that can lead to implicit withdrawal is loss to follow-up. In case of loss to follow-up, the general practitioner and/or referring physician will be contacted to find out whether the patient died, has moved or any other explanation. If the contact can be fully restored all study time is taken into account, otherwise the study time of that specific patient will end retrospectively at the last attended study-visit.

**Follow-up of subjects withdrawn from treatment**

Patients who have withdrawn from study therapy will be asked to attend on the regular study visits or to agree with telephonic follow-up. If they refuse, the protocol is equal to that of patients who have withdrawn consent.

**6.3 Premature termination of the study**

The study will be terminated if, after inclusion of 50 subjects, the randomization rate is less than 5% of invited subjects. Patients already randomized will continue for the intended duration of treatment.

There are no other pre-specified criteria for premature termination of the study. After every 10 endpoints reached, the DSMB will evaluate the study and advise the investigators accordingly. In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than

Deleted: 28-9

was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

## 7. AEs, SAEs and SUSARs

### 7.1 Adverse events (AEs)

Non-serious adverse events are only recorded if they are treatment complications (judged related to the study drug by the subject or the investigators). As both study drugs are registered for the indication investigated in this study, capture of unrelated adverse events does not contribute. All serious adverse events, whether related or not, are captured.

### 7.2 Serious adverse events (SAEs)

For the purposes of this trial, the following clinical efficacy endpoint events will not be considered adverse events or serious adverse events: myocardial infarction, ischemic stroke, and systemic embolism. They will be registered as endpoint events only. Hemorrhagic stroke and other major bleeds will be captured as endpoint and reported as adverse event.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- any other important medical event may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Definitions:

- Hospitalization: Any AE event leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least 1 of the following exceptions are met:
  - o The admission results in a hospital stay of less than 12 hours

OR

- o The admission is preplanned (i.e., elective or scheduled surgery arranged before the start of the study)

OR

Deleted: 28-9

- The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care)
- Disability: a substantial disruption of a person's ability to conduct normal life's functions.
- Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Any serious event should be assessed in terms of severity, burden and relation to study drugs. Therefore patients will be instructed to contact a medical doctor immediately in case of acute threatening situations and afterwards report the AE to the principal investigator of the Thrombosis Service. The principal investigator will report a SAE to the coordinating investigator within 72 hours from notification. The study coordinator will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the study coordinator has first knowledge of the serious adverse reactions.

### 7.3 Suspected unexpected serious adverse reactions (SUSARs)

All SUSARs will be reported to the accredited METC through ToetsingOnline

#### Annual safety report

This study does not include investigational medicinal products, so this is not applicable.

#### Follow-up of adverse events

All SAEs will be followed until they have abated, until a stable situation has been reached, until one month after end of study or until death, whatever comes first. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

## 8. DATA SAFETY MONITORING BOARD (DSMB) / SAFETY COMMITTEE

#### Composition of the DSMB

Prior to the start of the study, a data safety monitoring (DSM) plan will be finalized specifying all relevant data safety monitoring issues, including the formation of the DSMB committee. The DSMB will at least review the study after every 10 clinical events that qualify as primary study endpoint (stroke, systemic embolism, myocardial infarction, vascular death and major bleeds), and advise the investigators accordingly. No prespecified termination plan will be formulated, given the small size of the pilot study and the fact that both study strategies are registered for this indication.

Aims of the DSMB: To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical

Deleted: 28-9

trial. The DSMB will consist of two experts in the field, who are not otherwise involved in the study.

## 9. STATISTICAL ANALYSIS

A general description of the statistical analyses is outlined below. A more detailed statistical analysis plan (SAP) will be provided before database closure.

Summaries by allocated treatment using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. Descriptive statistics such as mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Kaplan-Meier method will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data. For patients on VKA, iTTR was calculated. The individual time patients on VKA spent in the therapeutic range will be calculated by linear interpolation (18,19).

In this pilot study, results of hypothesis tests will be considered as explorative rather than confirmative. In this respect, P-values are not used to indicate statistical significance. The primary hypothesis that will be explored is that VKA therapy is superior NOAC therapy with regards to the net clinical benefit.

### Primary study parameter(s)

Primary endpoint and efficacy endpoint:

The primary endpoint is the composite of stroke, major bleeds, systemic embolism, myocardial infarction and vascular death. The efficacy endpoint is the composite of ischemic or unspecified stroke, systemic embolism, myocardial infarction and vascular death.

The population for analysis is the intention-to-treat population (ITT). All randomized patients will be included in the ITT population, provided that written informed consent is given. All patients will be analyzed in the treatment group that was allocated by the computerized voice response system, irrespective of the actually received study drug. Time-to-event analyses will be performed using Cox proportional hazard survival analysis. In addition, survival will be depicted using Kaplan-Meier curves. Absolute risks will be expressed as incidence rates per 100 person years.

### Safety endpoint:

Safety endpoint is the composite of major bleeds (including haemorrhagic stroke) and non-major clinically relevant bleeds and all-cause mortality. The safety analysis will be performed in all patients who received at least one dose of a study drug. Unless otherwise stated, all safety analyses will be performed based on the safety population while on treatment (including washout). Time-to-event analyses will be performed using Cox proportional

Deleted: 28-9

hazard survival analysis. In addition, survival will be depicted using Kaplan-Meier curves. Absolute risks will be expressed as incidence rates per 100 person years.

**Secondary and other study parameter(s)**

All secondary and other endpoints e.g. individual components of primary endpoint, compliance, quality of life, patient satisfaction, burden of treatment complications, and cost-effectiveness will be analyzed over the entire course of the study using appropriate methods.

**Interim analysis**

not applicable

Deleted: 28-9

## 10. ETHICAL CONSIDERATIONS

### 10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (new version October 2013), and in accordance with the Medical Research Involving Human Subjects Act (WMO).

### 10.2 Recruitment and consent

The Thrombosis Service will select from its files those patients who, based on their quality of anticoagulation, would be candidates for the study. This information follows directly from the INR measurements for which patients visit the Thrombosis Service. The referring physician is informed about the study, and patients are only invited for the study if she/he does not object. Patients are invited by means of a patient information letter. If they are interested, they can return the attached card to the research nurse, who will then set up an appointment for a screening visit. The potential subjects will be explained the aims, methods, and potential hazards of the study. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. The research nurse or the principal investigator will be available for answering questions and will finally ask the patient to give informed consent. The patients will have sufficient time to consider their decision: there will be at least one week between the written information letter and the appointment. During or after the screening visit, the patient can take as much time as she/he needs before signing informed consent, with a maximum of 7 days. It is also important to note that the day of informed consent is at least 7 days before randomisation and start of study treatment.

#### Objection by minors or incapacitated subjects

Not applicable.

### 10.3 Benefits and risks assessment, group relatedness

All participants are exposed to the benefits and risks of anticoagulation for atrial fibrillation. For this indication, the benefits (decreased risk of stroke and systemic embolism) are well known and larger than the risks (mainly bleeding). This study randomizes between two strategies of anticoagulation. Both are registered for this indication, and the risk/benefit versus no anticoagulation for both strategies is clear. We do not know which of both strategies is superior in this patient group, so there is equipoise for bleeding risk and risk of stroke.

For participants who continue on VKA therapy, the disadvantage is the continued need for frequent monitoring. Their benefit is that they receive a therapy that is well known and has been used for a long time.

For participants who receive NOAC therapy, the disadvantage is using a newer drug with a shorter history of routine use. Another disadvantage is an increased risk of gastrointestinal complaints (mainly dyspepsia, completely reversible on discontinuation of drug). Also, the

Deleted: 28-9

use of NOACs is more expensive. If no other medical costs are made by the individual patient, this patient has to pay approximately 200 euros per year extra. Their benefit is the absence of frequent monitoring.

All participants will need to attend four study visits and undergo one venapuncture. They will need to spend time on keeping diaries and filling out questionnaires.

As this is a pilot study, the results are expected not to be conclusive and the participants will not be able to directly benefit from the outcomes. Results from a future trial would benefit similar patients.

#### Compensation for injury

This study compares two registered treatments. No injury related to study or study procedures is foreseen.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million and five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

#### Incentives

Not applicable.

Deleted: 28-9

## 11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### Handling and storage of data and documents

We will handle the data confidentially and anonymously. We will use a subject identification code list to link the data to the subject, when appropriate. The code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. The handling of personal data complies with the Dutch Personal Data Protection Act.

### Monitoring and Quality Assurance

This pilot study will be monitored by the coordinating investigator and/or the project leaders who will visit study centers at least monthly, to discuss any issues and check on conduction of the study. Logical checks are incorporated in the study database CRF.

### Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC-application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

### Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### End of study report

The coordinating investigator will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patients last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study

Deleted: 28-9

report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

**Public disclosure and publication policy**

The results of this study will be published in a peer-reviewed journal and presented at national and international meetings.

**12. STRUCTURED RISK ANALYSIS****12.1 Potential issues of concern**

We use registered medicinal products within the indication, not in combination with other products and with the care routinely provided with these medications. An additional safeguard is that participants can always contact study personnel, which might make their treatment in fact safer than in routine care. We do not foresee issues of concern.

**12.2 Synthesis**

We do not expect potential issues of concern as we will use registered medicinal products within the indication, not in combination with other products. and with the care routinely provided with these medications. As we exclude patients that have a contraindication against VKA or NOACs, this study will not provide any extra risk. We will also establish a DSMB to safeguard the interest of trial patients.

**13. REFERENCES**

- (1) Health council of the Netherlands. New anticoagulants: well-dosed introduction. The Hague: Health council of the Netherlands, 2012, publication no. 2012/07. (In Dutch, accesible through [www.gr.nl](http://www.gr.nl)).
- (2) Health care insurance board. Re-assessment of dabigatran (Pradaxa), 2012. Pharmacotherapeutic, cost-consequences reports, with accompanying letter to the Minister of Health, Welfare and Sport. ( In Dutch accesible through [www.cvz.nl](http://www.cvz.nl)).
- (3) Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983-988.
- (4) Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-2747.
- (5) Hirsh J, Fuster V, Ansell J, et al. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 2003; 107: 1692-1711.

Deleted: 28-9

- (6) Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139-1151.
- (7) Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883-891.
- (8) Veeger NJ, Piersma-Wichers M, Hillege HL, et al. Early detection of patients with a poor response to vitamin K antagonists: the clinical impact of individual time within target range in patients with heart disease. *J Thromb Haemost* 2006; 4: 1625-1627.
- (9) White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med* 2007; 167: 239-245.
- (10) Veeger NJ, Piersma-Wichers M, Tijssen JG, et al. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005; 128: 513-519.
- (11) Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131: 492-501.
- (12) Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857-867.
- (13) ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; 367: 1903-1912.
- (14) Amadeus Investigators, Bousser MG, Bouthier J, et al. Comparison of idraparinix with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008; 371: 315-321.
- (15) Diener HC, Executive Steering Committee of the SPORTIFF III and V Investigators. Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation. Pooled analysis from the SPORTIF III and V studies. *Cerebrovasc Dis* 2006; 21: 279-293.
- (16) van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002; 288: 2441-2448.
- (17) Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981-992.
- (18) Veeger NJ, Piersma-Wichers M, Tijssen JG, et al. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005; 128: 513-519.
- (19) Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; 69: 236-239.

Deleted: 28-9

## Appendix 1

**Gebruik van nieuwe orale anticoagulantia (NOACs) in het UMCG  
Versie 070114, niet gebruiken na 070115****Inleiding**

Dabigatran, rivaroxaban en apixaban zijn vertegenwoordigers van de klasse Nieuwe Orale AntiCoagulantia (NOACs). Ze zijn in gebruik bij atriumfibrilleren (AF) en veneuze tromboembolie (VTE). In beide indicaties vervangen ze de vitamine K antagonist (VKA, acenocoumarol en fenprocoumon). Daarnaast wordt een profylactische dosis gebruikt na heup- en knie vervanging.

Het belangrijkste voordeel van NOACs boven de VKA is grote voorspelbaarheid van het effect, waardoor routinematige controle (zoals de INR voor VKA) niet nodig is. Qua effectiviteit en veiligheid worden NOACs beschouwd als niet-inferieur aan VKA.

Als richtlijn voor het gebruik van NOACs wordt in het UMCG de 'Leidraad begeleide introductie nieuwe orale antistollingsmiddelen', door de beroepsgroepen opgesteld op verzoek van de minister van Volksgezondheid, gebruikt.

Op basis van deze richtlijn heeft de werkgroep 'Nieuwe orale anticoagulantia' van het UMCG het voorliggende protocol samengesteld.

**Indicatie**

AF voor boezemfibrilleren wordt de richtlijn ESC 2012 gevolgd. Zowel dabigatran, rivaroxaban als apixaban worden voorgeschreven, waarbij individuele patiëntfactoren zoals interacterende comedicaatie meespelen in de keuze.

VTE voor veneuze tromboembolie worden de NOACs nog niet routinematig gebruikt, nu de vergoeding nog niet geregeld is. In specifieke gevallen wordt soms een NOAC voorgeschreven. De voorkeur gaat dan uit naar rivaroxaban, vanwege de opgedane ervaring binnen fase 3 onderzoek en gebruiksgemak (initieel geen LMWH nodig, na drie weken over op eenmaal daagse dosering).

Tromboseproylaxe na TKA/THA voor deze indicatie worden NOACs in het UMCG niet routinematig gebruikt. Dit is conform het advies in de 'Leidraad'.

Deleted: 28-9

**Kenmerken van de middelen**

	Dabigatran		Rivaroxaban		Apixaban
Merknaam	Pradaxa		Xarelto		Eliquis
Mechanisme	IIa remming		Xa remming		Xa remming
Halfwaardetijd	Klaring > 80	13h	Klaring > 30	12h	12h
	Klaring 50-80	15	Klaring < 30	onbekend	
	Klaring 30-50	18			
	Klaring < 30	27			
Renale klaring	80%		66%		27%
Eiwitbinding	35%		> 90%		87%

**Dosering**Dabigatran

Dabigatran niet gebruiken bij een kreatinineklaring < 30ml/min.

Na TKA/THA            1-4h postoperatief 110 mg  
 Vanaf 1<sup>e</sup> dag postOK  
                                  Klaring > 50 ml/min, leeftijd ≤ 75 jr            1dd 220 mg  
                                  Klaring 30-50 ml/min of leeftijd > 75 jr            1dd 150 mg

- continueren gedurende 6 weken, cf gebruik nadroparine in standaard beleid
- in combinatie met amiodaron/kinidine/verapamil in principe geen dabigatran (als toch wordt gegeven: dosering verder verlagen, naar 1dd 150 mg bij klaring > 50 en leeftijd ≤ 75 jr, anders naar 1dd 110)

Bij AF:                    standaard 2dd 150 mg

altijd 2dd 110 mg als:

- Patiënten van 80 jaar of ouder
- Patiënten die gelijktijdig verapamil gebruiken

2dd 110 mg kan overwogen worden bij:

- Patiënten van 75 tot 80 jaar met laag trombo-embolisch risico en hoog bloedingrisico
- Bij patiënten met gastritis, oesofagitis of oesofagale reflux
- Voor patiënten met een matig verminderde nierfunctie (kreatinineklaring 30-49 ml/min) met een hoog bloedingrisico

Dabigatran is een substraat van P-glycoproteïne.

Combinatie met remmers van P-glycoproteïne leidt tot hogere spiegels van dabigatran:

- Niet combineren met ciclosporine, tacrolimus, itraconazol, systemische ketoconazol, posaconazol, dronedarone of HIV proteaseremmers.

Deleted: 28-9

- In combinatie met kinidine en amiodaron wordt voor de indicatie AF geen dosisaanpassing maar 'nauwgezet medisch toezicht' geadviseerd. Voor de indicatie VTE is advies verlagen tot 1dd 150 mg (advies gebaseerd op beperkte data, voor VTE dan liever rivaroxaban geven).

Combinatie met inductoren van P-glycoproteïne geeft lagere spiegels van dabigatran. Er zijn geen data over compenseren door dosisverhoging.

- Niet combineren met rifampicine, carbamazepine, fenytoïne of sint-janskruid

#### Rivaroxaban

Rivaroxaban niet gebruiken bij een kreatinineklaring < 30ml/min (de registratietekst laat gebruik tot een klaring van 15 ml/min toe, dit lijkt vooralsnog in de klinische praktijk risicovol)

Na TKA/THA 6-10h postoperatief starten met 1dd 10 mg, geen aanpassing op nierfunctie

- continueren gedurende 6 weken, cf gebruik nadroparine in standaard beleid

Bij AF 1dd 20 mg  
1dd 15 mg als

- klaring 30-49 ml/min
- hoog bloedingsrisico (ESC)

Bij VTE dag 1-21: 2dd 15 mg, geen aanpassing op nierfunctie  
Geen LMWH bijgeven!  
Vanaf dag 22: 1dd 20 mg  
1dd 15 mg klaring 30-49 ml/min

Rivaroxaban is een substraat van P-glycoproteïne en van CYP3A4.

Combinatie met remmers van P-glycoproteïne en CYP3A4 leiden tot hogere spiegels van rivaroxaban:

- Niet combineren met claritromycine, erytromycine, fluconazol, itraconazol, systemische ketoconazol, voriconazol, posaconazol of HIV-proteaseremmers

Combinatie met inductoren van CYP3A4 geeft lagere spiegels van rivaroxaban. Er zijn geen data over compenseren door dosisverhoging.

- Niet combineren met rifampicine, carbamazepine, fenytoïne, fenobarbital of sint-janskruid

#### Apixaban

Na THA/TKA 12-24h postoperatief starten met 2dd 2.5 mg, geen aanpassing op nierfunctie tenzij deze < 15 ml/min is. Dan wordt gebruik ontraden vanwege ontbreken van gegevens.

- continueren gedurende 6 weken, cf gebruik nadroparine in standaard beleid

Deleted: 28-9

Bij AF standaard 2dd 5 mg  
 Verlagen naar 2dd 2.5 mg bij

- Klaring 15-29 ml/min
- Twee uit leeftijd  $\geq 80$   
 Gewicht  $\leq 60$   
 Serumkreatinine  $\geq 133$

### Begeleiding van gebruik

De voorschrijver is verantwoordelijk voor de begeleiding van NOAC gebruik (controle nierfunctie, ontstaan van contra-indicaties, therapietrouw). Indien gewenst kan de patiënt hiervoor verwezen worden naar LabNoord/ Trombosedienst Groningen (gebruik het bekende aanmeldformulier, geef aan om welk preparaat het gaat). LabNoord/Trombosedienst fungeert als centraal aanspreekpunt voor vragen en problemen rond gebruik van NOACs in de eerste lijn. Binnen het UMCG vervult de dienstdoende stollingsarts (77038, buiten kantoor tijden via de centrale) deze taak.

### Laboratorium monitoring

De PT en aPTT zoals routinematig gebruikt in het UMCG zijn onvoldoende gevoelig om gebruik van NOACs met voldoende zekerheid uit te sluiten. Bepaling van de INR is niet zinvol voor NOACs.

Voor dabigatran is de trombinetijd (TT) geschikt om gebruik uit te sluiten: als de TT normaal is, is er geen relevante spiegel van dabigatran. Voor een kwantitatieve meting wordt de DTI gebruikt.

Voor rivaroxaban en apixaban is een aangepaste antiXa meting beschikbaar. Bij het aanvragen van de test moet aangegeven worden welk middel wordt gebruikt.

Afhankelijk van de situatie worden de testen als volgt aangevraagd:

1. **Spoed**, gebruik onbekend: TT + DTI + -antiXa (directe Xa inhibitor)
2. **Geen spoed**, bekend gebruik van **Rivaroxaban of Apixaban**: antiXa (directe Xa inhibitor)
3. **Geen spoed**, bekend gebruik van **Dabigatran**: Dabi-DTI
4. **Geen spoed**, gebruik onbekend: TT + antiXa (directe Xa inhibitor), reflex DTI bij TT > meetbereik

TT, DTI en antiXa zijn 24x7 beschikbaar, buiten kantooruren iom dd klinisch chemicus of stollingsarts.

Er zijn beperkte data over relatie tussen spiegel en bloedingsrisico bij ingrepen. Spiegels zijn dan vooral zinvol als de nierfunctie gestoord is, in de meeste situaties is tijdsduur sinds inname zinvoller informatie.

Voor beoordeling van therapeutisch effect is spiegelbepaling niet zinvol, relatie spiegel-kliniek is niet bekend

Deleted: 28-9

### Couperen

Er is nog geen specifiek antidotum beschikbaar. Bij bloedingen middel stoppen, maximaal inzetten op ondersteunend beleid. Geef actieve kool als inname van NOAC minder dan 2 uur geleden is geweest. Geef tranexaminezuur systemisch (1g iv of oraal, zo nodig na 8h herhalen) bij slijmvliesbloedingen, gebruik geen tranexaminezuur bij hersenbloedingen of nierbloedingen. In overige bloedingssituaties is tranexaminezuur te overwegen (1g iv of oraal, zo nodig na 8h herhalen).

Als dat onvoldoende is:

- Vierfactorenconcentraat (bv Cofact), 50<sup>F</sup>/kg. Voor rivaroxaban zijn aanwijzingen voor effectiviteit in gezonde vrijwilligers, voor dabigatran wordt gebruik gesteund door expert opinion.
- Dialyse voor dabigatran. Niet zinvol voor rivaroxaban vanwege hoge eiwitbinding.

Gebruik van recombinant stollingsfactor VIIa (Novoseven) en FEIBA wordt niet door data ondersteund, voor deze indicatie niet gebruiken.

### Random chirurgie

#### Electief

Gezien de korte halfwaardetijd is het voldoende de middelen te stoppen. Het is niet nodig/zinvol nog te overbruggen met LMWH.

Bij normale nierfunctie en een standaard\* bloedingsrisico ingreep laatste gift dabigatran/rivaroxaban 24h preOK. Bij normale nierfunctie en hoog\*\* bloedingsrisico ingreep laatste gift 48h preOK.

Bij gestoorde nierfunctie op geleide van voorspelde halfwaardetijd langer tevoren stoppen:

		Standaard risico	Hoog risico
rivaroxaban gift	klaring > 30	24h preOK laatste gift	48h preOK laatste
	klaring < 30	48h preOK laatste gift	96h preOK laatste
dabigatran gift	klaring > 50	24h preOK laatste gift	48h preOK laatste
	klaring 30-50	48h preOK laatste gift	72h preOK laatste gift
	klaring < 30	96h preOK laatste gift	144h preOK laatste gift

Postoperatief hervatten zodra duidelijk is dat hemostase bereikt is, gebruikelijk na 24 uur, maar nooit eerder dan 4-6h postOK. Als het tromboserisico niet uitgesproken hoog is (CHA2DS2-Vasc < 3 of VTE meer dan zes maanden geleden) NOAC pas 2-3 dagen postOK herstarten. Voor ingrepen met een uitgesproken hoog bloedingsrisico, waarbij LMWH gebruikelijk pas na 5 dagen herstart wordt (neurochirurgie), wordt voor NOAC dezelfde termijn aangehouden.

Deleted: 28-9

Als NOAC nog niet de dag van OK herstart wordt, moet de gebruikelijke tromboseprohylaxe (proylactische dosis LMWH) worden gegeven. Zodra NOAC is herstart, is extra tromboseprohylaxe niet meer nodig.

\* Ingrep met standaard risico: hartcatheterisatie, bepaalde (eenvoudige) ritme-ablaties, colonoscopie zonder verwijdering van grote poliepen, ongecompliceerde laparoscopische procedures, radiologische puncties en/of stenting met goede hemostase-mogelijkheid na ingrep

\*\* Ingrep met hoog risico: meer risico dan in bovenstaande regel

Specifiek voor cardiale ingrepen: Rondom CAG, PCI, ablaties, PM en ICDs en hartchirurgie (volgens leidraad NVVC)

De nierfunctie moet worden gemeten tijdens het pre-assessment polibezoek en de patiënt moet duidelijke instructies krijgen over wanneer te stoppen.

Ingrepen met een **standaard bloedingsrisico**

- Hartkatheterisatie
- Eenvoudige ritme-ablaties

Ingrepen met een **hoog bloedingsrisico**

- Hartchirurgie (inclusief pericardiale ingrepen)
- Inbrengen van pacemakers of defibrillatoren
- Complexe ablaties (PVI, congenitale ablaties, VT post-MI ablaties).

### Spoed

Schat antistollingseffect in op basis van laatste inname en nierfunctie. Er zijn op dit moment geen stollingstesten beschikbaar die hieraan bijdragen.

Geef trombocytentransfusie als er ook plaatjesaggregatieremmers worden gebruikt of bij trombocytën < 50.

Gebruik geen neuraxisblokkade

Stel ingrep zo mogelijk tot 1 halfwaardetijd na inname uit

Kan dat niet: overweeg 50<sup>E</sup> vierfactorenconcentraat (laag bewijsniveau)

Bij spoed-neurochirurgische ingrepen wordt altijd 50<sup>E</sup> vierfactorenconcentraat gegeven.

### **Overzetten**

*Van VKA naar dabigatran/rivaroxaban/apixaban*

Stop acenocoumarol (Sintrom®), wacht tot INR onder 2.0 is, start NOAC.

Stop fenprocoumon (Marcoumar®), wacht tot INR onder 2.0 is, geef 5 milligram vitamine K, start NOAC.

*Van NOACs naar VKA*

Deleted: 28-9

Start acenocoumarol/fenprocoumon, doseer en controleer volgens standaard, stop NOAC op dag 4. NB: INR = PT, wordt beïnvloed door rivaroxaban en apixaban! Bij ernstige nierfunctiestoornis (= langere halfwaardetijd) kan de NOAC eerder worden gestaakt. In situaties met een hoog tromboserisico: vervang NOACs door LMWH, start daarnaast VKA

*Van LMWH naar NOACs en vice versa*

Eerste gift LMWH op tijdstip dat NOAC gegeven had moeten worden, en vice versa.

#### **Poliklinische voorschrijfgeregels (zoals landelijk vastgesteld)**

De apotheek kan alleen NOACs afleveren als het recept voldoet aan de volgende regels:

- voorschrijver is een medisch specialist
- ingevulde artsenverklaring wordt bijgevoegd
- op het recept staan indicatie en nierfunctie (klaring, < 6 mnd geleden gemeten) vermeld
- als de NOAC in plaats komt van een VKA: datum stop VKA en datum start NOAC, of INR

#### **Incidentmelding**

Incidenten met NOACs moeten gemeld worden via het IMS (zoals gebruikelijk met een DIM melding). De apotheek verzamelt alle meldingen waarin een NOAC wordt genoemd.

Conform de Landelijke Standaard Keten zorg Antistolling worden tweemaal per jaar het aantal en de aard van de incidenten geëvalueerd door de afdeling Hematologie (in het kader van casemanagement antistolling).

#### **Referenties**

- Leidraad begeleidde introductie nieuwe orale antistollingsmiddelen. 2012.
- 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Camm AJ et al. Eur Heart J 2012;33:2719-47.
- Farmacotherapeutisch Kompas
- Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood 2012;119:3016-23.
- Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124:1573-9.

#### **Samenstelling van de werkgroep 'Nieuwe orale anticoagulantia'**

Prof.dr. I.C. van Gelder, cardioloog  
Dr. M.P.M. Harms, internist acute geneeskunde  
Dr. H.G.D. Hendriks, anaesthesioloog  
Dr. G.J. Luijckx, neuroloog  
Dr. K. Meijer, internist-hematoloog (voorzitter)  
Dr. A.B. Mulder, arts klinische chemie

Deleted: 28-9

Drs. P.V. Nannan Panday, ziekenhuisapotheker  
Drs. G. Piersma-Wichers, internist, directeur Trombosedienst

Deleted: 28-9