Treatment of Non-valvular atrial fibrillation with oral anticoagulants

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Europe-Expro has observed that as yet a Dutch guideline from the field of Cardiology about the new oral anticoagulants for the treatment of atrial fibrillation has been lacking. In this report experts in the field of anticoagulation and atrial fibrillation assess whether the new oral anticoagulants are clinically relevant superior to the standard therapy with vitamin K Antagonists (VKAs/coumarins) for the indication of non-valvular atrial fibrillation.
For more information on this expert procedure, please contact, in the Netherlands, Christiaan Caanen (tel. +31 6 5437 2520).

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Expert Procedures on Clinical, Economic, and Patient Relevance

Table of contents

Abbreviations

ACCP	American College of Chest Physicians
ACS	Acute Coronary Syndrome
AF	Atrial fibrillation
ASA	Acetylsalicylic acid (aspirin)
CBO	Central Counseling Body
CHADS2-score	Congestive heart failure, Hypertension, Age >75 yrs., Diabetes, Stroke or TIA
CHA2DS2-VASc score	Congestive heart failure, Hypertension, Age >75 yrs., Diabetes, Stroke or TIA Vascular diseases, Age 65-75, Sex category (female)
CVA	Cerebral Vascular Accident (stroke)
CVZ	Healthcare Insurance Board
CNS	Central Nervous System
DVT	Deep Vein Thrombosis
ETP	Endogenous Thrombin Potential
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FNT	Federation of Dutch Thrombosis Services
HARM	Hospital Admission Related to Medication
HAS-BLED	Validated scoring system to determine the risk of hemorrhage in patients with AF
Hb	Hemoglobin
IGZ	Healthcare Inspectorate
INR	International Normalized Ratio: a measure of the blood coagulation status
ISTH	International Society on Thrombosis and Hemostasis
IVM	Institute for Responsible Use of Medication
KRVP	Clinical Relevance and Validation Procedure
LMWH	Low Molecular Weight Heparin
NNT	Number Needed to Treat: the number of patients that must receive the new treatment to prevent the primary endpoint once extra in comparison with the standard treatment. Formula: NNT= 1/(p1-p2), where p is the absolute occurrence of the primary endpoint in the control group (p1) and the new treatment group (p2).
NNH	Number Needed to Harm: the number of patients that must receive the new treatment to prevent the primary endpoint once extra in comparison with the standard treatment without a serious adverse reaction related to the treatment occurs. Formula: NNH = 1/(p1-p2)*[1-(q1-q2)], where q is the absolute occurrence of the adverse reaction in the new treatment (q1) and in the control group (q2).
NOACs	New oral anticoagulants (here: dabigatran, rivaroxaban and apixaban)
OAC	Oral Anticoagulants
PCC	Prothrombin Complex Concentrate
PT	Prothrombin time
PTT (aPTT)	Partial Thromboplastin Time (activated partial thromboplastin time)
RIVM	National Institute for Public Health and the Environment
SPC	Summary of Product Characteristics
TEC	Thromboembolic Complication
TIA	Transient Ischemic Attack
VKA(s)	Vitamin K antagonist(s) (coumarin derivatives)

1. Assessment clinical relevance of the new oral anticoagulants for the treatment of non-valvular atrial fibrillation

1.1 Introduction

The introduction of the new oral anticoagulants (direct thrombin FIIa (factor IIa) inhibitor: *dabigatran*, FXa (Factor Xa) inhibitors: *rivaroxaban, apixaban*; called NOACs) requires assessment of the clinical relevance in comparison with the standard treatment with vitamin K antagonists (VKAs) for the indication of non-valvular atrial fibrillation (hereinafter referred to as AF). After all, a statistically significant improvement in efficacy and/or safety is no guarantee that the improvement is also relevant from a clinical perspective.

A clinically significant improvement occurs when a new treatment in comparison with an existing treatment shows an improvement that is assessed as significant medical progress by experts. Based on a chosen clinical parameter or clinical aspect of the treatment, a meaningful or relevant improvement in comparison with an existing therapy is defined. Definition of what is clinically relevant arises from interpretation and translation of scientific data into practice. This is pre-eminently a task for physicians with expertise in the relevant field and sufficient practical experience.

This report describes the clinical relevance of the new treatment in comparison with the existing treatment for non-valvular atrial fibrillation.

The clinical relevance is described in this chapter. Chapter two contains a brief substantiation and chapter three contains the references and appendices.

1.2 Clinical relevance

1.2.1 Summary

The authors conclude that treatment with NOACs is clinically significantly better than the treatment with VKAs in AF. This assessment is based on the significant improvement in the balance efficacy/safety between the two treatments and the practicability of both treatments.

Assessment of the clinical relevance is based on published phase III clinical trials in which a direct comparison was made with a vitamin K antagonist (VKA, warfarin). Three studies are available: RELY (dabigatran)[1], ROCKET-AF (rivaroxaban)[2] and ARISTOTLE (apixaban)[3].
In addition to evidence-based data (published scientific data), there are practice-based data (published data generated from experience expertise and daily practice, such as the reports IGZ [4], FNT [5], RIVM [6], HARM-study [7], EXAMINE-AF [8], and GARFIELD data [9]) are included in this finding.

For a more detailed substantiation, please refer to the guidelines of the American College of Chest Physicians (ACCP)[10], of the European Society of Cardiology (ESC)[11], of the Canadian Cardiovascular Society [12], to the opinion of the ESC Thrombosis Working Group [13], to the report of the Institute for Responsible Use of Medication (IVM) [14], and to the refereed literature (see chapter three).

1.2.2 The efficacy/safety balance

Ischemic cerebrovascular accident and systemic embolism are among the most serious complications of atrial fibrillation. Therefore, oral anticoagulants have been indicated in patients with an increased risk of these complications. During the last decades, VKAs have shown to be the most effective treatment in the prevention of ischemic CVA and systemic embolism in patients with non-valvular atrial fibrillation. VKAs prophylaxis reduces the risk of a CVA by 68%. [15]
At the same time, this treatment introduces the risk of severe hemorrhages, including intracranial hemorrhages. Intracranial hemorrhage is considered the most severe adverse reaction to anticoagulants, which is fatal in approximately 50%.[5] Therefore, the efficacy of the treatment should be balanced against the risk of intracranial hemorrhages.

Based on the available data it can be concluded that each statistically significant improvement

in the risk of this severe complication for an efficacy/safety balance of the oral anticoagulant treatment that is at least the same, is a clinically relevant improvement.

In the studies where the NOACs were directly compared with warfarin at least an equivalent or superior efficacy was observed in the prevention of CVA or systemic embolism, with a significantly and consistently reduced risk of intracranial hemorrhages. [1,2,3] Treatment with the NOACs resulted in a 21 - 35% relative reduction of the risk of a stroke or systemic embolism. Based on the Number Needed to Treat (NNT), with respect to treatment with the VKA, warfarin, 167-303 NOAC patients need to be treated to prevent 1 extra CVA or systemic embolism. The relative risk reduction with respect to cerebral hemorrhages is 29-58%. Based on the Number Needed to Harm (NNH), with respect to treatment with VKAs, 166-302 patients need to be treated with NOAC to prevent 1 extra CVA or systemic embolism without an intracranial hemorrhage occurring as an adverse reaction. Extrapolated to the Dutch situation, this means that if the 225,568 AF patients [5] who are currently being treated with VKA were to be treated with NOAC, theoretically approximately 747-1,359 intracranial hemorrhages can be prevented. Even if the achievable clinical benefit in the daily practice varied, the extent will remain substantial.

In the ACCP Guidelines [10] on antithrombotic policy for non-valvular AF published in February 2012, the use of dabigatran 150 mg 2dd is preferred to VKAs (dabigatran was, at the time the directive was being drafted, the sole NOAC approved by the FDA) for treatment of patients with ≥ 1 risk factor (CHADS2 score ≥ 1) on the basis of the results from the clinical trials. The Canadian Cardiovascular Society (CCS 2012)12 confirms the preference for NOACs.
The thrombosis working group of the European Society9 of Cardiology (ESC 2012)[13] also confirms the preference for NOACs, except in patients with intolerance of NOACs, with severe renal insufficiency or where intensive monitoring is required or when the clinical situation requires experience with the anticoagulant.

On the basis of clinical trials, NOACs show at least an equivalent efficacy/safety balance in the prevention of ischemic CVA and systemic embolism, for a significantly reduced risk of the most severe complication, intracranial hemorrhage, of anticoagulant treatment.

Based on available data and experience, it is assumed that this improvement in efficacy/safety balance will at least be maintained in the daily practice. This assumption is validated by extrapolation of the clinical data of warfarin to the VKAs phenprocoumon and acenocoumarol as used in the Netherlands and by means of extrapolation of the daily practice of similar anticoagulants to NOAC.

Validation: **substitutability of acenocoumarol, phenprocoumon and warfarin**

The trials with NOAC have been conducted with warfarin. Warfarin is the most prescribed VKA class medication in the world. In the Netherlands it is not available, however, other than in study protocols, and acenocoumarol or phenprocoumon is used. In the trials described, the treatment outcome of warfarin is measured against the INR; the INR is a standard unit for all VKAs. For a similar INR, the results of the different VKAs are comparable. The results of the trials with NOAC versus warfarin may be extrapolated to the Dutch situation where phenprocoumon and acenocoumarol are used.

Validation: **the efficacy/safety balance in daily practice**

The balance efficacy/safety of anticoagulants which is observed in the trials, is a reflection of protocolled treatment, a selected patient population (use of inclusion and exclusion criteria) and strict monitoring of intake of medication (compliance). In the recently conducted directly comparative RE-LY (dabigatran) clinical trial, the average time within the internationally accepted therapeutic range (INR 2-3) with the VKA warfarin was 64.2%[1]; in the ROCKET-AF (rivaroxaban) trial, this percentage was 55%[2] and 62.2%[3] in the Aristotle (apixaban) trial. This percentage is in line with other trials. [15]

The balance efficacy/safety in daily practice may be different from those in clinical trials. Not only can the patient population in daily practice be more complex (comorbidity, interaction with concomitant medications, old age), but factors such as interaction with food, degree of patient participation in the

treatment, quality of the integrated care (thrombosis services) and in addition, compliance may play an important role.
In the Netherlands, a thrombosis services structure has been established to check the critical efficacy/safety balance (the narrow therapeutic range and the relatively large number of interactions) of VKAs in daily practice.

In daily practice, the 2010 [5] FNT report shows lower INR percentages (63.2%) within the therapeutic range (INR 2-3.5) in AF patients who have received long-term treatment than in the clinical trials. The therapeutic INR range used is broader than the international INR range (2-3).
The achieved INR varies between the approximately 60 thrombosis services. This may be due to the measuring frequency use, the patient population, the use of acenocoumarol or phenprocoumon within the region, but also due to a difference in quality between the thrombosis services. Dutch INR percentages, measured in accordance with the international therapeutic range (2-3), of approximately 50% were reported in an analysis from 30 different centers within the Netherlands. (Statement author RACE-II trial [16]).

Research has shown that despite INR checks, the therapy compliance for VKAs is an issue of concern [17]. Direct observation techniques to establish monitoring the intake of VKA confirm that. [18]
Published Dutch studies on other indications, such as the secondary prevention of cerebral infarction, showed that compliance among patients with VKAs monitored by thrombosis services was not better after 3 years of use than compliance among patients with acetylsalicylic acid who were not being monitored [19]. Moreover, compliance with VKAs use is no guarantee for a good efficacy/safety balance, since the INR depends on many factors, such as interactions with medication and nutrition and it has a strong individual component (pharmacogenetic)[20]. In circumstances where compliance with anticoagulation therapy was guaranteed (hospital), frequent complications occurred due to the complexity of the treatment.[21]

Various reports and evaluations have shown that treatment with VKAs did not result in the desired efficacy/safety balance in a large portion of the patients (Gasse et al.[22]; the HARM study [7], the RIVM evaluation [6] and the IGZ4 report). The Dutch HARM study [7] showed that an anticoagulant played a role in nearly 25% of avoidable medication-related hospital admissions. In just under half of these cases it concerned VKAs.[7] The RIVM described the treatment of atrial fibrillation with VKA as a therapy with elevated risk.[6] The IGZ found that integrated care services by thrombosis services was not conclusive due to lack of coherence in coordination and communication.[4] In view of the risk of death due to severe hemorrhage, in 2007 the FDA included a serious warning in the package insert, a so-called blackbox warning.[23]

Practical information on NOACs in the treatment of AF are currently not fully available. However, practical information on the indications post-operative knee and hip operations of rivaroxaban are available. The safety in that practice situation turned out to be similar to that found in the clinical trials (Xamos trial [24]). For the application of the NOACs in daily practice no laboratory monitoring is needed due to the broad therapeutic range and few interactions. The question whether the absence of a monitoring mechanism has an effect on the degree of compliance and thus the efficacy/safety balance of NOACs in daily practice, can be approximated on the basis of extrapolation. For example, the similarly [11] risky anticoagulant therapies with anti-platelets, such as aspirin and clopidogrel, used on a long-term basis occurs without monitoring network, neither for treatment risks nor for monitoring compliance [25]. Dutch research on other indications, such as secondary prevention of a cerebral infarction, showed that after three years of using VKAs (with monitoring) approximately 14% and for aspirin (without monitoring) approximately 10% of the patients was not therapy-compliant.[19]

Even though the treatment with NOACs and other similar anticoagulants therapies do not require monitoring, it is desirable that with respect to such usually complex patients more illness/condition-wide care or group care (such as frail elderly people) is organized by medical assistants, similar to, for example, the integrated care with heart failures.

1.2.3 Complexity of the treatment (treatment concept)

The treatment concept for VKAs is essentially different from treatment with NOACs. The therapeutic range of VKAs is small and the number of interactions is large, making monitoring INR necessary. The NOACs have a greater therapeutic range and fewer interactions. [26, 27.28] The use of NOACs occurs in principle without monitoring, just as with all other (non-VKA) anticoagulants.

Validation: **monitoring by thrombosis services**

The anticoagulant treatment with VKAs needs to take place within a narrow INR range for an acceptable efficacy/safety balance (narrow therapeutic range). The VKA dosage is based on the INR and is determined individually for each patient. The elevated risk of interactions of VKAs with other medication and with food, in combination with individual (pharmacogenetic) sensitivity and the narrow therapeutic range of these drugs, makes it necessary to regularly determine the INR and to adjust the dosage accordingly.[29]

An INR that is too high does not only lead to risk of severe hemorrhages, an INR that is too low may lead to a risk of thrombosis (such as CVA and systemic embolism). In the Netherlands monitoring takes place via the thrombosis services. On average, a patient visits the thrombosis services 20 times annually. [5] In situations where monitoring treatment and compliance of anticoagulants was guaranteed (hospital), frequent complications occurred due to the complexity of the treatment.[21] The use of VKAs is a complex treatment that interferes with the daily living conditions of the patient due to the aforementioned factors.

Despite all efforts of the thrombosis services, the high proportion of VKAs among the number of avoidable medication-related hospital admissions (HARM-study [7], RIVM,[6]) and the poor coherence in coordination and communication in the integrated care by thrombosis services is a matter of concern (IGZ)[4]. The number of severe hemorrhages reported by the FNT [5] in 2010 was 4,781 (1.7%/year) for 271,245 patient treatment years with VKAs (heterogeneous group of a total of 398,312 patients treated with VKAs, of which 225,568 patients were given these drugs for AF indication).

The number of hemorrhagic CVAs in this total group was 773 (0.3%/year), of which 343 were fatal CVAs12 (0.1%/year). In 2009 the number of reported serious hemorrhages was still 3,298 (heterogeneous group of a total of 383,145 patients treated with VKAs, of which 208,555 patients were given these drugs for AF indication).

This creates the impression of underreporting, partly because there is no obligation to report hemorrhages and because there are major differences between the figures of the thrombosis services regions.

The absence of the many interactions with substances the patient is exposed to in daily life, makes the method of monitoring when taking NOACs unnecessary. For the NOACs a standard dose (once or twice daily) applies, which can be taking every day without adjustment or monitoring. For patients with a renal insufficiency, reduction of the daily dose is required. By analogy with anticoagulant therapy with anti-platelets, the application in daily practice seems very practicable.

Validation: **anticoagulant policy on elective surgery**

For elective (planned) surgery, the anticoagulant treatment should be stopped, to be resumed afterwards. The complexity of stopping and resuming the use of VKAs is greater than with the use of NOACs.[29] When using acenocoumarol and in particular when using phenprocoumon, the efficacy lasts longer after stopping treatment than with NOACs due to the longer half-life. Unlike the NOACs, the effective period can be reduced through administration of vitamin K. Upon resuming the treatment it takes longer for patients to reach the target value again. Depending on the risk, subcutaneously administered low-molecular weight heparins may be considered as a bridging therapy.

For NOACS it can generally be stated that the medication must be discontinued 24 hours prior to the surgery [30]. Upon resumption of the treatment, an adequate level of anticoagulation is quickly reached.

Validation: **acute situations**

In the case of hemorrhagic complications when taking VKAs or during acute surgery, the policy with respect to these agents has been crystallized over the last few years. For the VKAs, Vitamin K (effective within 12 hours) is used as antidote or for acute prothrombin complex (PPSB = four coagulation factors concentrate) reversal, based on the INR.[29]

For the new drugs no specific antidote is available (yet). Moreover, for other antithrombotics such as anti-platelets aspirin, clopidogrel, ticagrelor, prasugrel and abciximab, and the anticoagulants of the low-molecular weight heparin class no antidote is available either.
Nevertheless, these drugs were quickly registered at the time and included in the healthcare package and have rightfully found their way into daily practice due to their superior efficacy and acceptable safety.

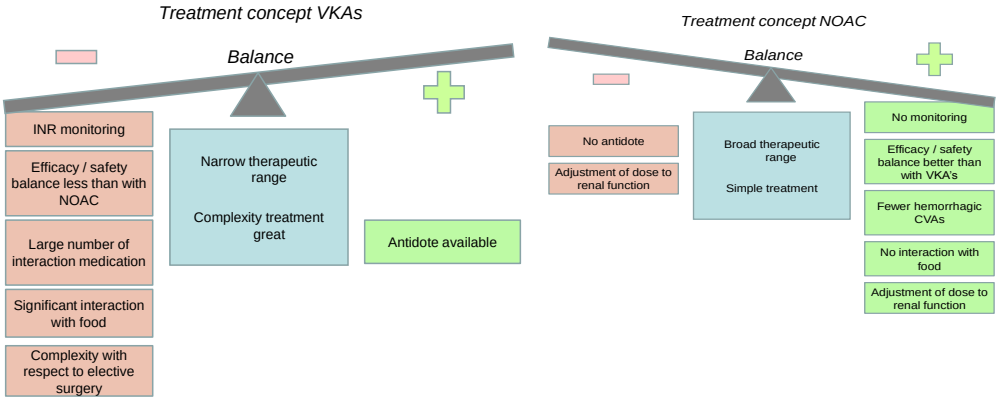
Guidelines for reversal of the anticoagulant effect of NOACs were recently published.[31,32] For acute surgery, an interval of at least 12 hours after intake of the last tablet is aimed for. For rivaroxaban it would appear that the anticoagulant effect can be reversed with a prothrombin complex.[33] For dabigatran, hemodialysis or charcoal are advised immediately after administration, in combination with a laxative or hemodialysis. [31, 32]

Based on the study results, the absence of an antidote does not mean that the number of severe hemorrhages, or even fatal hemorrhages, increases with the new anticoagulants. For patients who were treated with dabigatran 150mg 2dd, an equal number of severe hemorrhages but significantly fewer intracranial hemorrhages (-59%), life-threatening hemorrhages (-20%), non-serious hemorrhages and ' serious or non-serious' hemorrhages were measured in relation to properly adjusted warfarin dosage.[1] Treatment with dabigatran 150mg 2dd did show significantly more gastrointestinal hemorrhages, however.
Patients who were treated with dabigatran 110mg 2dd had a significantly reduced risk of both serious hemorrhages (-20%) and intracranial hemorrhages (-70%), life-threatening hemorrhages (-33%), non-serious hemorrhages and 'serious or non-serious' hemorrhages in relation to properly adjusted warfarin dosage1. Patients who were treated with rivaroxaban had a similar risk of severe hemorrhages and non-serious relevant hemorrhages. However, in the rivaroxaban study significantly fewer intracranial hemorrhages were observed, significantly fewer critical organ hemorrhages and significantly fewer people died as a result of hemorrhages in the rivaroxaban group (-49%). For treatment with rivaroxaban, significantly more gastrointestinal hemorrhages were observed.[2] Patients who were treated with apixaban 5mg 2dd had significantly fewer severe hemorrhages (-30%), both intracranial (-51%) and severe hemorrhages elsewhere in the body, significant reduction of the number of debilitating or fatal CVAs and a significant reduction in the number of deaths during the trial period.[3]

Given the above results, the absence of an antidote does not result in more severe hemorrhage complications than when using VKAs. It should be clear, however, that it is desirable for an antidote to be available or in any case to be able to enhance or normalize coagulation in case of acute hemorrhages and acute surgery.

The treatment concept with NOACs in comparison with the treatment concept of VKAs is a significant improvement of the anticoagulant treatment in NVAF.

Figure 1: Treatment concept NOACs versus treatment concept VKAs.



1.3 Summary

On the basis of evidence-based data and practice-based data it is concluded that treatment with NOACs is clinically relevant better than treatment with VKAs in non-valvular atrial fibrillation.

From a medical perspective, NOACs contribute significantly based on an, at least, equivalent efficacy/safety balance with a concurrent reduction of the most serious complication of anticoagulant treatment, the prevention of intracranial hemorrhages, and on the basis of the essentially different, more favorable treatment concept.

As is common with each pharmacological therapeutic treatment, in the case of NOACs other less significant differences in favorable and unfavorable effects and other, usually individual patient factors, such as comorbidity, need to be taken into consideration. There are also differences in unfavorable effects between the NOACs themselves. For these differences, please refer to the package inserts of the NOACs and VKAs.

It is recommended to closely monitor the introduction and the use of these agents (e.g. by means of post-marketing observation), in order to establish whether the results from the randomized trials with selected patients are also observed in daily practice.

2. Brief substantiation of clinical relevance

This chapter contains a brief substantiation of the most relevant aspects in determining the clinical relevance of NOACs in comparison with the standard treatment with VKAs in non-valvular atrial fibrillation. For a more detailed substantiation please refer to the guidelines of the American College of Chest Physicians (ACCP)[10], of the European Society of Cardiology (ESC)[11], of the Canadian Cardiovascular Society[12], to the opinion of the ESC Thrombosis Working Group[13], to the report of the Institute for Responsible Use of Medication (IVM)[14], and to the refereed literature (see chapter 3).

2.1 The condition atrial fibrillation

Atrial fibrillation (AF) is the most frequently occurring cardiac arrhythmia and affects 1-2% of the population.[11] It is estimated that there are more than 300,000 people with atrial fibrillation in the Netherlands.[6] Approximately 70% of the total number of patients with atrial fibrillation has non-valvular atrial fibrillation. The prevalence of AF increases with age and affects more than 8% of people aged 80 and older. It also occurs more frequently in men than in women. The expectation is that the prevalence will increase in the next 50 years due to aging of the population.[34]

Atrial fibrillation is a supraventricular tachycardia consisting of an uncoordinated atrial activation. This results in an impaired mechanical function of the heart. As a result, the atria lose their ability to pump and heartbeat becomes irregular. Due to the absence of a normal pump function, trombi may develop, in particular in the auricle of the heart of the left atrium. These trombi may subsequently embolise to other organs. In 70% of the cases, such thrombi end up in the brains, resulting in a TIA or a CVA. Using the CHA2DS2-Vasc score, the individual risk of a CVA can be calculated.[11] Using the HAS-BLED risk scorecard allows assessing the risk of hemorrhages in a patient.[11]

AF increases the risk of a CVA by a factor of five. In non-anticoagulated patients with AF, the risk of a CVA is on average 5% per year.[35] The risk of a CVA increases with age: the Framingham study shows in patients with atrial fibrillation an age-dependent increase in the number of CVAs of 1.5% in the age group 50-59 years to 23.5% in the age group 80-89 years.[36]

The number of people with a CVA in the Netherlands (irrespective of cause) in 2003 was 216,500: 106,900 males and 109,600 females (13.3 per 1,000 males and 13.4 per 1,000 females).[37]
The nature and severity of the consequences of a CVA depend on the part of the brain that is damaged and the extent of the damage. The consequences for the functioning of the patient determine the gravity of the condition. It is estimated that 30% of all CVAs are of cardiac origin.37 AF-related CVAs are more serious, have an elevated risk of recurrence, cause more disability than non-AF-related CVAs and have a mortality risk of 50% within 1 year.[38] A possible explanation is the size of the embolism from the left atrium.

2.2 Anti-thrombotic management of patients with non-valvular atrial fibrillation

2.2.1 Treatment criteria and guidelines

CHA2DS2-VASc score

To determine the risk of an embolism (systematic or cerebral) in patients with AF, the CHA2DS2-VASc score is used.[11] This score replaces the older CHA2DS2 score by adding three risk factors, namely the female sex, the 65-75 years age group and the presence of vascular disease.

Table 1: Explanation CHA2DS2-VASc score and CHADS2 score.11

Risc factor	CHA2DS2-VASc score Points	CHADS2-score Points
Congestive heart failure	1	1
Hypertension	1	1
Age (>75 years)	2	1
Diabetes	1	1
CVA or TIA	2	2
Vascular disease (Myocardal infarction in the anamnesis , peripheral arterial disease, aortic plaque)	1	-
Age 65-74	1	-
Sex (female)	1	-
Maximum score	**9**	**6**

European directive

An overview of the recommended anti-thrombotic therapy in AF in accordance with the European directive 201011 is shown in Table 2. At the time of drafting the Directive the NOACs had not yet been registered in Europe.

Table 2: European treatment directive atrial fibrillation (AF) (European Society of Cardiology, ESC 2010).[11]

Risk category	CHA2DS2VASc score	Recommended anti-thrombotic therapy
1 major risk factor or ≥2 clinically relevant 'non-major' risk factors	≥ 2	OAC
1 clinically relevant 'non-major' risk factor	1	OAC or ASA. Preference for OA
No risk factors	0	No treatment or ASA. Preference for no treatment

In a recent opinion of the Thrombosis Working Group of the European Society of Cardiology (ESC) a preference was expressed for NOAC, except for with patients with intolerance of NOAC, with severe renal insufficiency or where intensive monitoring is necessary or where the clinical situation requires existing experience with the anticoagulant.[13]

American guideline

An overview of the recommended anti-thrombotic therapy in AF according to the authoritative American ACCP guideline 2012 [10] is shown in table 3.

Table 3: American treatment guidelines Atrial fibrillation (AF) (ACCP, 2012).10

Risk category	Recommended anti-thrombotic therapy
CHADS2 score ≥2	OAC
CHADS2 risk score =1	If there are contraindications for OAC (other than an elevated risk of hemorrhages), a combination of aspirin and clopidogrel is recommended.
CHADS2 risk score =0	No therapy If treatment is desired, however, aspirin is preferred to a combination of aspirin and clopidogrel.

The guideline recommends the use of dabigatran 150 mg where oral anticoagulants are recommended over the use of VKAs (at the time of writing the guideline, dabigatran was the only registered NOAC in the United States).

Canadian guideline
An overview of the recommended anti-thrombotic therapy in AF according to the Canadian Cardiovascular Society (CCS) 2012 [12] is shown in table 4.

Table 4: Canadian treatment guidelines Atrial fibrillation (AF) (CCS, 2012)0.12
Risk category Recommended anti-thrombotic therapy

Has-Bled	**Score**
Hypertension	1
Abnormal renal and/or hepatic function (1 point each)	1 of 2
Stroke (CVA)	1
Hemorrhage	1
Unstable INRs	1
Elderly (age> 65 years)	1
Drugs (Use of medication or alcohol (1 point each))	1 of 2
Maximum score	**9**

CHADS2 score ≥2 OAC
CHADS2 score =1 OAC (sometimes ASA can be indicated)
CHADS2 score =0 No therapy, ASA or OAC depending on the risk of an CVA

For the majority of patients the guideline recommends the use of NOACs (dabigatran, rivaroxaban and apixaban (once apixaban is registered for AF indication)) where oral anticoagulants are recommended over the use of warfarin.

HAS-BLED score [11]
The main side effect of anticoagulants is the occurrence of intracranial hemorrhages.
The HAS-BLED risk scorecard is a method to determine the risk of hemorrhages in a patient and partly on the basis of these results, to determine the treatment.

Table 5: Explanation HAS-BLED score.[11]

Table 4. Hazard Ratios From the Cox Regression Analysis of Risk of Bleeding Using Warfarin Monotherapy as a Reference

	Hazard Ratio (95% CI)					
Variable	Aspirin Monotherapy	Clopidogrel Monotherapy	Aspirin + Clopidogrel	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Nonfatal bleeding	0.84 (0.80-0.89)	0.94 (0.76-1.16)	1.64 (1.33-2.03)	1.77 (1.66-1.90)	3.16 (2.47-4.03)	3.93 (3.05-5.05)
Fatal bleeding	1.37 (1.13-1.65)	2.22 (1.30-3.77)	1.16 (0.43-3.15)	1.96 (1.50-2.57)	2.45 (0.78-7.70)	1.11 (0.16-7.94)
Fatal or nonfatal bleeding	0.93 (0.88-0.98)	1.06 (0.87-1.29)	1.66 (1.34-2.04)	1.83 (1.72-1.96)	3.08 (2.32-3.91)	3.70 (2.89-4.76)
Intracranial bleeding	0.78 (0.68-0.89)	1.24 (0.78-1.97)	0.39 (0.12-1.21)	1.44 (1.19-1.73)	1.32 (0.49-3.53)	1.36 (1.30-1.42)
Airway bleeding	0.55 (0.50-0.61)	0.63 (0.39-1.01)	1.49 (1.02-2.19)	1.57 (1.37-1.79)	4.81 (3.42-6.75)	4.94 (3.40-7.19)
Gastrointestinal bleeding	1.28 (1.17-1.41)	1.18 (0.84-1.67)	2.60 (1.87-3.60)	2.30 (2.03-2.60)	3.46 (2.19-5.46)	5.38 (3.48-8.32)
Urinary tract bleeding	0.84 (0.76-0.94)	1.12 (0.75-1.67)	1.52 (0.99-2.34)	1.57 (1.37-1.79)	1.75 (0.94-3.27)	2.12 (1.13-3.97)

Abbreviation: CI, confidence interval.

Table 4. Hazard Ratios From the Cox Regression Analysis of Risk of Bleeding Using Warfarin Monotherapy as a Reference

An HAS-BLED score > 3 implies an elevated risk of hemorrhagic complications. This score should be taken into consideration for the choice of therapy.

Current treatment policy

According to a Dutch survey, EXAMINE-AF [8], 84% of all patients with AF have an elevated risk of a CVA and should receive anticoagulant treatment with VKAs.[8] Only 64% actually receives treatment with VKAs.[8] Reasons for this under treatment with VKAs include contraindications, old age, increased risk of hemorrhages, poor accessibility and preference of the patient. In this survey, Dutch medical professionals (cardiologists, general practitioners and internists) were asked about their prescribing behavior, in the form of a questionnaire. Another source for prescribing behavior in AF is an international survey (REALISE AF), in which cardiologists and engineers from 26 countries participated and the data of more than 10,000 patients have been recorded and assessed.[39] Of the patients who according to the treatment guidelines should be treated with a VKA, this was the case in less than 45% (for CHADS2 score 1, 42.4% received a VKA, for CHADS2 score =2 44.8% received a VKA). In the patient population with a CHADS2 score of 0, 42.3% was treated with VKAs, unjustifiably so according to the guidelines. Furthermore, the recently presented patient registration GARFIELD9 (Global Anticoagulation Registry in the FIELD) showed similar outcomes: 46.9% of the patients with a CHADS2 score of 1 was treated with a VKA. For a CHADS2 score =2, 51.7% received a VKA. Overtreatment occurred in 38.4% of the patients with a CHADS2 score of zero. The absence of a correlation between risk and treatment was first convincingly demonstrated as part of the Euro Heart Survey on Atrial Fibrillation.[40]

In 2010, the Dutch thrombosis services treated approximately 225,000 patients with VKA for the indication atrial fibrillation. The number of patients with atrial fibrillation is rising sharply. Annually, approximately 44,000 new patients with atrial fibrillation are registered with the thrombosis services.[5]

2.2.2 Oral anticoagulants

• Acetylsalicylic acid

In various studies VKAs have shown a significantly greater efficacy than anti-platelets, such as acetylsalicylic acid, even though the risk of intracranial hemorrhages with VKAs is greater.[11] Acetylsalicylic acid can be described for patients with a low risk of ischemic stroke according to the CHA2DS2-Vasc score.[11] A Danish study describes the number of hemorrhages as complication in treatment with warfarin, aspirin or clopidogrel, or a combination of these agents for a large number of patients with AF.[41] Patients who were treated with aspirin monotherapy were generally older and more frequently female. Clopidogrel therapy was mainly initiated if patients were known to have a myocardial infarction or an ischemic cardiac disease. Warfarin and aspirin monotherapy and dual therapy were initiated in particularly for long-term treatments.

The risk (Hazard Ratios on the basis of Cox regression analysis) of a hemorrhage for the different treatment options is shown in the table below. Monotherapy with warfarin is used as a reference here.

Table: Risk of hemorrhage as complication with oral anticoagulants.[41]

Table 4. Hazard Ratios From the Cox Regression Analysis of Risk of Bleeding Using Warfarin Monotherapy as a Reference

	Hazard Ratio (95% CI)					
Variable	Aspirin Monotherapy	Clopidogrel Monotherapy	Aspirin + Clopidogrel	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Nonfatal bleeding	0.84 (0.80-0.89)	0.94 (0.76-1.16)	1.64 (1.33-2.03)	1.77 (1.66-1.90)	3.16 (2.47-4.03)	3.93 (3.05-5.05)
Fatal bleeding	1.37 (1.13-1.65)	2.22 (1.30-3.77)	1.16 (0.43-3.15)	1.96 (1.50-2.57)	2.45 (0.78-7.70)	1.11 (0.16-7.94)
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Intracranial bleeding	0.78 (0.68-0.89)	1.24 (0.78-1.97)	0.39 (0.12-1.21)	1.44 (1.19-1.73)	1.32 (0.49-3.53)	1.36 (1.30-1.42)
Airway bleeding	0.55 (0.50-0.61)	0.63 (0.39-1.01)	1.49 (1.02-2.19)	1.57 (1.37-1.79)	4.81 (3.42-6.75)	4.94 (3.40-7.19)
Gastrointestinal bleeding	1.28 (1.17-1.41)	1.18 (0.84-1.67)	2.60 (1.87-3.60)	2.30 (2.03-2.60)	3.46 (2.19-5.46)	5.38 (3.48-8.32)
Urinary tract bleeding	0.84 (0.76-0.94)	1.12 (0.75-1.67)	1.52 (0.99-2.34)	1.57 (1.37-1.79)	1.75 (0.94-3.27)	2.12 (1.13-3.97)

Abbreviation: CI, confidence interval.

Table 4. Hazard Ratios From the Cox Regression Analysis of Risk of Bleeding Using Warfarin Monotherapy as a Reference

For the above analysis warfarin monotherapy is the reference value. The use of aspirin monotherapy or the combination with clopidogrel scores relatively high on fatal hemorrhages, but as expected relatively low on intracranial hemorrhages for the above described patient population.

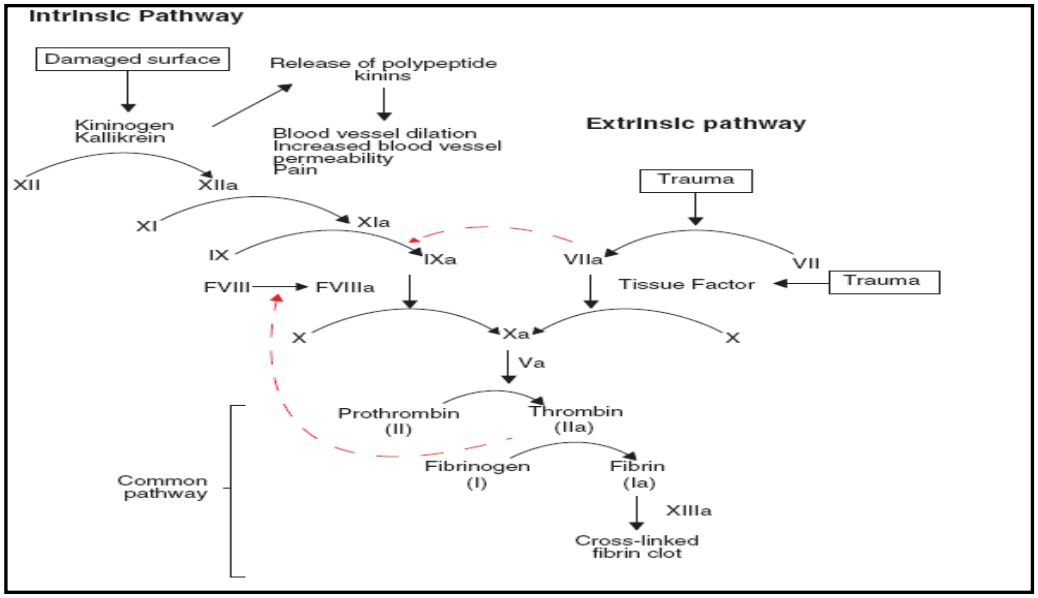
• Vitamin K antagonists (VKAs)

The prevention of embolisms with VKAs in patients with AF has proven to be an effective treatment in past years; it reduces the risk of a CVA by 68%. According to the FNT [5], the incidence of a severe hemorrhage when using VKAs is about 1.7% per year; the incidence of intracranial hemorrhages is about 0.3% / year. In the international literature, a higher incidence (approximately 0.7% / year) is found. The risk of hemorrhage is higher in elderly people and in patients with a malignity.[42]

Mechanism of action VKAs

The mechanism of action is based on competitive inhibition of the synthesis of vitamin K in the liver and as such the synthesis of the vitamin K-dependent coagulation factors. These are prothrombin (factor II), factor VII, IX and X (see Figure 2). In addition, protein-S and protein-C are inhibited. As a result, VKAs inhibit both the intrinsic and the extrinsic pathway.

Figure 2: Mechanism of action VKAs.



The various VKAs do not differ in mechanism of action and are all dosed based on the same INR (therapeutic range). The most important difference between the various VKAs is their half-life.

Table 6: VKAs.

Middle	Half-life	Wash out
Phenprocoumon[42]	140 hours (5-7 days)	7-14 days
Acenocoumarol[43]	8-11 hours	2 days
Warfarine	40 hours (40-50 hours)	3-5 days

Worldwide 80% uses the VKA warfarin. In the Netherlands warfarin is not available and acenocoumarol and phenprocoumon are used. There is no medical reason for the absence of warfarin in the Netherlands. Phenprocoumon yields a more stable delivery of acenocoumarol. Still, in the Netherlands cenocoumarol is prescribed in 80% of the cases, thus actually opting for an agent with more fluctuations and thus more risk. Because VKAs are dosed on the basis of the INR, the difference with warfarin in clinical trials is not relevant. The choice between acenocoumarol and phenprocoumon differs per region and is often based on local preference and experience.[5]

The INR

The INR (International Normalized Ratio) is a standard unit used to report the results of a coagulation test, the so-called prothrombin test (PT). The INR is a measure of the ratio of the PT of a patient with respect to the standard PT, related to the standard thromboplastin preparation. The target level is dependent on the indication.

In a person with normal coagulation who does not take any anticoagulants, the INR is approximately 1. The higher the INR, the longer it takes for the blood to coagulate, thus an elevated risk of hemorrhage. A low INR increases the risk of thrombus formation.

INR target values

All guidelines recommend an INR between 2 and 3 for the treatment with VKAs in patients with atrial fibrillation (AF). Generally, it is considered adequate treatment if more than 70% of the monitoring provisions fall within this range (TTR).

The Dutch thrombosis services do not operate according to the internationally applicable targets, but have adjusted their target values as follows [5]:

● Two levels of anticoagulation intensity are recommended, a 1st and a 2nd intensity group. Both groups have an optimal target value and an area to either side of this value, also referred to as target area.
● For the above levels, the lower limit of the target area, based on methodical considerations, has been set at 0.5 INR higher than the clinically acceptable lower limit of the therapeutic range (CBO consensus)[45]. The upper limit of both the target area and the therapeutic range has been set at 0.5 INR higher.
● Atrial fibrillation falls into the first intensity group. For this group of patients, the Dutch thrombosis services use the following criteria:
-Optimum target value: 3.0
-Therapeutic range: 2.0-3.5
-Target area: 2.5-3.5

It is expected that the TTRs in the Netherlands are higher due to the greater therapeutic range used (2-3.5 rather than 2-3). Because of this, Dutch TTRs cannot be directly compared with TTRs from international trials. Another important reason why TTRs are not comparable is the method of the FNT, as part of which the first six months of the use of VKAs is not included in the evaluation This creates a more positive picture because right at the start and during the first three months the greatest INR fluctuations and thus risks of hemorrhage or thrombosis are observed.

Dosage of VKAs

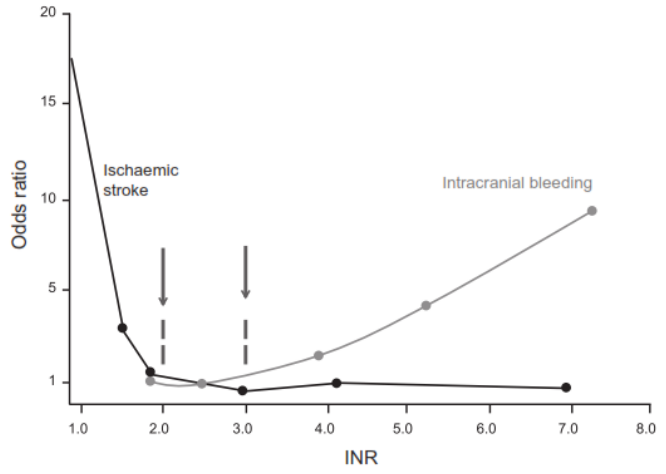
Treatment with VKAs is characterized by a narrow therapeutic range, a broad spectrum of interactions with food and medication and in addition, the greater inter-individual and intra-individual differences in the dosage required to achieve the desired level of coagulation.

Interactions

● Food: the intake of food with high or low concentrations of vitamin K has a direct impact on the INR. Examples of Vitamin K rich food include: spinach, cauliflower, kale, Brussels sprouts, broccoli, cabbage, lettuce, sauerkraut, liver. A standard Dutch diet contains a higher level of vitamin K in winter and lower levels in summer.
● Concomitant medications: antibiotics such as macrolides, doxycycline, co-trimoxazole, azole antimycotics, metronidazole, propranolol and substances such as glucagon, acetylsalicylic acid, heparins, cardiac agents, thyroid hormones, steroid hormones, barbiturates, St. John's Wort, thiazide diuretics, NSAIDs and SSRIs.[46] Commonly used analgesics: acetaminophen and tramadol cause disruption of INR in some patients , for NSAIDs, naproxen gives the highest risk. [47,48] Many of these substances are frequently prescribed for heart patients and/or elderly people. A number of these agents is also available without prescription.

The relationship between therapeutic range, INR and clinical incidents for treatment with VKAs is shown in the figure below.[49] Furthermore, it is of importance when using short-acting acenocoumarol, that the patient takes the medication each day around the same time in order to prevent variation outside the INR range as much as possible.

Figure 3: Relationship between therapeutic range, INR and clinical incidents with VKAs.[49]



INR values below or above the therapeutic range can be considered as potentially hazardous in the delicate balance between coagulation and anti-coagulation. Setting and keeping the INR values within the target area during treatment with VKAs requires continuous alertness, anticipation and coordination by the caregivers involved. Due to the large number of related failure probabilities, it can be concluded that it concerns a high-risk therapy. [6]

Organization around the use of VKAs in the Netherlands

Monitoring during the use of VKAs in the Netherlands is carried out by the thrombosis services. There are currently approximately 60 thrombosis services in the Netherlands Patients can qualify for measuring at home if they are going to use VKAs for more than six months.
In 2010, 398,312 patients were treated with VKAs and supervised by the thrombosis services. Approximately 57% of these patients had the indication AF. Of the total number of patients, approximately 80% was treated with acenocoumarol and the remaining 20% with phenprocoumon.[5] On average, one check is performed every 18 days (on average 20 checks per year: spread 14.4 to 27 days).[5] The visiting frequency to the thrombosis services is higher at the beginning of the treatment and may reduce once the patient is controlled.

Clinical trials

Clinical trials have shown that for a strictly protocolled treatment on average 55-64% of the trial population remains within the INR target values of 2-3. [1,2,3] In a clinical trial from the Netherlands, an average TTR of 68% was achieved in patients who were treated with acenocoumarol and phenprocoumon.[50]

Daily practice

Outside the trial setting, usually lower percentages are observed.11 In daily practice the 2010 FNT report 5 shows lower INR percentages (63.2%) within the therapeutic range (INR 2-3.5) in AF patients who have received long-term treatment than in the clinical trials. Dutch INR percentages, measured in accordance with the international therapeutic range (2-3), of approximately 50% were reported in a more detailed analysis from 30 different centers within the Netherlands that participated in the RACE-II trial.[16]

The Dutch HARM study has shown that an anticoagulant plays a role in nearly 25% of the avoidable medication-related hospital admissions.[7] In just under half of these cases it concerns the use of VKAs.[6,7] The picture in other countries is similar: in 20-25% of the avoidable medication-related hospital admissions, anticoagulants were involved, in particular VKAs.[34]

The above data were reason for the RIVM [6] and the Health Inspectorate [7] to conduct further studies into this. This study describes, among other things, the coordination from within the thrombosis services with other healthcare providers and has identified the following bottlenecks:[7]

● The absence of formal agreements between healthcare providers or non-compliance with agreements.
● Different medical protocols are applied or protocols are not observed.
● Practical problems with information transfer, resulting in information not arriving or arriving too late at the relevant healthcare providers.

The study also describes the fact that the medication itself forms an important risk for the patient. A large number of biological factors and the lifestyle of the patient have a potential effect on the tendency of the blood to coagulate. The RIVM describes the current treatment of atrial fibrillation with VKA as a high-risk therapy.[6]

In addition to measuring the number of avoidable hospital admissions during use of VKAs, the number of severe hemorrhages was also assessed and published by the FNT.[5] The number of severe hemorrhages recorded by the FNT in 2010 was 4,781 (1.7%/year) out of 271,245 patient treatment years with VKAs (heterogeneous group of a total of 398,312 patients treated with VKAs, of which 225,568 patients were given these drugs for AF indication). The number of hemorrhagic CVAs in this total group was 773 (0.3%/year), of which 343 were fatal CVAs12 (0.1%/year). This is lower than what is published in the international literature (0.7%/year). The reason for this difference is not clear. In 2009 the number of reported severe hemorrhages was 3,298 (heterogeneous group of a total of

383,145 patients treated with VKAs, 208,555 of whom were given these drugs for AF indication). Considering the big increase in the number of registered hemorrhages in 2010 in comparison with 2009, there may still be a few cases that have not yet been recorded. Furthermore, there is a large regional spread.[5]
Atrial fibrillation may, despite adequate anticoagulation with VKAs, also lead to the occurrence of thromboembolic complications. It can be assumed that underreporting of this occurs (after all, it forms part of the disease).

• New oral anticoagulants: NOACs

The last few years the results of the extensive phase III clinical studies of three new oral anticoagulants (NOACs) have been published.[1,2,3]

The primary endpoint for the efficacy of these agents is the prevention of CVA and systemic embolism in non-valvular atrial fibrillation. Since efficacy and safety are closely related with these agents, a primary endpoint for safety has also been determined: the prevention of serious hemorrhages and in particular intracranial hemorrhages.

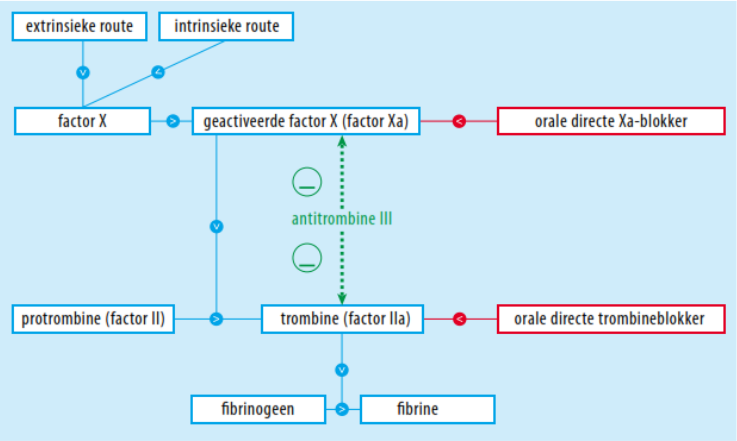
NOACs are already widely used for post-operative prophylactics in knee and hip surgery. Rivaroxaban is also approved for the treatment of deep vein thrombosis (DVT) and the prevention of recurring DVT and pulmonary embolism (PE) following acute DVT in adults. The indication Acute Coronary Syndrome (ACS) is under development.

Mechanism of action

Apixaban and rivaroxaban are direct Factor Xa inhibitors, dabigatran is a direct thrombin Factor IIa (FIIa) inhibitor. They ultimately inhibit the conversion of fibrinogen into fibrin.

There are no known food interactions with the above agents.[26,27,28]

Figure 4: NOAC mechanism of action.[51]



FIGUUR Vereenvoudigde weergave van de activatie van de stollingscascade via de intrinsieke en de extrinsieke route, die beide leiden tot de activatie van factor X: het begin van de laatste gemeenschappelijke route ('final common pathway') van de stolling. Het endogene antitrombine III oefent een remmende werking uit. Het aangrijpingspunt van nieuwe antithrombotica is aangegeven.

Dabigatran (Pradaxa®)[1,15 26]

Dabigatran etexilate is an oral prodrug which, after absorption, is converted into the active dabigatran. The absorption rate is a mere 6%. Dabigatran is a competitive, reversible and direct inhibitor of thrombin and prevents the formation of fibrin from fibrinogen and thus the development of thrombus.

Excretion occurs entirely via the kidneys; 80% of dabigatran is excreted unchanged via the urine. A reduced renal function thus increases the concentration of dabigatran.

Dabigatran is contraindicated in people with an impaired renal function (creatinine clearance < 30ml/min; severe renal failure), when using ketoconazole, cyclosporine, itraconazole or tacrolimus.

Rivaroxaban (Xarelto®)[2,27]

Rivaroxaban is an oral selective direct factor Xa inhibitor. This prevents rivaroxaban thrombin formation and thus the development of thrombus.

Two thirds of Rivaroxaban is converted in the liver; excretion occurs for 65% via the kidneys. For a creatinine clearance <30ml/min (severe renal impairment), a custom dosage of 15mg/day (AA) applies. For a creatinine clearance <15ml/min (renal failure), the use of rivaroxaban is not recommended.

Rivaroxaban is contraindicated for concomitant treatment with antimycotics (e.g. ketoconazole, itraconazole).
This does not apply to fluconazole. The concomitant use of HIV protease inhibitors (for example, ritonavir) may result in elevated concentrations of rivaroxaban.

Apixaban (Eliquis®)[3,28]

Apixaban is an oral, reversible, direct and selective inhibitor of coagulation factor Xa. This prevents apixaban thrombin formation and thus the development of thrombus.

Excretion occurs for 25% via the kidneys. Apixaban is not recommended for a creatinine clearance <15ml/min (renal failure) in connection with lack of experience in this group. Prudence is called for with a creatinine clearance <30ml/min (severe renal impairment).

Conversion takes place in the liver; therefore, the medication is contraindicated in severe liver disorders.

Apixaban is also contraindicated for treatment with antimycotics (e.g. ketoconazole, itraconazole). This does not apply to fluconazole. The concomitant use of HIV protease inhibitors (for example, ritonavir) may result in elevated concentrations of apixaban.

Clinical results with NOACs.

Table 7 shows the clinical trials with NOACs in comparison with warfarin.

Table 7: Clinical trials with NOACs in comparison with warfarin.

	Number of patients	Trials set-up	CHADS2 score (average)	% of patients with VKA for inclusion
Dabigatran				
RE-LY[1] Conolly 2009	18.113	2dd 110mg or 150 mg compared with warfarin	2.1	50%

Rivaroxaban				
ROCKET-AF[2] Patel 2011	14.264	1dd 20mg (1dd 15mg in patients with creatinine clearing 30-49 ml/min) compared with warfarin	3.48 (rivaroxaban) and 3.46	62%
Apixaban				
ARISTOTLE[3] Granger 2011	18.201	2dd 5mg compared with warfarin	2.1	57%

In the various trials where the new drug was compared with warfarin, the primary endpoints in the area of efficacy and safety were matching.

Primary endpoint for efficacy[1,2,3]
CVA: defined as a sudden, focal neurological defect with an assumed cerebral vascular cause, not reversible within 24 hours and categorised as ischemic, haemorrhagic or 'unspecified'.
Patients who died within 30 days after the CVA were considered patients with a fatal CVA.

Non-CNS systematic embolism is defined as an abrupt vascular insufficiency associated with clinical or radiological evidence for arterial occlusion in the absence of other probable mechanisms, documented by means of imaging, surgery or autopsy. In patients with atherosclerotic peripheral arterial disease, the diagnosis embolism in the lower extremities needed to be confirmed by means of an angiography.

Primary end point for safety[1,2,3]
The composite primary endpoints for safety consisted of severe hemorrhages and non-severe clinically relevant hemorrhages.
- Severe hemorrhage was defined as:
● a clinically apparent hemorrhage associated with one of the following causes: fatal, in a critical area and (intracranial), intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal)
● or a clinically apparent hemorrhage associated with an Hb reduction of = 2 g/dl or with a blood transfusion of 2 units of erythrocyte concentrates or whole blood

- Clinically relevant, non-severe hemorrhage was defined as an apparent hemorrhage that does not meet the criteria for severe hemorrhage, but is cause for medical intervention, non-planned contact with the physician, postponed or discontinued intake of trial medication, pain interfering with daily activities.

An important secondary endpoint for the safety is the prevention of intracranial hemorrhages.
This endpoint was measured for all NOACs. The remaining secondary endpoints varied per study, but have been included in the summary of the study results below.

Table 8: Setup RE-LY, ROCKET AF, and ARISTOTLE.[1,2,3]

	RE-LY[1] (dabigatran)	**ROCKET AF**[2] (rivaroxaban)	**ARISTOTLE**[3] (apixaban)
Patients	18.113	14.264	18.201
Study arms	3	2	2
Trial medication	Double-blind dabigatran 110 mg 2dd 150 mg 2dd	Double-blind rivaroxaban 20 mg 1dd (15mg 1dd in CrCL 30-49 ml/min)	Double-blind apixaban 2dd 5mg

Treatment control	Open-label warfarine (INR 2–3)	Double-blind warfarine (INR 2–3)	Double-blind warfarine (INR 2–3)
Inclusion criteria			
Atrial fibrillation	Non-valvulair	Non-valvulair	Non-valvulair
Risk factors	History of a CVA/TIA or systemic embolism and ≥ 1 of the following risk factors: -Ejection fraction < 40%, -Symptomatic heart failure NYHA class II of higher ≥ 75 years OR 65-74 years and 1 of the following: -DM -coronary arterial disease -Hypertension	History of a CVA/TIA or systemic embolism OR ≥ 2 of the following risk factors: -Heart failure or left ventricle Ejection fraction ≤ 35% -Hypertension - Age ≥ 75 years; - DM	≥ 1 of the following risk factors: -History of a CVA/TIA or systemic embolism -Ejection fraction < 40%, -Symptomatic heart failure - DM type II - Treated - hypertension - ≥ 75 years
Primary outcome measure efficacy	CVA and non-CNS systematic embolism	CVA and non-CNS systematic embolism	CVA and non-CNS systematic embolism
Primary outcome measure safety	Severe hemorrhage	Composition of severe hemorrhages and non-severe clinically relevant hemorrhages	Severe hemorrhage
Treatment after discontinuation of the trial medication			
	Transferring (all patients) to open-label VKA, ASA or no treatment	Transferring (all patients) to open-label VKA, ASA or no treatment	Transferring (all patients) to open-label VKA, ASA or no treatment

Results

Primary endpoints for efficacy:

With respect to the primary endpoint for the efficacy, dabigatran, rivaroxaban and apixaban show at least equal or superior efficacy (occurrence of CBA or a systemic embolism) in comparison with warfarin.[1,2,3]

Primary and secondary endpoints for safety:
With respect to the primary endpoint for the safety, dabigatran, rivaroxaban and apixaban show at least equal or superior safety (occurrence of severe hemorrhages and non-severe relevant hemorrhages) in comparison with warfarin.[1,2,3]

In the dabigatran 150mg 2dd an equal number of severe hemorrhages, but significantly fewer intracranial hemorrhages (-59%), life-threatening hemorrhages (-20%), non-severe hemorrhages and 'severe or non-severe' hemorrhages were measured in comparison with well-controlled warfarin.[1] However, significantly more gastrointestinal hemorrhages were observed in treatment with dabigatran 150mg 2dd.
Patients who were treated with dabigatran 110mg 2dd had a significantly lower risk of both severe hemorrhages (-20%), and intracranial (-70%), life-threatening hemorrhages (-33%), non-severe hemorrhages and 'severe or non-severe' hemorrhages in comparison with well-controlled warfarin.[1] Patients who were treated with rivaroxaban had a similar risk of severe hemorrhages and non-severe relevant hemorrhages. However, in the rivaroxaban study significantly fewer intracranial hemorrhages were observed, significantly fewer critical organ hemorrhages and significantly fewer people died as a result of hemorrhages in the rivaroxaban group (-49%). Treatment with rivaroxaban showed significantly more gastrointestinal haemorrhages.2 Patients who were treated with apixaban 5mg 2dd had significantly fewer severe hemorrhages (-30%), both intracranial (-51%), and severe hemorrhages elsewhere in the body, a significant reduction of the number of debilitating or fatal CVAs, and a significant reduction of the number of deaths during the trial period.[3]

The results from the clinical trials are summarized in the review by Bassand et al.[52] and confirmed in the recently published meta-analysis by Miller et al.[53]

Subgroup analyses
In a review of the RE-LY data, Wallentin plotted the average treatment results in a treatment centre against the average of the time in the therapeutic range (INR 2.0-3.0) (subdivision in TTR quartiles with the highest quartile >78%).[15] In the RE-LY study the average TTR was 64.2%, whereas for Dutch patients this was 70.2%.[15] This value corresponds with a clinical trial in which the effect of acenocoumarol and phenprocoumon was studied.[50] Wallentin et al. described the results for a subgroup of patients of the RE-LY study who during treatment with warfarin had an average TTR of 70.3%. The incidence of CVA/systemic embolism was not statistically significantly decreased in patients who were given dabigatran 150 mg twice daily when compared with patients with a mean TTR of 70% during treatment with warfarin (1.04% versus 1.51%; HR 0.69 (0.44-1.09)). The risk of a CVA/systemic embolism was not affected by the TTR (interaction p=0.20). The effect of dabigatran on the net clinical benefit is comparable with that of warfarin (7.41% versus 7.13%; HR 1.05 (0.87-1.27)). For all outcome measures dabigatran 110 mg was non-inferior to warfarin. The incidence of intracranial hemorrhages remained statistically significantly reduced with dabigatran compared to warfarin.

It appears that the significantly elevated risk of an intracranial hemorrhage during treatment with VKAs can be explained by the blockade of Factor VIIa complexes in the brains when using VKAs. The formation of the TF/VIIa complex reduces the tendency to coagulate in the brains, causing intracranial hemorrhages to occur earlier.[54] With the new oral anticoagulants, factor VII is not blocked.

With respect to the NOACs, attention is focused on three aspects in which NOACs appear to mutually distinguish themselves and therefore partially distinguish themselves from the VKAs.

Gastrointestinal hemorrhages:
- dabigatran 150mg 2dd: significant increase in the number of gastrointestinal hemorrhages
- rivaroxaban: significant increase in the number of gastrointestinal hemorrhages
- apixaban: non-significant decrease in the number of gastrointestinal hemorrhages

Myocardial infarctions

● dabigatran: significant increase in the number of myocardial infarctions55
● rivaroxaban: non-significant decrease in the number of myocardial infarctions
● apixaban: non-significant decrease in the number of myocardial infarctions (MI)

As is common with each pharmacotherapeutic treatment, in the case of NOACs other less significant differences in favorable and unfavorable effects and other, usually individual patient factors, such as comorbidity, need to be taken into consideration when choosing an NOAC or VKA.

2.3 Anticoagulant policy on elective surgery

For elective surgery, the anticoagulant treatment should be stopped, to be resumed afterwards. If necessary, low-molecular weight heparin may be used as a bridging therapy.

The complexity of stopping and resuming is greater when using VKAs than when using NOACs. The half-time of VKA is longer. Reducing and resuming VKAs takes longer and, therefore, involves more risk for the patient.

Table 9: Policy for treatment with VKAs regarding elective surgery.[29]

	A slightly elevated risk of thrombosis	Moderate/highly elevated risk of thrombosis
Acenocoumarol before surgery	Stop acenocoumarol 3 days prior to the surgery,	Bridging therapy is indicated: Day -3 / -5 Stop VKA Day -2 Check INR, correction if necessary Day -2 Start LMWH (therapeutic dose) Day –1 0 Stop LMWH 24 hours prior to surgery Day of surgery, check INR, target value <1.5
Acenocoumarol after surgery	resume 24 hours after surgery No bridging therapy	Day +1 Resume LMWH and VKA 24 h after surgery Day X Stop LMWH if INR is at desired level for two consecutive days
Phenprocoumon before surgery	Stop phenprocoumon 5 days before surgery No bridging therapy	Bridging therapy is indicated: Day -3 / -5 Stop VKA Day -2 check INR, correction if necessary Day -2 Start LMWH (therapeutic dose) Day –1 0 Stop LMWH 24 hours prior to surgery Day of surgery, check INR, target value <1.5
Phenprocoumon after surgery	Resume after 24 hours No bridging therapy required	Day +1 Resume LMWH and VKA 24 h after surgery Day X Stop LMWH if INR is at desired level for two consecutive days

For NOACs it can generally be stated that the medication must be discontinued 24 hours prior to surgery. Resumption of NOACs may occur after achieving proper postoperative hemostasis. The policy regarding elective surgery for dabigatran has been described by Huisman.[30]

Table 10: Policy for treatment with dabigatran in elective surgery.[30]

Renal function (creatinine clearing) ml/min	**Half-time (hours)**	**Discontinuation policy**	
		Standard hemorrhage	Risk Elevated risk of hemorrhages
≥80	13	24 hours prior to surgery	2 days prior to surgery
≥ 50 to <80	15	1-2 days prior to surgery	2-3 days prior to surgery
≥30 to <50	18	> 48 hours prior to surgery	4 days prior to surgery

2.4 Policy during hemorrhagic complications or acute surgery

Management of acute hemorrhages in use of VKAs

In the case of hemorrhagic complications when taking VKAs or during acute surgery, the policy with respect to these agents has been crystallized over the last few years. The anticoagulant effect can usually be directly reversed with four-factor concentrate. Reversing with the antidote vitamin K takes longer.

Table 11: Policy during hemorrhagic complications or acute surgery.[29]

Acute surgery or severe hemorrhage complication	Action to stop the hemorrhage	Resumption phenprocoumon or acenocoumarol
In case of hemorrhages	Stop Vit K antagonist -Four-factor concentrate -10 mg vitamin K per os, If necessary, repeat for 2 to 4 days; With acenocoumarol use repeated administration for two days (on the basis of the INR) after 12, 24 and 48 hours, with phenprocoumon use repeated administration for 3 to 4 days (on the basis of the INR) after 12, 24, 48, 72 and 96 hours	Day +1 Resume LMWH and VKA 24 h after surgery Day X Stop LMWH if INR is at desired level for two consecutive days

Management of acute hemorrhages with NOAC

The policy for the new drugs in case of hemorrhagic complications or acute surgery has not yet been crystallized. For the new drugs no specific antidote is available (yet). Moreover, for other antithrombotics such as anti-platelets aspirin, clopidogrel, ticagrelor, prasugrel and abciximab, and the anticoagulants of the low-molecular weight heparin class no antidote is available either. Nevertheless, these drugs were quickly registered at the time and included in the healthcare package

and have rightfully found their way into daily practice due to their superior efficacy and acceptable safety.

Incidentally, there is no antidote for aspirin either. Currently, research is conducted into a specific antidote for these new drugs. In the study of Eerenberg[33], it was examined in a trial with healthy volunteers whether the anticoagulant effect of dabigatran and rivaroxaban could be reversed with a prothrombin complex concentrate (PCC). Both the extended prothrombin time (PT) and the endogenous thrombin potential (ETP) following a rivaroxaban dose were immediately normalised after infusion of the PCC. This effect persisted for 24 hours. After a dose of dabigatran the extension of the APTT and ECT and ETP was measured, but no normalisation of these values was observed following administration of PCC (prothrombin complex concentrate). For dabigatran a shortened hemorrhage time was observed following administration of PCC.

Guidelines for reversing the anticoagulant effect of NOACs were recently published.[31,32]
For acute surgery the aim is an interval of at least 12 hours after the intake of the last tablet. For rivaroxaban, it appears possible to reverse the effect with a prothrombin complex.[33] For dabigatran, hemodialysis or charcoal immediately after administration are recommended, combined with a laxative or hemodialysis.[31, 32]

Consequences of the absence of an antidote
Based on the study outcomes, the absence of an antidote does not mean that the number of severe hemorrhages or even fatal hemorrhages with the new anticoagulants increases. However, it is desirable to have an antidote available. For the studies the most important advice concerning the management of hemorrhages, was to adhere to the protocols with respect to hemorrhages of the relevant center.

Determining the coagulation status
Measuring the INR for NOACs does not create any added value. Measuring the aPTT for dabigatran or the PT (prothrombin time) for rivaroxaban are good methods to objectify the degree of anticoagulation.[30,31] Considering the fact that apixaban has the same point of action as rivaroxaban, the PT can also be used to determine the degree of anticoagulants for apixaban. Meanwhile, specific anti-Xa stipulations are being developed.[56] When using dabigatran 150mg 2dd, the PTT will be twice the baseline. An aPTT > 80 seconds (or 2-3 times the baseline) is suspicious for an elevated risk of haemorrhage.[30] The Hemoclot ® is developed to measure the degree of anticoagulation when using dabigatran; a test result of 200n/ml (or higher) indicates an elevated risk of haemorrhage.[57] The TT is more sensitive and significantly higher when using normal doses of dabigatran.

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