

***The patient perspective on the treatment
with oral anticoagulants in
atrial fibrillation***



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J.R.B.J. Brouwers, J.M.L. Hendriks, H. van Laarhoven, C.M. van der Ree, E. Visser, M.H. G.A. van Woerkom

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Europe-Expro identifies issues where identifying relevant differences between an existing treatment and a new treatment requires specific input and expertise from the experts. To this end Europe-expert Expro facilitates procedures. An expert procedure comprises a specific medical or pharmaceutical issue, assessed by a group of experts in the field. The expert group strives to bring forth a validated position on the relevant improvements (relevance) of a new treatment (medical and/or pharmaceutical) by comparing it to an existing treatment. This position may be a clinical perspective, a health economics perspective or a patient perspective. Thus we speak of clinical relevance, economic relevance or patient relevance and validation procedure.

The position of the expert group is captured in a report for external use.

This report investigates whether meaningful differences exist between the new anticoagulants and standard therapy with vitamin K antagonists (VKAs/coumarins) in the indication atrial fibrillation, seen from the patient perspective.

For more information about this expert procedure you may contact Christiaan Caanen in the Netherlands (ph. +31 (0)6 5437 2520).

Expert Procedures on Clinical, Economic, and Patient Relevance
Europe-Expro, division of MH PRONK Health Care Consultancy GmbH
Zeppelinstrasse 73
D-81669 Munich, Germany
Ph.: +49 1717577031
E-mail: info@europe-expro.eu



Expert Procedures on Clinical, Economic, and Patient Relevance



Expert group

Core members of the expert group:

J (Koos).R.B.J. Brouwers, em. Professor, Clinical Pharmacologist, UMC Utrecht Geriatrics Epor Ele Visser, Director Patient Academy, The Hague

Expert members:

Mr Jeroen M.L. Hendriks, PhD student/Health scientist/Nursing specialist, cardiology and CAPHRI Maastricht University Medical Centre

Hans van Laarhoven, Policy Advisor, The Heart and Vascular Group, The Hague

Cor M. van der Ree, General Practitioner, Dronten

Mr Menno H.G.A. van Woerkom, Advisor, Institute for Responsible Medicine Use (IVM), Utrecht

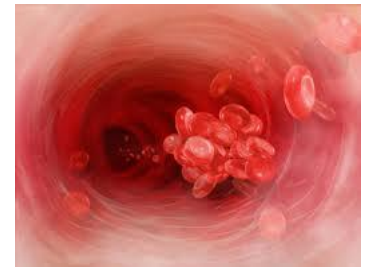
Advisors:

Ms H.I. (Hilda) Paans-Wubbolts, Policy Advisor, Health Insurers in the Netherlands (ZN), Zeist

Mr A.M. (Marco) W. Alings, Cardiologist, Amphia Hospital, Breda

Summary

The caregiver's and the patient's knowledge do not count enough when it has to be decided whether a new treatment should be included in the basic health insurance package.



Essential aspects for the success of a treatment such as ease of use, greater applicability, self-management and well-being are acknowledged, but are not taken into account. Nor do patients' and caregivers' practical experiences play a role in the assessment process.

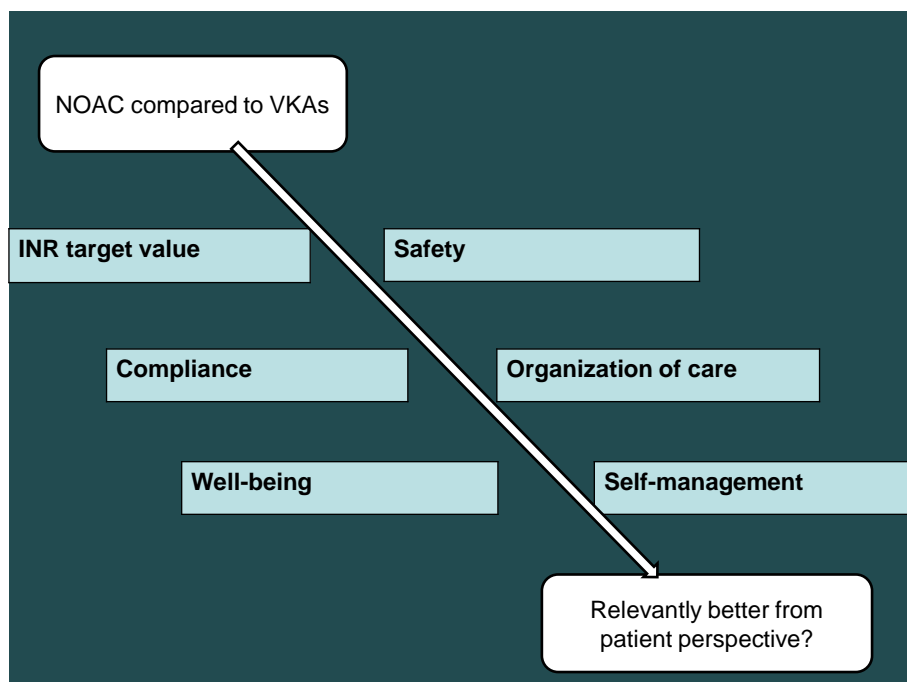
Internationally the patient perspective as an item for political policy and decision making is considered relevant (Hansen et al. 2011). Patient participation is increasingly viewed as a significant link in both the decision on placement (directive) and in the direct use of a medicinal product in patient care (De Rijk et al. 2011, Schipper et al. 2012).

Patient perspective is, however, too much of an amorphous concept and for the various patient aspects generally there are no qualitative or quantitative measures and no standard by which the relevance of the patient aspect can be determined. The selection of patient relevant aspects of a treatment and the establishment of measures and standards for relevance is based on using data from scientific literature and practical experience gained by caregivers and patients to validate these patient aspects on relevance.

Thus experts on patient aspects are able to objectively formulate the patient perspective in terms of qualitative and/or quantitative criteria. If these criteria relevantly improve with the use of a new treatment, then these improvements should be considered in the assessment for inclusion of treatment in the basic health insurance package.

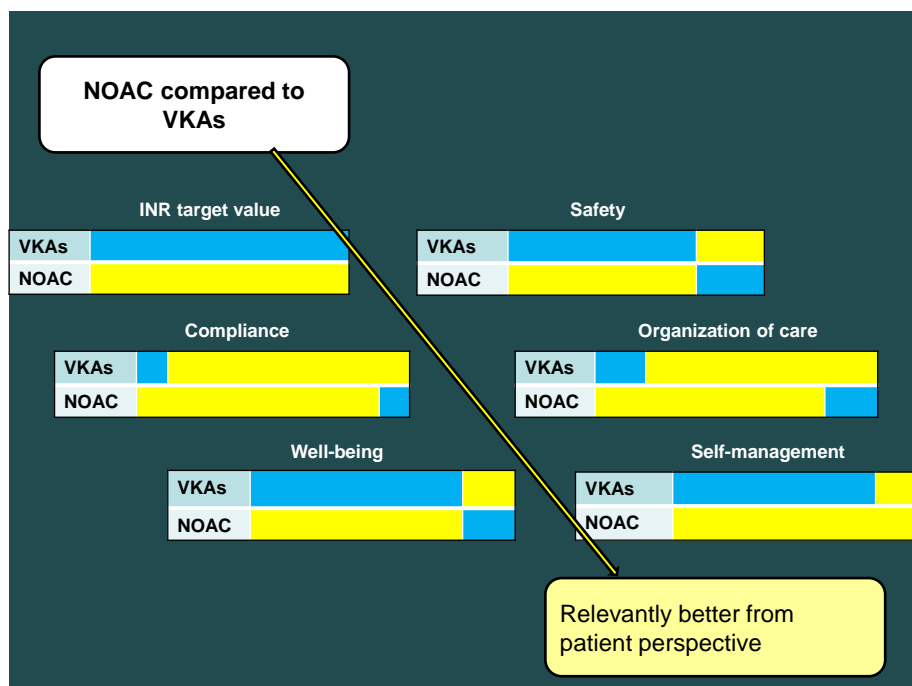
To a great extent the Patient Relevance and Validation Procedures (PRVP) in the domain of 'treatment with new oral anticoagulants in patients with atrial fibrillation (AF)', presented in this report, are viewed by the authors as an ideal tool for taking into consideration the relevant patient aspects in the assessment on inclusion of the new anticoagulants in the basic health insurance package. Indeed, this treatment in particular has great impact on the patient, because in principle it is a lifetime and high-risk therapy, especially for elderly and fragile patients.

In this procedure six patient aspects were identified as core areas and were assessed on relevance. These core areas are shown in the chart below.



For each of these core areas it is evaluated whether the change brought about by the new treatment is a relevant improvement for the patient compared to the standard treatment. Here 'patient' is defined as a population of comparable individuals. The 'patient relevance' is developed and validated from the core area. Based on the outcomes of the combined core areas, the hypothesis 'the treatment with the new anticoagulants is relevantly better from the patient perspective compared to the current treatment with vitamin K antagonists' is either confirmed or rejected.

Experts in the field of patient aspects have found that in four of the six core areas there are relevant improvements to be found in the average population of patients with AF when they use the new oral anticoagulants instead of VKAs. The other two core areas were assessed as equivalent. An improvement of at least >10% is defined by the expert group as a relevant improvement. The improvements are expressed as an improvement on a scale of 0-100%. The improvements in four of the six core areas amount to $\geq 50\%$. From the perspective of the average population of patients with AF, this is a relevant improvement.



Because an assessment is based on the experience of the typical patient it is important to bear in mind that patient typology is an important determinant in the final choice of the treatment. Insight and choice in treatment options for patients is of great importance for the therapy to succeed (Nemerovski et al. 2011.)

Keywords: Medicine Assessment, Patient Relevance, Patient Participation, Anticoagulation, Atrial Fibrillation.

Organisations involved

This report was made possible with input and support from the Expertise Centre for Pharmacotherapy in the Elderly (Ephor), Patient Academy, Institute for Responsible Medicine Use (IVM), Dutch Association of Cardiovascular Nurses and The Heart and Vascular Group.



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Abbreviations

ACTA	Academic Centre for Dentistry Amsterdam
ACCP	American College of Chest Physicians
AF	Atrial fibrillation
ASA	Acetosal, Acetyl Salicylic Acid
CBG	Medicines Evaluation Board (Utrecht)
CFH	Pharmaceutical Assistance Commission (an independent advisory CVD, Diemen)
COXIB	COX-2 selective NSAID
CVA	Cerebrovascular Accident (brain haemorrhage or infarction)
CVZ	Health Care Insurance Board (Diemen)
CFH	Pharmaceutical Assistance Commission of the Healthcare Insurance Board
DVT	Deep Vein Thrombosis
Ephor	Expertise Centre for Pharmacotherapy in the Elderly (UMC Utrecht-geriatrics)
EMA	European Medicines Agency (London)
FNT	Federation of Dutch Thrombosis Services
IGZ	Dutch Healthcare Inspectorate
IVM	Institute for Responsible Medicine Use (Utrecht)
ITTR	Time in which the INR value falls within the therapeutic range
LE	Lung Embolism
LESA	National Primary Cooperation Agreements
NICE	National Institute for Clinical Excellence (United Kingdom)
NOAC	New Oral Anticoagulants (here: apixaban, dabigatran, rivaroxaban)
NZa	Dutch Healthcare Authority (Utrecht)
PPSB	Four Coagulation Factors Concentrate (prothrombin complex; Cofact [®] , Beriplex [®])
PRVP	Patient Relevance and Validation Procedure
RIVM	National Institute for Health and the Environment of the Netherlands
TARs	Thrombocyte Aggregation Inhibitors (acetosal, clopidogrel etc.)
TEC	Thromboembolic Complication
TIA	Transient Ischaemic Attacks
VKA(s)	Vitamin K antagonist(s) (here: warfarin, phenprocoumon, acenocoumarol)
VWS	Ministry of Health, Welfare and Sport (The Hague)



1. Rationale expert procedure

The company sets high standards on the quality of the development and review process for the authorisation of medicinal products. If an agent is authorised under the applicable registration procedure (CBG-EMA), then a second procedure follows to determine whether the product should be included in the basic health insurance package. On the basis of a request by the Minister of Health and/or the NZa (Dutch Healthcare Authority) this assessment is submitted to the Health Care Insurance Board (CVZ) for approval. Then the CVZ advises about it, usually based on a CFH advice. The decision to include a treatment or the use of a new medicinal product in the basic health insurance package is based on the efficacy-safety ratio supplemented with pharmaco-economic data.

In the authorisation process for inclusion of a medicinal product in the basic health insurance package little attention is paid to patient relevant aspects such as self-management, convenience, well-being and applicability of the treatment. Also, patients' and caregivers' practical experience and knowledge play a very modest role, if they play a role at all in this process.

The lack of a timely available position or guideline from the caregiver and the lack of established relevant patient aspects make it more difficult for authorities to assess the relevant improvement on their own and thus to determine the placement and value of a new, usually more expensive treatment. Despite higher spending on care, a new treatment may indeed be cost-effective on a macroeconomic scale (Gage et al. 2011; Pink et al. 2011). Sometimes, those revenues fall outside the healthcare budget (the Ministry of Health's budget for health care expenditures) and are then not always taken into account. Barriers in the funding of a new treatment in the basic healthcare insurance package delay the acceptance in daily practice and hold back the inclusion in directives.

The patient perspective as an item for health political decisions is internationally considered relevant (Hansen et al 2011. Patient participation is increasingly viewed as a significant link in both placement (directive) and in the direct use of a medicinal product in patient care (De Rijk et al. 2011, Schipper 2012).

In the literature, a design in which various criteria are used to assess the value of a treatment is called a 'multicriteria decision support' (Dolan et al. 2010).

The rationale of the expert procedure described here is that besides identification and validation of clinically relevant improvements, identification and validation of patient relevant improvements of a new treatment compared to the existing treatment(s) is pre-eminently a task for the care providers and patients involved in the treatment. Indeed, the greatest substantial expertise lies with the caregivers and the patients.

By setting up and facilitating expert procedures on medical-pharmaceutical issues Europe-Expro promotes the timely input of the expertise of caregivers and the timely input of relevant patient aspects from the patient perspective. Europe-Expro provides this expertise in the public domain.

2. Objective of Patient Relevance and Validation Procedure

The purpose of the procedure described here is to make it possible to involve relevant patient aspects in the process of inclusion of a new medicinal product in the basic healthcare insurance package.

In that sense the Patient Relevance and Validation Procedure is an essential complement to the traditional method of assessing a new treatment. In this procedure the relevant differences between a new and an existing treatment are assessed from the patient perspective.

Clinical relevance and health economic aspects must continue to play an important role in the development of directives and inclusion in the basic healthcare insurance package. In addition, we see the use of this patient relevance and validation procedure in the domain ***'treatment with new oral anticoagulants in patients with atrial fibrillation'*** as a good option to define and validate the qualitative and/or quantitative measures for patient relevance. Hereinafter it is called the "Expert Procedure".

The position of the Expert Group is captured in a public report aimed at stakeholders and interested parties, such as professional association(s), patient association(s) and agencies in the field of public health. We explicitly ask recipients of the report for comments and contributions. The data from the report is to be published and made available in the public domain.

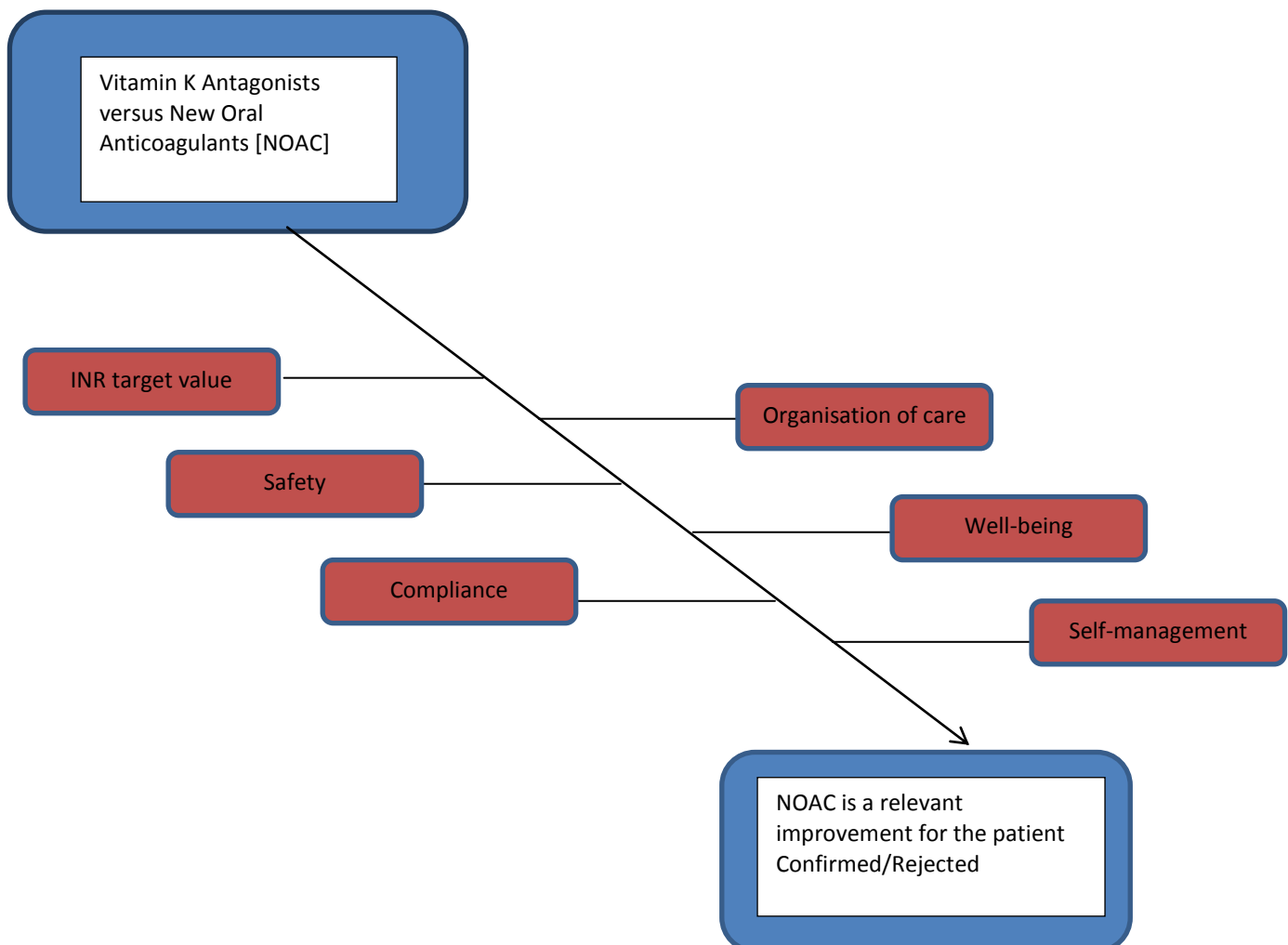
3. Methods

This chapter describes the procedure for patient relevance and the procedure for validation in the domain 'new oral anticoagulants'. The reference treatment for the new oral anticoagulants (direct thrombin inhibitors and Factor Xa inhibitors) is the classic oral anticoagulants: Vitamin K antagonists (VKAs).



3.1 Hypothesis

The hypothesis is that 'from the patient perspective, treatment with the new anticoagulants is relevantly better compared to the current treatment with vitamin K antagonists'. This hypothesis was tested from several closely defined core areas, which are relevant to the patient. The core areas were defined after plenary meeting by the two core members in the expert group. Six core areas have been formulated, which are given in the chart below. For each of these core areas it is evaluated whether the change brought about by the new treatment is a relevant improvement for the patient compared to the standard treatment. Here 'patient' is defined as a member of a population of comparable individuals. The 'patient relevance' is developed and validated from the core area. Based on the joint outcomes of the core areas, the hypothesis is either confirmed or rejected.



3.2 Core areas

The experts have identified the following relevant core areas from the patient's perspective under the expert procedure: INR target value, safety (safe use), compliance, organisation of care, well-being and self-management. For these core areas it must be determined whether they show a relevant difference between the existing oral anticoagulant treatment (VKAs) and the new oral anticoagulant treatment (NOAC). Based on a predefined hypothesis it is tested whether the difference found between the two treatments is relevant or not. For this purpose a measure and an associated value is defined for each core area. The findings are also validated by experts in the review process. The process is described in greater detail under the heading 'Procedure'.

Core area 1: INR target value (VKAs - measuring = knowing – bleeding and coagulation risk

- Measure: Achieving the treatment aim = prevent ischaemic CVA or other TEC
- Value: Number of patients (percentage) who achieve the treatment aim.
- Hypothesis: Is it feasible to achieve the same treatment aim by using NOAC, without using a measure such as the target INR value?
- Relevant improvement: Achieving the same treatment aim by using a treatment that, unlike VKAs, does not have to be monitored with an INR target value.

Core area 2: Safety

- Measure: Safe use.
- Value: What percentage of patients are limited in the use of intake by factors such as interaction potential, comorbidity and diet pattern?
- Hypothesis: Is safe use increased with NOAC?
- Relevant improvement: A majority of patients do not have to take applicability into account (safety aspects such as diet, interaction potential and comorbidity) when taking the medicine.

Core area 3: Compliance

- Measure: Complexity of intake.
- Value: Measure of simplicity of intake.
- Hypothesis: Is the complexity of intake reduced?
- Relevant improvement: Change in the complexity of intake.

Core area 4: Organisation of care

- Measure: Complexity of care.
- Value: Number of disciplines involved.
- Hypothesis: Is the complexity of care reduced? (E.g. less fine tuning and transfer, care closer to the patient?)
- Relevant improvement: The number of links in the care chain (transfer moments) are reduced.

Core area 5: Well-being

- Measure: Daily functioning.
- Value: Measure of freedom in daily activities (e.g. work, travelling, holiday).
- Hypothesis: Measure of well-being of patients with AF in respect of the use of oral anticoagulants strongly depends on the patient's subjective experience?
- Relevant improvement: Increase in well-being by freedom in daily functioning.

Core area 6: Self-management

-Measure:	Self-management of the anticoagulation regime.
-Value:	Number of patients for whom self-management is possible or for whom it has increased.
-Hypothesis:	Measure of self-management as regards the anticoagulation regime has increased by using NOAC?
-Relevant improvement:	More control of own activities and time.

The core areas were worked out in expert pairs and were validated interdisciplinary.

3.3 Experts

The experts are from the public health sector and deal with patient aspects directly or indirectly. They all have specific experience in 'anticoagulant therapy' and are often part of an organisation that is engaged with this topic. The following bodies have provided delegates for this project:

Ephor, Expertise Centre for pharmacotherapy in the Elderly associated with the department of geriatrics of the University Medical Centre in Utrecht (www.ephor.nl)

Patient Academy, The Hague (www.patientenacademie.nl)

Institute for responsible medicine use, Utrecht; IVM (www.medicijngebruik.nl)

The Heart and Vascular Group, The Hague (www.hartenvaatgroep.nl)

Dutch Society of Cardiovascular Nursing; secretariaat@NVHVV.nl)

Family Medicine

Furthermore, experts have been consulted in the areas of:

- Thrombosis Services
- Epidemiology and Methodology of investigation of cardiovascular diseases
- Healthcare Insurance
- Cardiology, in particular, atrial fibrillation

3.4 Procedure

The validation process can be categorised as follows:

1. Systematic collection of scientific literature
 - EBM (evidence based medicine) perspective: judgement based on (scientific) publications, and
 - PBM (practice based medicine) perspective: judgement based on practical experiences of doctors, patients and other experts/bodies.
 - Patient based medicine (PaBM) is the patient (user) perspective: Is the treatment aim of the patient better achieved both medically/pharmaceutically, as well as individually, socially, (giving meaning); the own autonomy may be enhanced by less dependence on care and better participation in school, work; the quality of life increases. In this project we aim to validate the patient relevance. The core areas investigated are partly based on the basic set of quality criteria for Quality of Care (KIZ 2010). *(This basic set of quality criteria is a product of the programme Quality in View (Kwaliteit in Zicht), in which the Diabetes Association of the Netherlands (DVN), the Asthma Society/Lung Patient Society, the Rheumatism Patients Association, the Association of Neuromuscular Diseases of the Netherlands (VSN), The Heart and Vascular Group, the Dutch Federation of Cancer Organisations (NFK) the Health Interest in the Netherlands and the Dutch Consumers Federation cooperate to realise care that (even) better suits the demands and wishes of patients).*
2. Analysis and interpretation of information
3. Formulation of a measure, value and 'relevance measure' pertaining to the core area
4. Development and establishment of preliminary outcomes
5. Methodological penetration
6. Formulation of preliminary conclusions
7. Preliminary final conclusion on relevance measure core area/validation
8. Draft report of all core areas

At this stage, expert peer review is requested of two advisory experts: a cardiologist and a health insurance expert. These experts will give relevant feedback from the clinical perspective and health insurer perspective on the findings from the patient perspective.

9. Final conclusions and final report by the expert group

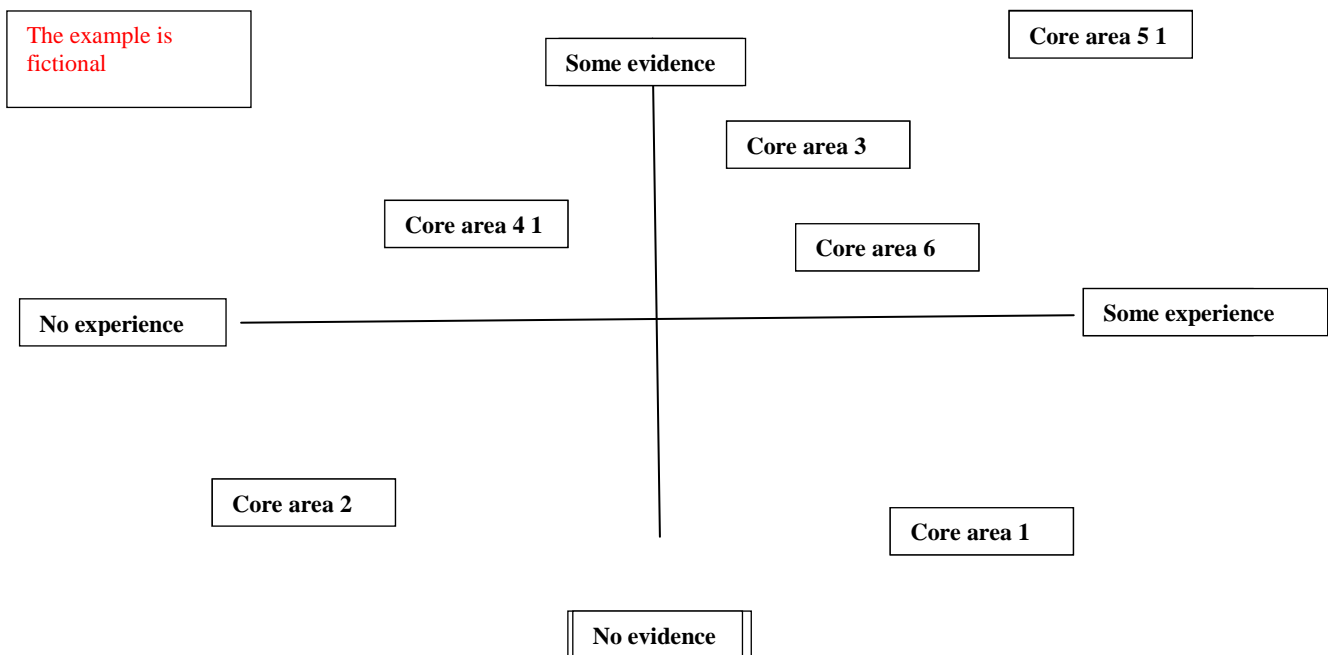
Parts 1 to 8 are developed in expert pairs; step 9 is developed by the core members of the expert group. During steps 2 to 6 the pair of experts requests input and comment from their own colleagues.

Representation of 'Hardness relevance'

Methodologically patient relevance cannot be based on scientific evaluation (Evidence Based Medicine) alone, because much of the relevance stems from the (long) experience in daily practice (more subjective) of benefits/disadvantages experienced by the patient. This also applies to the establishment of clinical relevance. Only from the expertise of clinicians and from the expertise of professionals, who deal directly with patients and the patient perspective, can a relevant improvement of a specific parameter ultimately be set as norm. In other words, a standard for relevance can only be established in the presence of expert experience.

Therefore, methodologically it is appropriate to establish the patient relevance for each core area with input from Evidence Based Medicine (EBM), Practice-Based Medicine (PrBM) and Patient Based Medicine (PaBM) (input/available information). In the literature a design in which a variety of criteria are used to assess the value of a treatment is referred to as a 'multicriteria decision support' (Dolan et al. 2010).

Depending on the quantity and quality of available information by category, Evidence Based Medicine (EBM), Practice-Based Medicine (PrBM) and Patient Based Medicine (PaBM), the basis of the patient relevance may not support all core areas equally 'hard'.



The combined expert team is the appropriate forum to pronounce a judgement on:

- the hardness of the conclusion as regards the six core areas (patient relevance and validation per core area)

AND

- the hardness of the overall conclusion as regards the hypothesis that treatment with the new oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) has added value compared to the current treatment with vitamin K antagonists considered from the patient perspective.

4. Information on anticoagulants

In this analysis the use of the oral anticoagulants is directed solely at patients with atrial fibrillation (AF).

Oral anticoagulants for AF as indication used in the Netherlands comprise: acetylsalicylic acid (in low risk patients), or VKAs (warfarin or phenprocoumon). Patients who are prescribed VKAs are counselled by a Thrombosis Service in reference to the risks associated with VKA use and the need for good anticoagulation within the therapeutic INR range. In the Netherlands approximately 10-20% of the patients employ self-management with or without self-dosing.

The new ACCP directive (Guyatt et al. 2012) considers the use of acetyl salicylic acid for the indication AF as inadequate even in low risk patients, and with too great a risk of bleeding. Therefore, acetylsalicylic acid is not mentioned further in this report.

The NOAC are characterised by the fact that laboratory tests are not necessary to monitor the regulation of coagulation. Meanwhile, experience has been gained in the Netherlands with NOAC for the indication of postoperative thrombosis prophylaxis in elective hip/knee surgery. For these indications NOAC are administered in the short-term: 2-6 weeks. In most Western countries these agents have now also been registered for the treatment of deep vein thrombosis (DVT). Published data for pulmonary embolism are available for rivaroxaban. The registration for use in AF is currently authorised to dabigatran and rivaroxaban; registration for apixaban is expected in the course of 2012. Use of oral anticoagulants in AF has a major impact on the patient, because in principle, it is a life-long therapy. Insight and choice in treatment options for patients are of great importance for the therapy to succeed and to enhance safety (Nemerovski et al. 2011).

Oral anticoagulants available in the Netherlands:

VKAs: *acenocoumarol*, *phenprocoumon*

NOAC: direct thrombin inhibitor: *dabigatran*, FXa inhibitors: *rivaroxaban*, *apixaban*

NOAC are used for the following indications:

- In the 1st and 2nd line: prevention of thromboembolism in atrial fibrillation (AF).
- In the 2nd line: postoperative thrombosis prophylaxis in knee-hip surgery.
- In the 1st and 2nd line: treatment and prophylaxis (relapse) deep vein thrombosis (DVT).

Research for use in acute coronary syndromes has been completed for apixaban and rivaroxaban and is running for dabigatran. The research results for the various agents are not uniform.

The analysis below is limited to the effect on the care for the use of an NOAC in atrial fibrillation (AF). VKAs are used as reference preparations.

To reflect the treatment aim VKAs vs. NOAC the published comparative prospective studies are sufficient: RE-LY (Connolly et al. 2009), Rocket AF (Patel et al. 2011) and Aristotle (Granger et al. 2011). These prospective, controlled clinical trials were designed as non-inferiority studies. All studies were summarised in an article by ten Cate et al. (2011), and in the figures below.

In this report, no preference is given to one of the NOAC.

A preliminary analysis for the indication of AF (RE-LY, ROCKET AF, Aristotle) shows that:

Dabigatran: In efficacy on the primary outcome measure ischaemic or bleeding stroke or systemic embolism at a dosage of 110 mg 2x daily dabigatran is not inferior to warfarin, and at a dosage of 150 mg 2x daily it is superior to warfarin. At a dosage of 110 mg 2x daily Dabigatran gives significantly fewer major bleeding episodes and at a dosage of 150 mg 2x daily an equal number of major bleeding episodes. Both dosages of dabigatran give significantly fewer strokes (Connolly et al. 2009). Dosage adjustment in renal impairment is necessary. In the elderly, because of the slight risk of severe bleeding, an NOAC compared to VKA is recommended at a dosage of 110 mg 2x daily. Clinical experts assessed the outcomes of the RE-LY study as relevant.

This was reason enough for the inclusion of dabigatran in the recent authoritative ACCP guideline for non-valvular AF (Guyatt et al 2012) and in the NICE Guideline 2012.

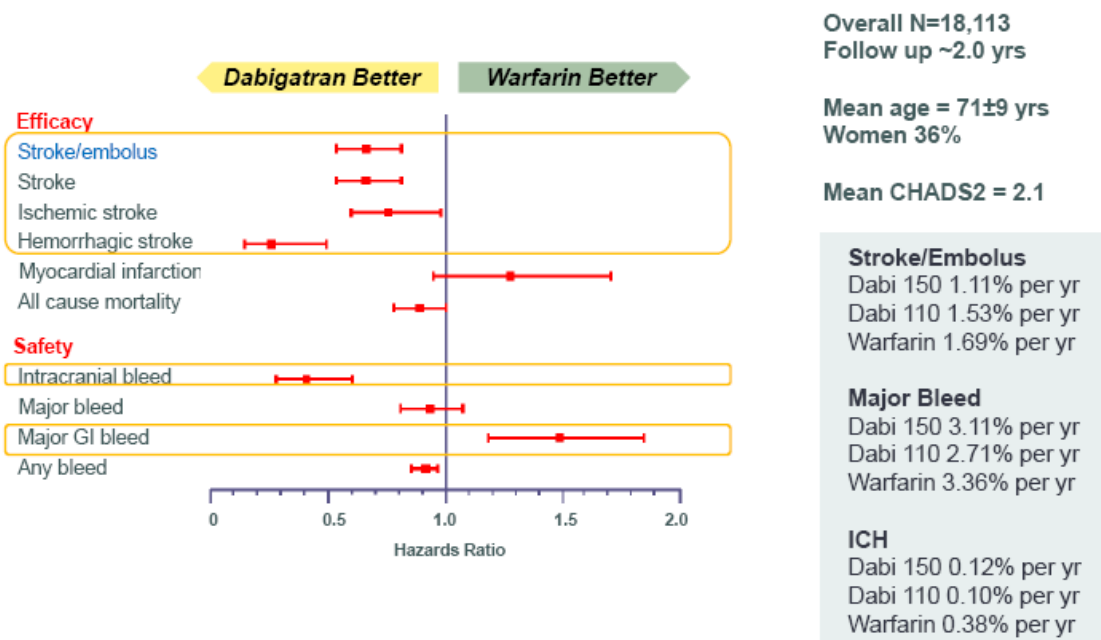
RE-LY: Dabigatran 110 mg BID



NEJM 2009;351:1139-1151; NEJM 2010;353:1875-1876

Fig. 1: Efficacy results and side effects of dabigatran 100 mg 2x daily in AF.

RE-LY: Dabigatran 150 mg BID

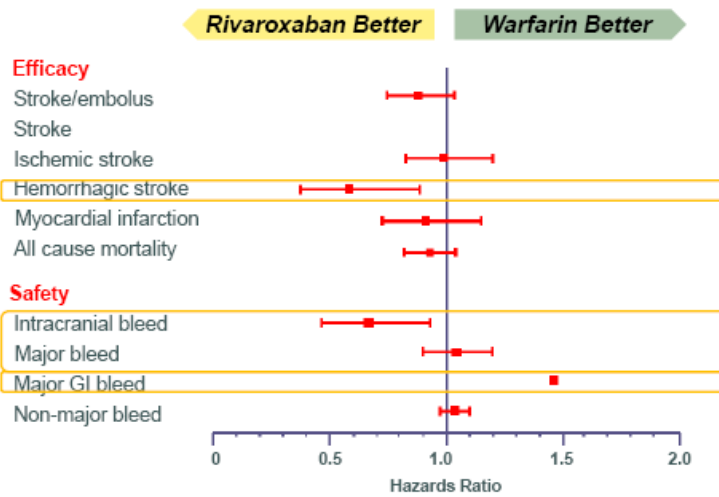


NEJM 2009;351:1139-1151; NEJM 2010;353:1875-1876

Fig. 2: Efficacy results and side effects of dabigatran 150mg 2x daily in AF.

Rivaroxaban 20mg 1x daily is not inferior in efficacy to warfarin on the primary outcome measure ischaemic stroke or systemic embolism. In the rivaroxaban study many more patients with advanced age, comorbidity and risk factors (higher CHADS2 score) were included than in the apixaban and dabigatran studies (Patel et al. 2011). The outcome measure for safety gave significantly fewer strokes. The treatment results of the ROCKET-AF study was assessed by clinical experts as relevant, despite slightly more gastrointestinal bleeding episodes in the rivaroxaban group. (De Caterina et al. 2012). Dosage adjustment is necessary in severe renal impairment.

ROCKET-AF: Rivaroxaban



Overall N=14,264
Follow up ~1.9 yrs

Median age = 73 yrs
(IQR 65-78 yrs)
Women 40%

Mean CHADS2 = 3.5

Poor warfarin control
(mean TTR 55%)

Stroke/Embolus

Riva 1.7% per yr
Warf 2.2% per yr

Major + CRNM Bleed

Riva 14.9% per yr
Warf 14.5% per yr

ICH (fatal bleed)

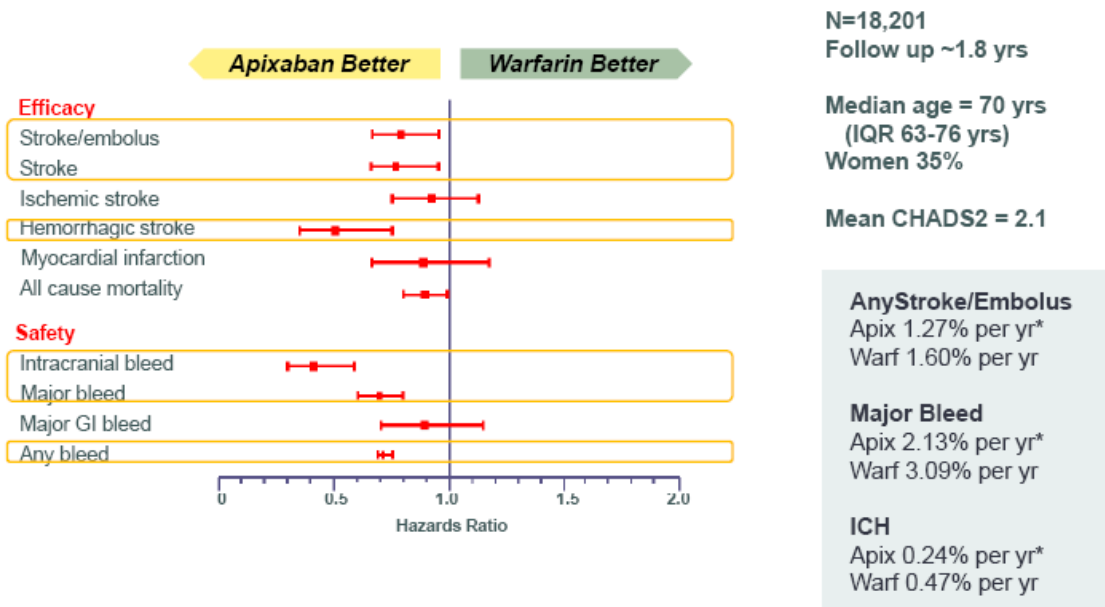
Riva 0.5% (0.2%) per yr*
Warf 0.7% (0.5%) per yr*

NEJM 2011;365:883-891

Fig. 3: Results on efficacy and side effects of rivaroxaban 20mg administered 1x daily.

Apixaban 5mg 2x daily (at a low dosage of 2.5 mg administered 2x daily for age > 80 years, weight < 60 kg or serum creatinine > 133 mmol/l) in terms of efficacy, had significant added value compared to VKA (see fig. 3). Apixaban gives significantly greater bleedings and fewer strokes, respectively 0.33% apixaban/year vs. 0.80% per year for warfarin. The clinical results of the ARISTOTLE study were assessed by clinical experts as relevant (De Caterina et al. 2012). Dosage adjustment is necessary in severe renal impairment.

ARISTOTLE: Apixaban



NEJM 2011;365:981-992

Fig. 4: Results on efficacy and side effects of apixaban 5mg (and 2.5 mg) administered 2x daily.

Table 1: Comparison various NOAC

Properties	Rivaroxaban	Apixaban	Dabigatran (etexilate)
Target	Factor Xa	Factor Xa	Thrombin
Administration	Oral	Oral	Oral
Pro-drug	No	No	Yes
Bioavailability %	80-100	50	6.5
Time to maximum blood clotting (hours)	1-4	1-4	0.5-2
Half-life T1/2 (hours)	5-13	8-15	12-17
Administration frequency	1x daily	2x daily	1x daily or 2x daily
Medicine interactions	CYP3A4 inhibitor PgP inhibitors TARs	CYP3A4 inhibitor PgP inhibitors TARs	PPis TARs
Elimination via kidneys	Yes, ~66%	Yes, ~25%	Yes, ~80%
Safety in pregnancy	No	No	No
Metabolism-dependent polymorph CYP enzymes	No	No	No

5. Elaboration and outcomes of core areas

5.1 Coordinates core area 1: INR target value

Core area 1: INR target value (VKAs - measuring = knowing bleeding and coagulation risk)

-Measure:	Achieving the treatment aim = prevention of ischaemic stroke or other TEC
-Value:	Number of patients (percentage) who achieve the treatment aim.
-Hypothesis:	Is it feasible to achieve the same treatment aim by using an NOAC, without using a measure such as the target INR value?
-Relevant improvement:	Achieving the same treatment aim by using a treatment that, unlike VKAs, does not have to be monitored with an INR target value.

5.1.2 Elaboration

The measure

VKAs

The monitoring by which 'the measure'=INR is determined, applies to VKAs only. The current internationally accepted target value for atrial fibrillations is 2-3 INR (Guyatt et al. 2012). In the Netherlands the target value is higher than internationally recommended, namely 2.5 - 3.5 INR, with additional broader therapeutic range 2-3.5 INR. These values are recommended by the Dutch Federation of Thrombosis Services. The argument for these deviant target values and therapeutic range is to prevent under-treatment as much as possible, that is, to prevent an INR <2, below the efficacy threshold.

From the summary of the annual report of the Federation of Dutch Thrombosis Services (FNT) 2010, it can be deduced that for all Thrombosis Services the INR in chronic patients (treatment duration > 3 months) the INR > 70% were within the therapeutic range of 2-3.5 INR, with a median of 78.5%. In scientific research for registration of medicinal products, as for the NOAC, the internationally accepted INR target value 'individual time in therapeutic range' (ITTR) of 2-3 is observed for the comparative treatment: the VKA warfarin. The Netherlands is the only country in the world that deviates here, in particular, to avoid under-treatment. This prevents the Dutch rates from being compared 1:1 to the INR values in international studies, in which warfarin has been compared with NOAC. The internationally reported values for ITTR are usually between 60-75%. These differences (range 60-75%) are associated with the quality of dosing of the thrombosis services, selection of patients, the method of ITTR determination and implicit and explicit deviations from target values (mathematical model, stabilised patients versus starters (Ageno et al. 2012).

The 'linear interpolation method' developed by Rosendaal (Leiden) is regarded internationally as the gold standard. In the report of the Dutch Federation of Thrombosis Services patients in the initial phase (3 months) are omitted from the statistics. An analysis by Veeger et al. (submitted 2012) in 3,700 starters on VKA in AF/DVT/LE patients shows ITTRs from 61% (2-3). Dutch INR, measured as the percentage of time in the international therapeutic range (INR 2-3), of approximately 50% was reported in an analysis originating from 30 different centres in the Netherlands (comment on the RACE II study by Gelder 2010). The Dutch statistics deviate from the international statistics because of other points of departure for INR target and

therapeutic INR values, mentioned earlier. Yet one can form an idea by comparing the Dutch centres that participated in international studies with warfarin (RE-LY compared to dabigatran and the ARISTOTELES compared to apixaban).

Other variables with the use of VKA are: the quality of the Thrombosis Service. The differences between the average 'within target INR range' among Thrombosis Services is 10-20%. Furthermore, the ranges 'within target INR range' vary significantly when phenprocoumon or acenocoumarol are predominantly used in the region of that particular Thrombosis Service (Rombouts et al. 2009). The Thrombosis Services ascribe this to the measure of experience with a VKA. Where experience is best, the best ITTR is achieved.

NOAC

The NOAC are characterised by the fact that laboratory tests are not necessary to monitor the regulation of coagulation.

We can only assess the question whether the new treatment, which is not tested by the institution, can achieve the treatment aim to the same standard only on the basis of achieving the treatment aim. For this purpose, the clinical outcomes are examined.

The treatment aim

The aim of treatment with anticoagulants is to prevent stroke and systemic embolism. Ischaemic stroke and systemic embolism fall under the most serious complications of atrial fibrillation. Therefore, oral anticoagulants are indicated in patients with an increased risk of these complications. Simultaneously, however, this treatment introduces the risk of serious bleedings, including intracranial haemorrhages. Intracranial haemorrhages are considered the most serious side effect. The efficacy of treatment should therefore be weighed against the risk of serious bleedings, and in particular, intracranial haemorrhage.

In its annual report for 2010 the FNT reported: 4,781 reported serious bleeding episodes in 378,629 patients. In the report no distinction is made as to the specific group of approximately 270,000 patients with atrial fibrillation. The percentage of fatal bleedings in the total group was 0.16% (n = 621 considerably more than in 2009, with n = 488, probably due to better reporting). The reported number of major bleedings and fatal bleedings from the field register is expected to be smaller than the actual number of incidents because some of the patients fall outside the purview of the Thrombosis Service, or they do not receive a signal from the clinicians. Thus in elderly patients who die of a stroke it is usually not examined whether death was caused by a thrombosis or in fact by haemorrhage. In particular, this applies to patients admitted to a nursing home with a progressively unfavourable course. An MRI/CT is required for diagnosis of the type of stroke. Generally, permission is not asked for an autopsy after death.

In a meta-analysis the pooled data from 8 major clinical trials in VKA users was compared for different indications. Bleeding risk of VKAs was 1.4 - 3.4% per year. The spread is due to differences in definitions of major bleedings in the various studies. The percentage of strokes under VKA was 0.33 - 0.8%. Because of the severity, extent and regional variation in the risk of bleeding episodes VKAs are considered as a risky therapy in the literature (Wysowski et al. 2007).

Measures are required to prevent bleeding complications. The mandatory introduction of HAS-BLED and CHA2DS2VASC score in the medical record of the patient and for the transfer of clinical data may contribute hereto for both VKAs and NOAC. A study by Van der Meer et al. (2011) shows that with the use of self-measurement devices and self-dosing with guidance via the internet the number of thrombotic complications is reduced compared to the regular guidance. This may be explained by the fact that compliance in this group is better and the INR upper threshold is exceeded less often.

Table 2: Therapeutic objective

Clinical measures	Vitamin K antagonists Acenocoumrol/ Phenprocoumon	Factor Xa inhibitors Rivaroxaban/ Apixaban	Thrombin inhibitor Dabigatran
Surrogate parameter	INR	Measurement not necessary modified PT possible (Barrett 2012)	Measurement not necessary Possible: aPTT (qualitative), HemoClot® (Semi-qualitative)
Therapeutic range	differs in the Netherlands among the Thrombosis Services; all >70% within INR target range of 2.0-3.5 Internationally in warfarin studies 60-70% within target range INR 2-3	N/a	N/a
Hard outcome measure	Efficacy vs. major bleedings	Efficacy vs. major bleedings	Efficacy vs. major bleedings

The clinical outcomes with use of NOAC compared to the VKA warfarin showed equivalent or superior efficacy in the prevention of the occurrence of stroke or systemic embolism, at a significantly lower risk of intracranial bleeding.

Therefore, it may be concluded that with NOAC a treatment aim is achieved that is at least equivalent, without the monitoring that is required with VKAs. This is considered a relevant improvement from the patient perspective.

The question of whether or not monitoring is necessary is widely discussed, especially in Thrombosis Services circles, where the Dutch adage 'meten is weten', which translates as 'knowledge through measurement', is eminently applied. Measuring the effects of NOAC may be especially important in acute situations (interventions, haemorrhage), or to establish the cause of the occurrence of a thromboembolic complication, for example, because of noncompliance. This also applies to other anticoagulant therapies similar to NOAC, such as platelet inhibitors. For therapies similar to these, no monitoring system has ever been set up – neither has it been done for monitoring complications, nor for monitoring compliance. Therefore, the NOAC need not be approached differently.

However, there are calls for a disease-oriented control system of patients. Patients with cardiovascular and/or metabolic diseases/syndromes are complex patients where monitoring multiple parameters could yield improved care. Thus there are currently initiatives with practice supporters in general practice and outpatient clinics to monitor these patients.

5.1.3 Conclusion relevance core area 1: INR target value

Value: difference 100% to the benefit of NOAC

Agent	Core area	0% ----- 100%
VKA	Measurement INR required	
NOAC	Measurement nor required	



5.2 Core area 2: Safety

5.2.1 Coordinates core area 2: Safety

Core area 2: Safety

- Measure: Safe use.
- Value: What percentage of patients is limited in use on intake by factors such as interaction potential, comorbidity or diet pattern?
- Hypothesis: Does safe use increase with NOAC?
- Relevant improvement: When taking the medicine the majority of patients does not have to take suitability into account (safety aspects such as diet, interaction potential and comorbidity).

5.2.2 Elaboration

General

The phase 3 studies have shown by comparison that for the entire study population the safety of using the new agents is superior to (fewer cerebral haemorrhages) the use of warfarin. However, in the study with rivaroxaban there is a shift towards slightly more gastrointestinal bleeding compared to warfarin. Nevertheless, gastrointestinal bleeding can be treated more easily by an intervention with endoscopic interventions (sclerotherapy). Brain haemorrhages, on the other hand, are often not treatable by intervention and in 50% of the cases they are fatal (FNT 2010).

Anticoagulation is always a high risk treatment

Following the Dutch HARM study (Leendertse et al. 2008), the IGZ classified anticoagulant treatment therapy as high risk therapy. Based on the extrapolation of data from the HARM study it can be seen that in the Netherlands 150-200 patients die each year because of a major bleeding episode while receiving VKA therapy. The 2010 annual report of the FNT mentions a higher figure of 621 (= 0.16% of users in 2010) reported deaths caused by a major bleeding episode while using VKA. The guidance of the patients treated with anticoagulants should ideally, for the sake of the patient's safety, take place in a care chain or be secured in some other way.

Within the structure of the Thrombosis Service relevant information is supplied and collected by a trained employee of the thrombosis service. The employee provides counselling on anticoagulant therapy with VKAs and asks for details with each check-up, in particular, about symptoms that may be suggestive of recurrent thrombosis and bleedings, planned interventions, medication changes, etc. Bleeding episodes are recorded as fully as possible, following international criteria in force. Thromboembolic complications (TECs), a recurrence or spread of the disease for which a patient is receiving VKA, on the other hand, are

probably under recorded. This is caused partly because on the one hand the patient may fall outside the scope of the thrombosis service, e.g. by death. On the other hand, a TEC is often not reported as a separate 'event' by the clinician (e.g. TIA) because it is regarded as part of the disease for which the patient is receiving VKAs. Therefore, upon death an ischaemic stroke (also a TEC) is generally not related to VKA use, while at the time of death information is always gathered about a relationship with VKA use, and especially after the incidence of a stroke.

In the case of a stroke, further information is requested in order to differentiate between bleeding and an ischaemic or thrombotic stroke. On death in the home situation it is understandable that often too little further diagnostic tests are carried out (according to the current international definition) to employ enough criteria by which the stroke can be classified as a thrombotic or a bleeding stroke. The same registration requirements will in the future apply to the recording of adverse events during use of NOAC in daily practice.

Interaction potential with other medical interventions and treatments

If the patient reports planned interventions, the policy based on the expected risk of thrombosis with discontinuation of treatment and the expected risk of bleeding due to the surgery is considered according to protocol and in consultation with the clinician. It is then decided whether a bridging treatment with LMWH should take place, or whether the anticoagulation treatment should be interrupted briefly, or the ACTA protocol (LESA): dental oral surgery should be used while continuing the use of VKA on (fringe) conditions) should be adhered to. The suggested policy is communicated from the Thrombosis Service to all the parties involved. If necessary, the general practitioner carries out the bridging at home, or delegates this task.

When using the new anticoagulants, assessment of the risk of bleeding will be done preoperatively, in particular, the question will be asked whether the medication was discontinued in time and whether there would no longer be any effect at the time of surgery. Ample margins can be set and they may possibly be bridged with LMWH. Because of the lack of measurement, fine tuning as desired in cases of high risk thrombosis is difficult here.

The efficacy of VKAs can be influenced significantly and can frequently be affected by interaction with other medicinal products and particularly autonomous by the role of polymorphic occurring cytochrome P450 enzymes and in particular VKORC1 and also CYP2C9 and CYP4F2 (Beinema et al. 2008; Teichert et al. 2011). The prior determination of the CYP2C9 and VKORC1 genotypes for warfarin therapy according to the new ACCP directive (Guatt et al 2012) does not add value. To determine the loading dose of a VKA these genotypes appear to be of value to prevent overshooting of the INR on days 3-5, and thus to improve the intrinsic safety (van Schie et al. 2011).

The patient who uses a VKA is instructed to report the use of new medications to the Thrombosis Service. With the aid of the 'Standard handling of coumarin interactions' an adjusted monitor date and advice are given. The pharmacy or the patient himself reports the use of a new possible interacting medicinal product to the Thrombosis Service. Reporting potential interaction should be secured within the thrombosis care chain (LESA Anticoagulation 2011). Because of the metabolic independence of the polymorphic occurring enzymes such as CYP2C9 or VKORC1, the NOAC do not cause any interactions with them. Compared with the VKAs significantly fewer pharmacokinetic interactions are expected from the NOAC. For dabigatran it concerns three medicines in particular, of which only two are also regularly used in patients with atrial fibrillation, namely amiodarone and verapamil. The third, quinidine, is rarely used as an anti-arrhythmic medication these days. In co-medication with amiodarone/verapamil the dosage of FXa antagonists must be reduced. This does not apply to dabigatran. In addition, the antibiotics clarithromycin and rifampicin, where for clarithromycin the dose should be reduced, and for rifampicine the dosage should be increased.

For rivaroxaban and apixaban interaction can be expected with CYP3A4 inhibitors: ketoconazole and related antifungal agents, ritonavir, rifampicin, phenytoin and carbamazepine.

In the case of interaction with a VKA the dosage can be adjusted based on the INR, that is to say, in the event of lowering for the sake of safety while maintaining efficacy. At first sight such fine tuning does not seem possible for the NOAC, but it is not necessary either. The interaction with thrombocyte aggregation inhibitors appears to be mainly of a pharmacodynamic nature, although the increased bleeding tendency and the impossibility of interrupting the effect of the new agents thus far, should be taken into account. Interaction with the new anticoagulants should be recognised, severity should be assessed and appropriate measures should be taken, such as currently guaranteed with the use of a VKA in the chain GP, pharmacy, dentist and Thrombosis Service (LESA Anticoagulation 2011).

Influence on diet pattern

With the use of the new anticoagulant agents a change in diet will have less influence on the anticoagulation, compared to the VKAs.

Comorbidity

To date there is little experience about the risks of NOAC in acute interventions such as coronary interventions in patients with AF. The thrombosis formation of different types (metal or drug eluting) stents has not yet been sufficiently investigated, regardless of the type of anticoagulant used.

There are limitation in use with impaired renal function (<30ml/min for dabigatran and <15ml/min for rivaroxaban/apixaban). At a creatinine clearance <30ml/min, dabigatran should not be used, while rivaroxaban and apixaban may be used at an adjusted lower dosage. In elective surgery stopping therapy 24 hours before surgery (36-48 hours in poor kidney function) is sufficient to allow the anticoagulant effect of the NOAC to clear.

Age

Advanced age is seen as a risk factor for use of anticoagulants (Bauer Sachs 2012). Although it has been established that VKAs in elderly patients with AF have greater efficacy, in practice prescribers are too reluctant because of the associated risks of bleeding. The result is under treatment with anticoagulants in the patient group that could benefit most (Singh et al. 2011). Advanced age is no longer regarded as a risk factor for the use of VKAs.

In a major study in 80+ patients it was shown that the bleeding risks in patients counselled by the Thrombosis Service were minimal (Poli et al. 2011). In studies with NOAC patients of a very advanced age are underrepresented. This is reason enough to once again question the safety of these medicines in the high age category.

Halting bleedings

Mechanism: Bleeding with the use of VKAs can immediately be halted with prothrombin complex (PPSB = four coagulation factors concentrate Cofact[®], Beriplex[®]) based on the INR. In many cases vitamin K is administered also, to halt the long-lasting effect of a VKA; this gives rise to long-term dysregulation of phenprocoumon, in particular. To date no specific antidote is available for the new agents and general supportive measures should be taken. For the Factor Xa inhibitors the prospects for four clotting factor concentrate and Factor VII as non-specific antidote seem favourable (Eerenberg et al. 2011; Kazmi et al. 2012). For both the direct thrombin inhibitor dabigatran and FXa neutralising antibodies are being developed as an antidote. A guideline for halting the anticoagulant effect of NOAC was recently published (Kaatz et al. 2012). It is provisionally recommended for a serious life-threatening haemorrhage – if a surgical or some other intervention is not possible – to administer prothrombin complex (4 factors), in case of insufficient effect FVIIa (NovoSeven[®]) and on indication in severe blood loss, to administer fresh frozen

plasma and red blood cell concentrate. In individual cases, certainly when combined with one or more thrombocyte aggregation inhibitors, a serious haemorrhage can occur, which is hard to stop. For this reason, the combination of NOAC with other anticoagulants is (relatively) contraindicated at present.

In practice

Table 3: Factors that affect safety: VKAs versus NOAC.

Treatment with vitamin K antagonists	Treatment with new agents (NOAC)
<ul style="list-style-type: none"> - Monitoring of use - Monitoring by Thrombosis Service employee/-guidance by dosing clinician - Information - Safety and efficacy/balance <p>Registration of bleeding (side effect)</p> <p>Registration of TEC (worsening or relapse)</p> <ul style="list-style-type: none"> • Intended interventions ACTA, discontinuation or bridging • Compliance • New medication/interaction 	<ul style="list-style-type: none"> - Monitoring of use - No monitoring/Optional monitoring by Thrombosis Service - Monitoring and supervision by cardiologist in cooperation with general practitioner/pharmacist - Information: cardiology-specialised nurse <p>Safety and efficacy/balance</p> <p>Registration of bleeding (side effect) LAREB</p> <p>Registration of TEC (worsening or relapse)</p> <p>Interventions: hospital guideline required</p> <p>Pharmacist:</p> <ul style="list-style-type: none"> * Compliance *Interaction monitoring/monitoring kidney and dosage: pharmacist.

<p>Interaction: VERY MANY >200</p> <ul style="list-style-type: none"> • Pharmacokinetic CYP 2C9, genetic polymorphism, inhibition/induction VKORCl: genetic polymorphism • Pharmacodynamic Vit K TARs 	<p>Interaction: VERY LIMITED <20</p> <ul style="list-style-type: none"> • Pharmacokinetic CYP3A4 inhibitors (only: rivaroxaban, apixaban) P-glycoprotein inhibitors (only: rivaroxaban, apixaban) Proton pump inhibitors (only: dabigatran) • Pharmacodynamic TARs
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<p>NSAID+COXIBs (partially also kinetic)</p> <p>SSRIs</p> <p>Dosage adjusted guided by Standard Handling of Medicine Interaction, INR</p>	<p>Classic NSAIDs (not COXIB)</p> <p>Dosage adjustment is an option. Incidentally, in clinical trials these agents were continued being used without any problems</p>
<p>Combination with TAR, NSAID + Coxibs, SSRI</p> <ul style="list-style-type: none"> Increased risk of bleeding (Gasse) 	<p>Combination with TAR, NSAID(excluding Coxibs), SSRI</p> <ul style="list-style-type: none"> Increased bleeding risk expected (no existing data)
<p>Food interaction</p> <ul style="list-style-type: none"> Vitamin K supplement (controversial) Drastic adjustments/fat 	<p>Food interaction</p> <ul style="list-style-type: none"> None
<p>Comorbidity</p> <ul style="list-style-type: none"> Disorders of the digestive tract/liver biliary tract Malignancy Thrombocytopaenia/-pathy 	<p>Comorbidity</p> <ul style="list-style-type: none"> Thrombocytopaenia/-pathy <p>Limitation</p> <ul style="list-style-type: none"> Poor kidney functioning (rivaroxaban, dabigatran) Dyspepsia (dabigatran)
<p>Halting</p> <ul style="list-style-type: none"> Vit K Prothrombin complex Bridging with LMWH under guidance of INR for elective interventions 	<p>Halting</p> <ul style="list-style-type: none"> Prothrombin complex (rivaroxaban) works in healthy volunteers)

5.2.3 Conclusion relevance core 2: Safety

NOAC are safer by at least similar efficacy (fewer strokes, fewer medicine interactions, no food interactions). Research data on suitability of using NOAC in the group of 'vulnerable elderly patients' lacking; however, this information is available for VKAs.

Value: 75% difference in of benefits NOAC.

Agent	Core area	0% ----- 100%
VKA	Applicability	
NOAC	Applicability	

5.3. Core area: Compliance

5.3.1 Coordinates core area 3: Compliance

Core area 3: Compliance

- Measure: Complexity of intake.
- Value: Measure of simplicity of intake.
- Hypothesis: Is the complexity of intake reduced?
- Relevant improvement: Change in the complexity of intake.

5.3.2 Elaboration

General facts about compliance

Improving patient compliance is a major challenge to optimise pharmacotherapy in general. In the period 2000-2010, more than 2500 articles were published about the item 'compliance' (Farmer 2011, Onzenoort 2012). A first problem is how to predict compliance and then how to measure it. Many models have been developed to predict compliance in the individual patient (Horne 1998, Horne et al. 2003, Thompson et al. 2011). One validated method is the Compliance Report Scale originally developed in 1999 by Horne and later translated into several languages re-validated to be language-specific (Mahler et al. 2010). Based on a 5-point scale the patient gives an opinion on 5 relevant items that represent a good prediction of the patient's expected compliance. It is recommended to identify in advance the chance of good compliance on the introduction of an NOAC in the individual patient and to follow it up.

Improving compliance appears to be a difficult problem to solve. However, the introduction of 'concordance' by cooperation between the pharmacist, the general practitioner and the patient seems to have a positive influence on compliance (Geurts et al. 2012).

Given the long market availability of VKAs, data should be available on compliance within the framework of thrombosis care in the Netherlands. There is only one Dutch study on compliance in patients who used either a VKA or acetyl salicylic acid for a neurological indication (CVA) (De Schryver et al. 2005). Furthermore, there is a study from the USA (Kimmel et al. 2007). To date there is no information available on NOAC and the existing knowledge about compliance could possibly be used. For comparison of compliance in these two treatment methods the existing information on VKAs could be compared to predictive information or comparable practice information about NOAC.

Compliance may depend on the setting in which NOAC or VKAs are used. In an institutional setting (hospital, nursing home) practically full compliance is guaranteed because the nurses administer the medication. Making use of caregivers and relief workers for vulnerable patients in the home situation could also ensure the compliance of the patient. More worrisome is the degree of compliance evidenced in the autonomous individual patient. Identifying factors that affect compliance in fully 'autonomous' patients who are prescribed anticoagulants in the long-term is very important.

In the field of cardiovascular agents a great volume of research data can be found on the negative impact of noncompliance (Munger 2008, Ho et al. 2008). Patients appear to know very little about the importance of their anticoagulant therapy for atrial fibrillation; 29% of the warfarin users were not convinced of the importance taking this medicine daily (Smith et al. 2010). The ability of the Thrombosis Services to improve the compliance of their patients is limited. Direct observation techniques to establish monitoring of warfarin intake confirm this fact (Deen et al. 2011). A Dutch study on patients' compliance comparing such compliance in those on aspirin and those on VKAs showed that despite the INR measurement required for VKAs, compliance was no better than for an agent where no INT measurement is required, such as aspirin (the Schryver et al. 2005). In both groups in the study in Utrecht compliance was approximately 10%. Despite INR monitoring compliance with warfarin therapy remains a concern: however, monitoring INR does not mean 100% compliance (Kimmel et al. 2007). There are, however, also indications that introducing a new medication, such as NOAC, could actually result in noncompliance and not in compliance (Barber et al. 2004).

Intensive guidance with modern ICT technology can help to make handling the risks of noncompliance of VKAs and NOAC more manageable (Salmela et al. 2012).

Based on the extrapolation of data from the Dutch study of Schryver (2005), no differences are expected in patients' compliance between VKAs and NOAC therapy.

Specific aspects relating to anticoagulants

An important question at hand is whether we can predict the extent to which an NOAC can result in a change in compliance compared to a VKA.

The definition used for compliance is:

Compliance is the average percentage of the actual amount of prescription medication administered, together with the period in which the patient complies with a prescription compared to the proposed period. It is the result of a complex of internal and external factors that can only partially be predicted and quantified.

Explanation: The World Health Organization [WHO 2003] defines compliance as the degree to which the behaviour of an individual taking medication by himself, following a diet or changing a lifestyle corresponds with the advice of a healthcare provider. In the English literature different terms are used to refer to compliance, namely: adherence, concordance, compliance and persistence. The WHO definition includes the term adherence. The degree of compliance is subsequently not stated quantitatively. Concordance

refers to joint consultation between patient and doctor or pharmacist about the treatment strategy - the patient explicitly consents to the proposed policy. The term compliance quantitatively represents compliance as the average percentage of the actual amount of prescription medicines administered. Usually a percentage of 80 to 120% of the prescribed dosage is considered adequate.

Finally, the term persistence is used for how long (days, weeks, months, years) the patient complies with a prescription compared to the proposed period.

For the core area 'compliance', we use the concepts of compliance and persistence applied to the treatment with oral anticoagulants in patients with atrial fibrillation.

For the sake of convenience we distinguish between directly modifiable factors and indirectly modifiable factors in compliance.

Directly modifiable factors:

1. Packaging
2. Use of auxiliary materials mainly relevant to self-monitoring
3. Instructions
4. Dosing regime
5. Intake
6. INR = Potential monitoring intake on the effect
7. Effect
8. Safety

Indirectly modifiable factors:

Examples of indirectly or difficultly modifiable factors are basic knowledge about disease and health, faith and sympathy for the practitioner and other social, cultural and/or psychological factors such as belief in the positive effect of medication and the disease itself (e.g. mental illness).

We assess each of the directly modifiable factors relating to compliance for the specific medicine. In our opinion the weighting and scoring of these factors will differ for each patient. For a good impression random patients would have to be interviewed or followed, based on the concepts in the list below.

We differentiate between conscious and unconscious adherence. The first relates to beliefs, attitudes and expectations and the second to limitations patients have in following the recommendations of their clinicians in practice. The factors that influence intentions and limitations are known, but the impact they have on the patients' behaviour is unknown.

The most important development in research on compliance is acknowledging that patients make a very personal decision between the pros and cons of treatment as they perceive it, while at the same time they tend to minimise the use of prescribed medications.

[Reading instruction for the table: First, a factor that is directly influenced is named, then the aspects associated with this factor are discussed.]

Table 4: Factors that affect safety: VKAs versus NOAC

Treatment with VKAs	Treatment with NOAC
<p>1. Packaging</p> <p>1.1. The packaging of the medicine must be simple to open.</p> <p>1.1.1 Blister packs are easy to open.</p> <p>1.2. Packaging recognisable</p> <p>1.2.1 For generic preparations the health insurers' preference policy applies</p> <p>Sometimes the packaging and the tablet form may change. This may affect compliance.</p>	<p>1. Packaging</p> <p>1.1. The packaging of the medicine must be simple to open.</p> <p>1.1.1 Blister packs and Baxter bags are easy to open.</p> <p>1.2. Packaging recognisable</p> <p>1.2.1 Not relevant, they are all products with brand names®.</p>
<p>2. Use of auxiliary materials in impaired cognition 2.1 Baxter related</p> <p>2.1.1 Not suitable for Baxter distribution</p> <p>2.2. Automated preparation (robot)</p> <p>2.2.1 Suitable for automated preparation</p> <p>2.3 Intake alert</p> <p>2.3.1 SMS</p> <p>Suitable for SMS alert</p> <p>2.3.2 Via smart blister packs Suitable for smart blister packs</p>	<p>3. Use of auxiliary materials in impaired cognition 2.1 Baxter related</p> <p>2.1.1 Suitable for Baxter distribution</p> <p>2.2. Automated preparation (robot)</p> <p>2.2.1 Suitable for automated preparation</p> <p>2.3. Intake alert</p> <p>2.3.1 SMS</p> <p>Suitable for SMS alert</p> <p>2.3.2 Via smart blister packs Suitable for smart blister packs</p>
<p>3. Effective instructions.</p> <p>3.1. Patient education</p> <p>3.1.1 Education on importance, effect and risks is required and complex</p> <p>3.2. Dosage summary</p> <p>3.2.1 Instructions must be set out schematically in a clear manner</p> <p>3.2.2 Instructions must be printed in large letter type.</p> <p>3.3. Maintenance</p> <p>3.3.1 Patient alertness</p> <p>3.3.1.1. Effect depends on frequency and approach.</p>	<p>3. Effective instructions.</p> <p>3.1. Patient education</p> <p>3.1.1 Education on importance, effect and risks is required and complex</p> <p>3.2. Dosage summary</p> <p>3.2.1 Not necessary</p> <p>3.4. Maintenance</p> <p>3.3.1 Patient alertness</p> <p>3.3.1.1. ?</p>
<p>Treatment with VKAs</p>	<p>Treatment with NOAC</p>

<p>4. Complexity of dosage schedule: Major</p> <p>4.1. Frequency a day</p> <p>4.1.1 Once a day.</p> <p>4.2. Daily dosing (=number of tablets to take) differs</p> <p>4.2.1 Varying dosages</p> <p>4.2.2 Varying number of tablets per intake. Requires studying the actual dosage summary</p> <p>4.2.3 Cannot be provided in Baxter dispenser roll.</p>	<p>4. Complexity of dosage schedule: Minor</p> <p>4.1. Frequency a day</p> <p>4.1.1 Once or twice a day.</p> <p>4.2. Daily dosing</p> <p>4.2.1 Mostly the same dosage</p> <p>4.2.2 One capsule per intake</p> <p>4.2.3 Can be provided in Baxter dispenser roll.</p>
<p>5. Complexity of intake: Yes, always</p> <p>5.1. Tablet size</p> <p>5.1.1 Small, easy to take, difficult to take out of packaging.</p> <p>5.2. Splitting of tablets</p> <p>5.2.1 N/a</p> <p>5.3. Instructions for mealtimes</p> <p>5.3.1 No, but should be taken at fixed time.</p> <p>5.4. Instructions for combinations with other medicines</p> <p>5.4.1 Interactions are discussed with the doctor or pharmacist, problems concerning interactions with antibiotics (concerning end date). Great risk (Gasse et al. 2005; Wysowski et al. 2007))</p> <p>5.5. Instructions for combination with food</p> <p>5.5.1 Not to be taken with green vegetables, liver, milk and vegetable oils mentioned) and vitamin preparations that are rich in vitamin K (analogues).</p>	<p>5 Complexity of intake: No, sometimes</p> <p>5.1. Size of capsules/tablets</p> <p>5.1.1 Normally, easy to take.</p> <p>5.2. Splitting of capsules/tablets</p> <p>5.2.1 N/a</p> <p>5.3. Instructions for mealtimes</p> <p>5.3.1 N/a</p> <p>5.4. Instructions for combinations with other medicines</p> <p>5.4.1 Interactions discussed with doctor or pharmacist.</p> <p>5.5. Instructions for combination with food</p> <p>5.5.1 N/a</p>
<p>6. Titre determination (monitoring intake and effect): Yes, effective</p> <p>6.1. At Thrombosis Service</p> <p>6.1.1 Positive effect on compliance</p> <p>6.2 Self-management</p> <p>6.2.1 Positive effect on compliance</p> <p>6.3. Home injection by Thrombosis Service</p> <p>6.3.1 Besides INR monitoring, also monitoring of medication use and social aspect</p>	<p>6. Titre determination: No, difficult</p> <p>6.1. Monitoring of intake and effect</p> <p>6.1.1 Only in rare cases in hospital. (In fact, compliance should be discussed in every contact situation (consultation with doctor or delivery of medication in pharmacy). The pharmacy can also monitor compliance (indirectly). Intensive counselling can – temporarily – increase compliance.)</p>
<p>7. Noticeable effect</p> <p>7.1. Patient feels better or worse due to use</p> <p>7.2.</p>	<p>7. Noticeable effect</p> <p>7.1. Patient feels better or worse due to use</p>

7.1.1. Effect is uncertain in deviant INR values	7.1.1 No direct effect
Treatment with VKAs	Treatment with NOAC
<p>8. Safety</p> <p>8.1. The medicine prevents damage to the patient 8.1.1. By compliance you prevent thrombosis or bleeding.</p> <p>8.2. The medicine is safe to use</p> <p>8.2.1 Bleedings and relapse thrombo-embolism. Most bleedings are clinically non-relevant. Serious bleedings: high mortality 500 deaths in NL every year, 2% of hospital admissions</p> <p>8.2.2 Antidote (vitamin K+ prothrombin complex) is available</p> <p>8.2.3 Risks of incorrect use of antidotes with risk of relapse VTE</p>	<p>8. Safety</p> <p>8.1. The medicine prevents damage to the patient 8.1.1. By compliance you prevent thrombosis or bleeding.</p> <p>8.2. The medicine is safe to use</p> <p>8.2.1 Little experience, only extrapolation from phase 3 study possible. Fewer brain haemorrhages than VKAs</p> <p>8.2.2 No specific antidote available.</p> <p>8.2.3 Indication that prothrombin complex and FVII are active with Fa inhibitors (Kazmi et al. 2012).</p>

Evidential value of different factors to improve compliance.

Directly modifiable factors have an influence on compliance. Little is known about the role of indirectly and difficultly modifiable factors.

Weighting and scoring

Based on extrapolation of the role of measurement, one can, on the basis of the Dutch study (DeSchryver et al. 2005) determine no difference in compliance between aspirin and VKAs. The fact that measuring (such as the INR in VKAs) has a positive effect on patient compliance cannot be converted into hard measurement based on literature data (Kimmel et al. 2007). Intensive intervention programmes such as 'concordance' will be necessary to maintain compliance at an acceptable level, regardless of the type of anticoagulant therapy.

Given the limited predictability of compliance and well-being from the literature, the patient is ultimately the appropriate source. Therefore, we propose to randomly present patients with data on how the listed factors will affect their own decisions. In a pilot study (Hendriks/van Woerkom 2012) research was carried out with a number of patients and in this study the following statements emerged.

- "The Thrombosis Service keeps me on my toes. Whenever I have something to ask they are immediately ready to help. You notice that it is very important to them that you should take your medicine correctly and it rubs off on you. Without them I would have stopped long ago." (Instruction and titre determination)
- "I absolutely do not want to get a stroke. It is my great anxiety to end up in a wheelchair as a vegetable" (Safety)
- "I have to take the medicines from the Thrombosis Service to prevent serious effects of heart rhythm abnormality." (Safety)
- "The reason I take blood thinners is because the doctor has prescribed them to me." (Effective instructions)
- "I am always very careful in taking the blood thinners. I use the list from the Thrombosis Service for this. If there are certain changes, for example, if I get other medications prescribed or if I've

been sick, for example, or have had a fever, I always report it to the Thrombosis Service immediately. I'm terrified that something may happen to me." (Safety and effective instructions)

- "If I'm very honest, I have to admit that I sometimes do forget to take the blood thinners. Especially when I go to a party. Actually, I always have to take the medicine, but occasionally I forget to do so. Well, then I go without medication for a day and simply continue the next day following the schedule of the Thrombosis Service." (Dosing regimen complexity)
- "The worst part of using these medications is that I have to go to the Thrombosis Service. I now have to go there every two weeks and every time I have to take a free morning from my work." (Titre determination /self-reliance)
- "I visited the first aid centre and there treatment with the tablets from the Thrombosis Service was started. I find it all very confusing; I received a schedule and I have to take some tablets every day. The number of tablets differ from day to day. So I have decided to take this medicine three times a week. (Complexity dosage regimen and effective instructions)
- "Sometimes I think I feel better when I do not take the medication. So, that also happens sometimes." (Noticeable impact and effective instructions).

5.3.3 Conclusion Relevance of Core Area 3: Compliance

-Measure:

VKAs	NOAC
Complexity of intake	No direct monitoring of intake (via INR)

-Value:

No direct monitoring of intake (via INR)

VKAs	NOAC
Major Complexity	Minor Complexity

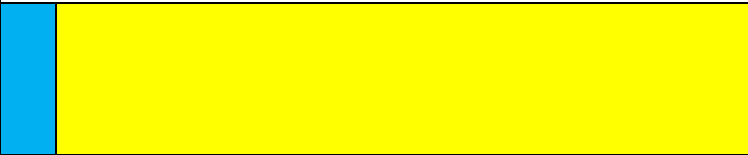
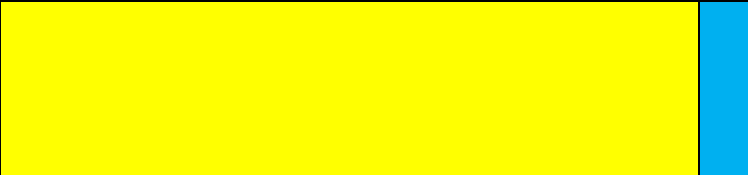
-Hypothesis:

Is the complexity of intake reduced? : YES

Is compliance reduced with no INR monitoring?: Yes

-Relevant improvement:

Neutral: Reason: if we extrapolate from acetyl salicylic acid compliance studies then no big difference is to be expected compared to INR monitoring in VKA

Agent	Core area	0% ----- 100%
VKA	Complexity of intake major/ with INR monitoring	
NOAC	Complexity intake minor/no INR monitoring	



5.4 Core area 4: Organisation of care

5.4.1 Coordinates core area 4

Core area 4: Organisation of care

- Measure: Complexity of care.
- Value: Number of disciplines involved.
- Hypothesis: Is the complexity of care reduced? (E.g. less fine tuning and transfer, care closer to the patient?)
- Relevant improvement: The number of links in the care chain (transfer moment) are reduced.

5.4.2 Elaboration

The organisation of the care should be viewed on three levels: macro, meso and micro levels.

Macro level: Guidelines

- The point of departure is that, in the interest of the patient, treatment to prevent thromboembolism in atrial fibrillation (AF) is based on evidence-based directives (NVC, NHG, CBO, CFH, European Society of Cardiology [ESC 2010]). In addition to these national and European guidelines the ACCP is an authoritative global guideline (Guyatt et al. 2012).

- The treatment of AF based on the ESC 2010 guideline consists of patients with a low CHADS2 score (1) from a VKA and with regulation problems on a VKA from aspirin and in high risk patients from a VKA. The

ACCP guideline 2012 gives preference to dabigatran over a VKA. In the NHG guideline there is still a prominent place for ASA; this position seems to have been outdated by new research data.

- From an investigation on compliance of the old guidelines it appears that low and high risk patients are treated in the same way. This over and under treatment of VKAs and ASA can lead to unnecessary complications (Steg, 2010; Nieuwlaat 2006; Singh 2011; Ogilvie 2011)).

Meso level: Monitoring INR

- The Thrombosis Service carries out the request for VKA dosing by the treating doctor, without being able to check the CHADS2VAsC score. Also, the Thrombosis Service does not have a view on the patients who do not receive anticoagulant medication, while an indication exists for this therapy.

- The VKA regulation is monitored by INR measurement and regulation by the Thrombosis Service, INR measurement by the patient and regulation by the Thrombosis Service (self-testing) and by INR measurement and regulation by the patient (self-monitoring). Several studies have shown that self-monitoring of VKAs is safe and results in better INR regulation (Henegan et al. 2011. This results in a significant drop in the thrombo-embolic processes and a trend towards fewer bleedings and deaths. In the various studies an average of 50% of the users could be included. It is accepted that this percentage will amount to approximately 20% in the Netherlands.

Micro level: selection process in the consulting rooms

- Based on the CHADS2VAsC score, the doctor along with the patient decides on the indication for and choice of AS. In this consultation, the pros and cons of AS and methods of monitoring the VKA regulation (Thrombosis Service, self-testing, self-monitoring) have to be discussed. Also, the benefits of a VKA (measuring = knowing, antidote) and a NOAC (fewer checks, simplicity of intake, fewer strokes).

Comparison:

In the table the effects of the different methods of therapy on health are compared between VKAs and NOAC (dabigatran, rivaroxaban, apixaban).

Table 5: Comparison of care between VKAs and NOAC

Methods of Anticoagulation (AC)	Improvement following guidelines	Reduction in the number of disciplines involved	Monitoring	Experience	Specific antidote	Know-ledge in compli-cations	Self-reliance
VKA+Thromb Service	+?	-	-	++	+	+	-
VKA+ self + Thrombosis Service	+?	-	-/-	+	+	+	+
VKA+ self-monitoring	+?	+/-	+/-	+	+	+	++
NOAC	+?	+	+	+/-	-	+/-	++

(+) positively assessed
 (-) negatively assessed

Explanation of the table

1. Improvement by following guidelines: It is generally not beneficial for the patient if the treating doctor does not follow the guideline. Co-medication or comorbidity may hinder following the guideline. The degree of vulnerability (elderly) also plays a role in the choice of VKA or NOAC. The Thrombosis Service could in practice, if the relevant medical data were available, play an evaluative role in preventing over treatment with VKAs at CHADS2 <2. However, the monitoring function and quality level of the Thrombosis Service will then have to be enhanced. The monitoring of over treatment can also take place as part of medication monitoring done by the pharmacist. The quality level can be improved by reducing the number of the Thrombosis Services. In the under treatment with VKAs at CHADS2 => 2, the Thrombosis Service can play no role. With an NOAC there is no evaluative role possible for the Thrombosis Service pertaining to over treatment. The under treatment may decrease, because an NOAC may be prescribed less reluctantly because of a less serious debilitating bleeding risk (bleeding stroke) and fewer other constraints (interaction with food, narrow therapeutic window) than a VKA (8).

2. Reduction in the number of disciplines: With VKAs the diagnosing doctor (usually the cardiologist, sometimes the general practitioner), the Thrombosis Service, the GP and the pharmacist are involved. The GP and the pharmacist are responsible for the extension, provision and monitoring of medication (interactions/kidney function/contraindications) and for counselling the patient. In self-monitoring the involvement of the Thrombosis Service in the monitoring of regulation is reduced. With the use of an NOAC the Thrombosis Service strictly speaking has no role. The RIVM was commissioned by the IGZ to bring out a critical report on the Thrombosis Services. One conclusion is that the transfer of patient data between the various healthcare providers is seriously inadequate. (IGZ 2010).

3. Minor monitoring: The complexity of care is the least in VKA + self-monitoring and when using an NOAC. However, with an NOAC more guidance is required from the GP and the pharmacist. Besides the tasks they already have with the VKAs they have an extra task of monitoring the correct dosage in the elderly and in patients with impaired renal function. Incidentally, these are tasks that the pharmacist already has to take care of for all medication. Due to the expected volume in the shift from VKAs it does constitute burdening the tasks of the first line.

4. Experience: As with any new medicinal product the experience of NOAC is limited and less than of VKAs (Alings 2011; FT Report CVZ 2008; Brouwers et al. 2010). Protocols exist for GPs, pharmacists and Thrombosis Services on how to deal with the VKAs (LESA 2011); however, for the new NOAC only the information from the manufacturer is available (e.g. Pocket guide Dabigatran 2011).

5. Antidote: Although the half-life time of an NOAC is relatively short, it remains a problem that there is no specific antidote available. Research into non-specific antidotes such as prothrombin was carried out on a small group of young healthy volunteers and animals only. When halting a bleeding caused by VKAs, often too much vitamin K or Prothrombin complex is administered. This not only leads to a thrombo-embolic risk, but also makes it difficult to justify additional costs and it constitutes inappropriate use of (scarce) human blood product.

6. Knowledge in complications: In contrast to the situation with the use of VKAs, doctors and pharmacists have limited knowledge of the prevention and treatment of bleeding complications associated with NOAC therapy. Evidence-based guidelines for the treatment of bleeding complications are not yet known (Brouwers et al. 2010; Huisman 2011). It is also unclear whom the doctor/pharmacist should contact in the event of complications with the use of an NOAC. The manufacturers of NOAC have addressed the need for information by publication of 'Guidelines for use of NOAC in special situations' (e.g. Zakboek 2011).

7. Self-reliance: Self-reliance is at a maximum in the self-monitoring of VKAs and in the use of an NOAC.

5.4.3 Conclusion core area 4: Organisation of care

- Interestingly, it was following the not very complex old guideline that has led to over and under treatment with VKAs and ASA. Given the recent guideline, with no more ASA in AF, there is now over-treatment with ASA and under-treatment with VKAs.

- Self-monitoring has the most positive effect on the quality and/or organisation of care (decrease in thromboembolic events, managed by Thrombosis Service, less complexity of care, previous experience/specific antidote/knowledge of complications and high self-reliance). In the Netherlands 15% to 20% of patients use self-monitoring. Internationally, that number is much higher, normally 50%. With NOAC this self-monitoring percentage is basically 100%, although the doctor and pharmacist have to guarantee their respective roles for monitoring the medication and renal function.

- Because NOAC have fewer side effects than VKAs, using them can result in less under-treatment and fewer strokes. Self-reliance is high. The task of the pharmacist and the GP is extended, while there is still little experience and knowledge in complications.

- There are no known specific antidotes for the NOAC. Furthermore, the halting of bleeding in an overdose with a VKA also leads to a greater risk of thromboembolic incidents and additional costs.

- Note: The organisation of care around anticoagulants must improve. Regardless of the introduction of NOAC, it is proposed to integrate anticoagulants in AF in some form or other in a care chain.

Agent	Core area	0% ----- 100%
VKA	Organization of care	
NOAC	Organization of care	



5.5 Core area 5: Well-being

5.5.1 Coordinates core area 5: Well-being

Core area 5: Well-being

- Measure: Daily functioning.
- Value: Measure of freedom in daily activities (e.g. work, travelling, vacation).
- Hypothesis: The degree of well-being of patients with AF with the use of oral anticoagulants strongly depends on the patient's subjective experience?
- Relevant improvement: Increase in well-being because of freedom in daily functioning.

5.5.2 Elaboration

General

The use of medication can have a great impact on the patient's well-being. This definitely applies to the use of anticoagulants in patients with AF, because in most of these cases the medicines have to be prescribed life-long. Adaptation or adjustment is essential to integrate the condition and the relevant therapy as part of daily living. Practical adaptation leads to an increase in the (subjective) experience of well-being or welfare.

The following definition is used for a good understanding of the concept 'well-being' as it relates to the patient with AF who undergoes anticoagulant treatment for this condition:

the degree to which the patient experiences the treatment from his or her actual ongoing disease experiences). It is the result of the patient's perception of the dimensions of health, involvement, social relationships and therapeutic climate.

Well-being is closely associated with quality of life and it can be assessed in terms of quality of life. Under quality of life we understand

the functioning of individuals in the physical, psychological and social domain and the subjective evaluation thereof.

Modifiable factors in well-being

The following main items can be identified when predicting the change in well-being resulting from the advent of the new medicines

1. Instructions
2. Dosing regimen
3. Intake
4. Titre determination
5. Safety

For each main item the aspects that may affect the patients' well-being for these specific medicines are mentioned. The weighting and score of these factors differ for each patient.

[Reading instruction for the table: First, a factor that is directly influenced is named, then the aspects related to this factor are discussed.]

Table 6: Modifiable factors with an effect on well-being: VKAs versus NOAC

Treatment with vitamin K antagonists	Treatment with new agents
<ol style="list-style-type: none"> 1. Effective instructions <ol style="list-style-type: none"> 1.1. Patient education <ol style="list-style-type: none"> 1.1.1 Education about the importance and relation to the disease is important 1.1.2 Education of method of action and risks 1.2. Dosing summary <ol style="list-style-type: none"> 1.2.1 Instructions set out schematically in a clear manner 1.2.2 Essential to follow dosing schedule 1.3. Maintenance <ol style="list-style-type: none"> 1.3.1 Patient alertness <ol style="list-style-type: none"> 1.3.1.1. Patient involvement (self-management) 1.3.1.2. Influence on social relationships 1.3.2 Repetition factor education <ol style="list-style-type: none"> 1.3.2.1. Recurring item in contact caregiver/Thrombosis Service 	<ol style="list-style-type: none"> 1. Effective instructions <ol style="list-style-type: none"> 1.1 Patient education <ol style="list-style-type: none"> 1.1.1 Education about the importance and relation to the disease is important 1.1.2 Education is essential and complex 1.2 Dosing summary <ol style="list-style-type: none"> 1.2.1 n/a 1.3 Maintenance <ol style="list-style-type: none"> 1.3.1 Patient alertness <ol style="list-style-type: none"> 1.3.1.1. Patient involvement (self-management) 1.3.1.3. Influence on social relationships 1.3.2 Repetition factor education <ol style="list-style-type: none"> 1.3.2.1. Recurring item in contact with caregiver/Thrombosis Service
<ol style="list-style-type: none"> 2. Complexity of dosing schedule: <ol style="list-style-type: none"> 2.1. Frequency a day <ol style="list-style-type: none"> 2.1.1 Once a day. 2.2. Daily dosing (=number of tablets to take) differs 	<ol style="list-style-type: none"> 2. Complexity of dosing schedule: <ol style="list-style-type: none"> 2.1. Frequency a day <ol style="list-style-type: none"> 2.1.1 Twice a day. 2.2. Daily dosing

<p>2.2.1 Changing dosages</p> <p>2.2.2 Essential to study the actual dosing schedule</p> <p>2.2.3 Cannot be in Baxter dispenser roll.</p> <p>2.2.4 Consultation with the Thrombosis Service Treatment with vitamin K antagonists</p>	<p>2.2.1 Mostly the same dosing</p> <p>2.2.2 One capsule per intake</p> <p>2.2.3 Can be in Baxter dispenser roll.</p> <p>2.2.4 Consultation with the Thrombosis Service Treatment with new agents</p>
is essential in the event of incorrect intake	is essential in the event of incorrect intake
<p>3. Complexity of intake</p> <p>3.1. Tablet size*</p> <p>3.1.1 Small, easy to take, difficult to take out of packaging.</p> <p>3.2. Splitting of tablets</p> <p>3.2.1 n/a</p> <p>3.3. Instructions for mealtimes</p> <p>3.3.1 At six o' clock</p> <p>3.4. Instructions for combinations with other medicines</p> <p>3.4.1 Interactions discussed with doctor</p> <p>3.5. Instructions for combination with food</p> <p>3.5.1 n/a</p> <p>*depending on patient's subjective perception</p>	<p>3. Complexity of intake</p> <p>3.1. Capsule size*</p> <p>3.1.1 Normally, easy to take.</p> <p>3.2. Splitting of capsules</p> <p>3.2.1 n/a</p> <p>3.2. Instructions for mealtimes</p> <p>3.3.1 n/a</p> <p>3.4. Instructions for combinations with other medicines</p> <p>3.4.1 Interactions discussed with doctor</p> <p>3.5. Instructions for combination with food</p> <p>3.5.1 n/a</p> <p>*depending on patient's subjective perception</p>
<p>4. Titre determination (monitoring intake and effect)</p> <p>4.1. At Thrombosis Service</p> <p>4.1.1 Positive/negative effect * on well-being</p> <p>4.2. Self-management</p> <p>4.2.1 Positive/negative effect * on well-being</p> <p>4.3. Home injection by Thrombosis Service</p> <p>4.3.1 Besides INR monitoring, also monitoring of medication use and social aspect</p> <p>*depending on patient's subjective perception</p>	<p>5. Titre determination (monitoring intake and effect)</p> <p>4.1. No monitoring at Thrombosis Service</p> <p>4.1.1 Positive/negative effect * on well-being</p> <p>4.1.2 More/less uncertainty because of absent contacts</p> <p>4.2. Self-management</p> <p>4.2.1 Positive/negative effect * on well-being</p> <p>4.3. No monitoring of effect</p> <p>4.3.1 More/less uncertainty because of absence of INR monitoring</p> <p>*depending on patient's subjective perception</p>
<p>5. Safety</p> <p>5.1. The medicine prevents damage to the patient</p> <p>5.1.1 Positive effect on well-being; intake of medication prevents the developing of embolism or CVA/TIA.</p>	<p>5. Safety</p> <p>5.1. The medicine prevents damage to the patient</p> <p>5.1.1 Positive effect on well-being; intake of medication prevents the developing of embolism or CVA/TIA.</p>

<p>5.1.2 Negative effect on well-being: side effects such as bleedings?</p> <p>5.2. The medicine is safe to use</p> <p>5.2.1. Coumarin use has been shown to be very risky</p> <p>5.2.2 Unstable INR values cause more uncertainty</p>	<p>5.1.2 Negative effect on well-being: side effects such as bleedings?</p> <p>5.1.3 Scientific research has proven the effect of the medication</p> <p>5.2. The medicine is safe to use</p> <p>5.2.1 Findings become available in the longer term only?</p>
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The question arises whether based on the above points, quantification of well-being can be done using the SF-36. Quality care criteria for people with atrial fibrillation have recently been put forward by the Heart And Vascular Group and others interested groups (draft version 1.0, 2011). In this care continuum little attention is still being paid to well-being. An item that comes close and that is part of well-being is 'emotional support, empathy and respect'.

SF-36 questionnaire

Not only the transition from vitamin K antagonists to the new oral anticoagulants with the involvement of the Thrombosis Service, but also the use of these new agents by patients on their own can affect the well-being of patients. The SF-36 questionnaire (certain parts thereof) can be used to form an impression of (changes concerning) the well-being of this patient category.

This 36-item Short Form Health Survey (SF-36) is an instrument for measuring quality of life; a so-called multidimensional self-reporting questionnaire. Eight health profiles are derived from the combined scores of the 36 items, namely: physical functioning, role limitations due to physical health problems, pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. This information is deduced from the combined scores. All dimensions are independent of each other and can be grouped in two main dimensions: the physical well-being (physical functioning, role limitation by physical health problems, pain, general health) and psychological well-being (social functioning, role limitation by emotional problems, mental health, vitality). The main dimension well-being (or welfare) in the SF-36, in particular, is characterised by the health profiles dealing with mental health, vitality and pain.

The SF-36 allows for well-being (relevant to a certain area) to be quantified. Having the patient articulate his or her own score can give further insight into the well-being of the patient. It can also be useful to compare an individual score on the various health profiles to an average score of a 'healthy population in the Netherlands'. In this way an assessment can be made of the various elements of well-being. What the patient finds important should, however, expressly be taken into account. The dimension/health profile on physical functioning, for example, will be weighted differently by someone who has been wheelchair dependent (e.g. paraplegia) for many years, than by someone who temporarily uses a wheelchair because of a broken leg. The individual assessment and subjective perception of the patient play a vital role.

Because the SF-36 can be administered at several time points, it is possible to closely study the evolution of the transition and also to set goals or simply to adjust according to the results obtained.

To the best of our knowledge, there is no experience with the implementation of the SF-36 for measuring/predicting well-being with the transition to the new agents and the use of NOAC. Hypothetically speaking it is already possible to pronounce several findings about the expected effect on well-being.

For instance, if a patient had a lower score on 'social functioning': when using the new anticoagulants the patient is 'liberated' from the trips to the Thrombosis Service, he or she no longer needs to adapt their agenda to fit in this visit, and therefore has more time for other things. In this way, the SF-36 is used in the quantification and expression of well-being, on the basis of the items listed in Table 5.

Value Effective instruction and complexity of dosing regimen

Value VKA: patient is well informed	Value NOAC: patient is well informed
<p>Well-being will ultimately increase:</p> <ul style="list-style-type: none"> - detailed instructions necessary - patient knows what is expected of him - possible uncertainty about medication schedule (number of tablets to be taken a day) - right to self-management <p>→ increase in mental health score</p>	<p>Well-being increases:</p> <ul style="list-style-type: none"> - instructions are simpler - patient knows what is expected of him - medication schedule is simpler and each day is the same - right to self-management <p>→ increase in mental health score</p>

Value Complexity of intake

Value VKA: patient takes the correct number of tablets once a day	Value NOAC: patient takes one tablet twice daily
<p>Wellbeing decreases (depending on patient's subjective experience)</p> <ul style="list-style-type: none"> - uncertainty about how many tablets to take - uncertainty about interactions with food - uncertainty about time of intake <p>→ effect on mental health score</p> <p>→ effect on vitality score</p>	<p>Well-being increases.</p> <ul style="list-style-type: none"> - one tablet per intake moment - no interactions with food - fixed times for intake <p>→ score mental health increases</p> <p>→ score vitality score increases</p>

Value Titre determination

Value VKA: Titre determination essential	Value NOAC: Titre determination not possible
<p>Well-being strongly decreases depending on patient's subjective experience</p> <ul style="list-style-type: none"> - certainty about INR value/uncertainty if deviant INR value - regularly visit the Thrombosis Service (neg: travel, extra costs, less time, less freedom) (pos: extra monitoring, social aspect) - experience pain because of blood collections <p>→ effect on mental health score</p> <p>→ effect on physical score vitality, social functioning</p>	<p>Well-being strongly depends on patient's subjective experience</p> <ul style="list-style-type: none"> - uncertainty about clotting of the blood - no visit to the Thrombosis Service (neg: loss of social contact) (pos: more freedom) <p>→ effect on mental health score</p> <p>→ effect on physical score physical functioning, vitality, social Functioning</p>

→ increase in pain score	→ decrease in pain score
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5.5.3 Conclusion relevant core area 5: Well-being

-Value: Safety

Value VKA: prevention of complications	Value NOAC: prevention of complications
Well-being increases - optimal treatment give peace of mind → score mental health score increases	Well-being increases - optimal treatment give peace of mind → score mental health score increases

-Measure: The degree of well-being decreases by structuring 'living' around numbers (=INR)

Measure VKA	Measure NOAC
'living with INR' translated as SF36	'living without measurement' translated as SF36

-Value: More freedom in daily activities (work, travelling, vacation)

Value VKA: freedom decreases	Value NOAC: freedom increases
Well-being depends on age Age >75+ – more contact with Thrombosis Service (social function Thrombosis Service) 65-75 intermediate Younger<65+ : limited by visits to Thrombosis Service	Well-being increases for all ages (more freedom)

Agent	Core area	0% ----- 100%
VKA	Well-being	
NOAC	Well-being	



5.6 Core area 6: Self-management

5.6.1 Coordinates core area 6

Core area 6: Self-management

- Measure: Self-management and anticoagulation regimen.
- Value: Number of patients in whom self-management is possible or in whom it has increased.
- Hypothesis: The measure of self-management as regards the anticoagulation regimen has increased by using NOAC – Relevant improvement: More control of own activities and time.
- Relevant improvement: More control of own activities and time.

5.6.2 Elaboration

The accent in the assessment lies here in the long-term use of NOAC, such as with atrial fibrillation. Because of this new use we can now speak of a completely new 'anticoagulation' regimen'. For the sake of brevity this is also the term used here..

Self-management

In many cases, promoting self-management seems to be a main policy goal and it is often named as an instrumental change, something that can be switched 'on or off'. Much has been said and documented, but there seems to be little evidence of true self-management in thrombosis care in the Netherlands. This is partly because the realisation of self-management requires several changes to be made by the patient and the caregiver; these changes are brought about in a deliberate, guided and constant manner and carried out with the parties believing in their value. It is a mindset, which touches domains, power, commitment and responsibilities and which also requires persistence. By nature it is a social care development that will better meet the needs of the baby boom generation who are now retiring. In addition, the government may save money because costs on professional care can be saved.

Not every patient is an effective self-manager. Care providers determine, in consultation with the patient, whether and to what extent self-management is an option. That depends on the patient and may also vary at different times, and it requires continuation. People with a chronic disease often have no more than two days a year of contact with a caregiver, while on all the other days they are responsible for the treatment and choices that affect their health and their lives. Self-management is therefore shaped mainly by the patient's daily life. Caregivers who are committed to help people make choices that fit in with their

lifestyles, health and treatment, should learn that in practice, and in the Netherlands Vilans has mapped this out (Vilans).

NIVEL states: 'Enhancement of self-management as an integral part of care for people with chronic disease is not automatic. Patients and caregivers should be willing and able to fulfil the role assigned them. This requires a further development of the view on the responsibilities and duties of patients and caregivers, as well as an accessible and proven effective support system tailored to the needs of various groups of patients and caregivers. Financial obstacles will have to be eradicated' (Platvorm 2009).

A definition of self-management is: 'the individual ability to deal with symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic health problem' (Nivel 2011).

Self-management and the new anticoagulation regimen.

Applied to the subject, the '*chronic health problem*' taken from the definition can be referred to as '*a condition which requires the long-term regulation of blood coagulation*'. The *treatment* involves the regulation itself and in this case the question must be whether the new regimen, compared to the former, enhances the individual ability of the patient.

A new anticoagulant regimen does not a priori lead to greater self-management. Conversely, the current way in which healthcare is organised around anticoagulation does not stand self-management in the way either. What's more, a patient who wants self-management should be able to choose for or against the method of Thrombosis Service, with or without a self-measuring and self-regulation.

Self-management is essentially independent of circumstances, but circumstances do, for example, affect the feasibility and attractiveness of some of the elements of self-management.

Vilans found the following parameters that are affected by supporting self-management in the literature (Vilans).

- Autonomy
- Own planning
- Assertiveness
- Self confidence
- Quality of life
- Participation
- Costs

All these elements are positively affected by self-management. The drop in costs is the only non-patient bound element. We examine what effect change in anticoagulant regimen has on these elements. They have to be weighed against the measure in which the change takes place and the value of relevance of that change.

Measure and value in self-management

Table 7: Parameters for self-management evaluated: VKAs versus NOAC.

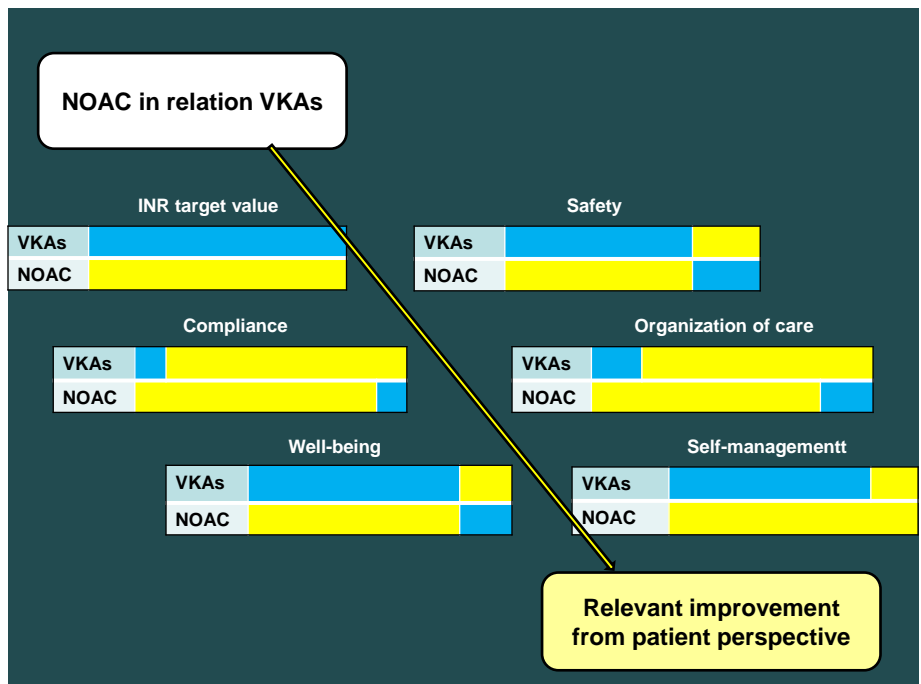
Parameters for self-management in the treatment with vitamin K antagonists	Parameters for self-management with new indications for NOAC
<p>1. Autonomy (in)dependent of caregivers and organisations.</p> <ul style="list-style-type: none"> - Patients are independent of caregivers for determining the prescription, coagulation value and dosing regimen - Patients are dependent on caregivers to determine the prescription, coagulation value and dosing regimen - certain measure of self-regulation is possible, depending on the individual 	<p>1. Autonomy (in)dependent of caregivers and organisations.</p> <ul style="list-style-type: none"> - Except for the prescription, patients are not dependent on the caregivers - Possibility of self-regulation is established as complete.
<p>2. - Own management Self-organisation of own care</p> <ul style="list-style-type: none"> - Managing the care is very limitedly possible, dependant on the organisation of others 	<p>2. - Own management Self-organisation of own care</p> <ul style="list-style-type: none"> - Care is less complex and simpler to organise individually - More management of compliance is required
<p>3. Assertiveness Able to maintain what has been acquired</p> <ul style="list-style-type: none"> - Patient must be able to assert himself in relationship with the caregiver because of the existing relationship 	<p>3. Assertiveness Able to maintain what has been acquired</p> <ul style="list-style-type: none"> - Fewer contacts with caregivers less need for assertiveness
<p>4. Self-confidence Confidence in own acts and decisions</p> <ul style="list-style-type: none"> - Relative simple to acquire with good compliance - Stable because of good anticoagulation 	<p>4. Self-confidence Confidence in own acts and decisions</p> <ul style="list-style-type: none"> - Any uncertainty because of greater personal responsibility - Eradicated by successful anticoagulation, monitoring it may contribute to confidence (de Schryver et al. 2005)
<p>5. Quality of life Functioning of individuals in the physical, psychological and social areas as subjectively experienced by them</p> <ul style="list-style-type: none"> - Any limiting by responsibilities because of thrombosis care - Food prescriptions 	<p>5. Quality of life Functioning of individuals in the physical, psychological and social areas as subjectively experienced by them</p> <ul style="list-style-type: none"> - No limiting by responsibilities - No food prescriptions
<p>6. Participation Participation in daily life</p> <ul style="list-style-type: none"> - Participation may be limited by responsibilities relating to anticoagulation monitoring 	<p>6. Participation Participation in daily life</p> <ul style="list-style-type: none"> - Participation not hampered by responsibilities - More freedom to participate

5.6.3 Conclusion relevant core area 6: Self-management

Agent	Core area	0% ----- 100%
VKA	Self-management	
NOAC	Self-management	

6. Conclusion and Discussion

Experts in the field of patient aspects have found that in four of the six core areas relevant improvements are gained in the average patient population of patients with AF when they use the new oral anticoagulants instead of VKAs. The improvements are expressed as a relative improvement on a scale of 0-100%. The improvements in all four core areas amount to $\geq 50\%$. From the perspective of the patient population this is a relevant improvement.



Because an assessment is based on the experience of the typical patient it is important to bear in mind that patients' typology is an important determinant in the final choice of the treatment. Insight and choice in treatment options for patients, from the patient perspective, is of great importance for the therapy to succeed (Nemerovski et al 2011). The number of frail elderly is strongly underrepresented in clinical trials with NOAC. Caution is advised with extrapolation of the data presented here for this group (Bauer Sachs 2012). After a correlation conversation between clinician and patient, based on 'shared decision making' the appropriate customised treatment can be selected.

Because there is basically no need for monitoring with the NOAC, as is required for the VKAs, the workload of the Thrombosis Service will drop because of the lower number of VKA users. Much has been said about whether or not there is a need to monitor NOAC, especially in 'thrombosis circles' where the Dutch adage, translated as 'knowledge through measurement', is eminently true. Measuring the effects of NOAC may be important in acute situations (interventions, bleeding), or to establish the cause of the occurrence of a thrombo-embolic complication, for example, because of noncompliance. This also applies to other anticoagulant therapies comparable to NOAC, such as platelet inhibitors, acetyl salicylic acid and clopidogrel. However, for platelet inhibitors no monitoring system has ever been set up; neither has it been done to monitor complications, nor to monitor compliance. The question arises why the NOAC should be approached differently in this respect.

Disease-oriented monitoring of patients from an entirely general framework is currently being advocated. In the field of diabetes and COPD there are already far advanced initiatives and structures. In the same way, patients with cardiovascular disease/syndromes are complex patients often with comorbidity. Generally speaking, monitoring multiple parameters would result in improved the health care. In this way there now exist initiatives with practice support nurses in the clinic to counsel patients with AF by using advanced software (Cardio Consult All[®]), also with a very favourable outcome (Hendriks et al. 2012.)

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