Health Council of the Netherlands

New Anticoagulants: A well-dosed introduction

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *New Anticoagulants: A well-dosed introduction*
Your reference : GMT/MVG-3081054
Our reference : I-1011/11/PE/db/004-B
Enclosure(s) : 1
Date : May 15, 2012

Dear Minister,

On 4 October 2011 you asked the Health Council for advice on the new anticoagulants which have recently provided an alternative to the drugs currently being used. In this you asked the Council to examine the efficacy and safety of the new medicines compared with the current anticoagulants in order to look at the cost-effectiveness and the consequences for the Thrombosis Services. A Committee specially formed for the purpose has drawn up the advice requested, which I provide for you here, after consultation with the Standing Committee on Medicine.

After careful analysis and evaluation of the clinical studies conducted with the new drugs, the Committee concluded that, on the basis of this, the medicines are to be recommended. As regards the registered indications and in the context of these studies they have proved to be at least as effective and safe as the drugs currently used. On the basis of that evidence the Committee argues that the drugs should be part of the doctor's arsenal of treatments and should be available to the patient. Because of the removal of the need for frequent checks, the new drugs in particular mean that anticoagulant treatment is greatly simplified, both for the patient and for the person treating him or her.

Considerable uncertainties do, however, persist about the safety of these drugs. For example, the population that will be treated in everyday practice differs from the population taking part in the clinical trials. Also there is (still) no antidote with which the anticoagulant effect can be stopped in emergency situations. And due to the absence of frequent checks, the risk of poor compliance with the treatment in some of the patients is considerable, directly leading to serious consequences.

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The cost-effectiveness study which the Committee has had carried out, shows that the drugs are expensive but that, offset against the benefit to health, the additional costs are within the limits of what is regarded to be cost-effective. Here too there are uncertainties, however. The added value of the new drugs, and therefore also the cost-effectiveness, is smaller the better the quality of the comparative anticoagulant treatment with the old drugs. If the quality in the Netherlands is high because of our system of Thrombosis Services, the cost-effectiveness will be less favourable. However, with the data available the Committee was not able to assess how the quality applying in the Netherlands relates to that in the clinical studies.

In the view of the Committee, the uncertainties about the safety and cost-effectiveness of the new drugs in the Dutch context require further investigation.

If the new drugs fulfil their promise, that will have clear consequences for the Thrombosis Services. Their income will reduce in proportion to the number of people switching over to the new drugs. However, for the time being, the old drugs continue to be indicated in a group of people.

The Committee recommends that the drugs are be part of the doctor's arsenal of treatment and that they are available to the patient. However, their introduction should be accompanied by further investigation into their safety, efficacy and cost-effectiveness, co-financed by the manufacturers, so that the remaining uncertainties can be removed after a few years and the added value can be established definitively. Also, the professional groups should adapt their guidelines to guarantee safe use, with particular attention being paid to ways of improving patient compliance. It should also be indicated how the withdrawal of the 'supervisory role' played by the Thrombosis Services will be compensated for.

I endorse the Committee's findings.
(signed)

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to:

the Minister of Health, Welfare and Sport

No. 2012/07, The Hague, May 15, 2012

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Preferred citation:
Health Council of the Netherlands. New Anticoagulants: A well-dosed introduction. The Hague: Health Council of the Netherlands, 2012; publication no. 2012/07E.

ISBN: 978-90-5549-940-3

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Executive Summary

Motive for the request for advice

Currently nearly 400,000 people in the Netherlands are being treated with anticoagulants of a type Vitamin K antagonists (VKAs). Although VKAs are very effective in treating and preventing thrombosis and embolisms, there are some important disadvantages to taking these 'blood thinners' on a daily basis. The primary objection is that treatment with VKAs requires intensive supervision and monitoring. VKAs also interact with a large number of foods and other medications. This means that people who use VKAs have to pay attention to what they eat and drink, and it is important to be aware of whether any other kind of medication they are prescribed can be taken with VKAs.

There is now an alternative: a new generation of anticoagulants with certain important advantages is in the process of being placed on the market. However, the introduction of these new oral anticoagulants (NOACs) brings with it a number of questions, as a result of which the Minister of Health, Welfare and Sport has asked the Health Council for advice.

The Health Council has set up a committee in preparation for issuing this advice. In its advice, the Committee is formulating answers to the following questions: How does the safety and effectiveness of the NOACs compare to that of the VKAs? Are the NOACs cost-effective? What will the consequences be for the Thrombosis Services? The Minister has also asked the Committee to examine experiences in monitoring the anticoagulant treatment in other countries.

The context

Treating patients with VKAs requires precision. If the dose is too low, clots could form in the bloodstream; and if the dose is too high, haemorrhages could occur, with the expected consequences. For this reason the effects of the treatment must be frequently monitored so as to adjust the dose. In order to offer patients this intensive supervision, a system of Thrombosis Services has been set up in the Netherlands.

The largest group of VKA users consists of people with the cardiac arrhythmia atrial fibrillation. They must take this type of anticoagulant their entire life in order to prevent a dangerous complication of atrial fibrillation; in particular a stroke resulting from an embolism. A smaller group of VKA users consists of patients under treatment for deep vein thrombosis or pulmonary embolism (the two manifestations of the disease venous thromboembolism, or VTE) or who have an increased risk of VTE. This treatment can last anywhere from three months upwards. Patients who have undergone operations with a high risk of thrombosis are also temporarily treated with VKAs. Finally, there is a group of patients who do not fit into the above groups and who use VKAs for a variety of reasons.

The NOACs

There are currently four NOACs in advanced clinical development: dabigatran, rivaroxaban, apixaban and edoxaban. The first two were included in the Dutch medicines reimbursement system (*Geneesmiddelenvergoedingssysteem*, GVS) a few years ago for "prevention of thromboembolism after hip or knee replacement surgery". More recently, apixaban was also included in the GVS for the same medical grounds. Last year dabigatran was registered in Europe for 'prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation' ('indication AF'). The manufacturer then submitted a request to the Dutch Minister of Health, Welfare and Sport to extend the reimbursement for dabigatran to the newly registered medical grounds. The same is true for rivaroxaban, with the difference that rivaroxaban has also been registered for 'treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and lung embolism following an acute DVT in adults' ('indication DVT'). Both files are still being processed.

Efficacy and safety on the basis of clinical studies

As a starting point for the advice, the Committee has made a careful analysis of the clinical studies on the new medications; so far these publications are the only evidence of the efficacy and safety of the NOACs. This analysis differentiated between the studies relating to the indication AF and the indication DVT.

In the case of the indication AF, publications were available documenting a large-scale phase-three clinical trial for each of the medications dabigatran, rivaroxaban, and apixaban. These studies were set up in accordance with a so-called non-inferiority design, meaning that it was necessary to demonstrate that the NOACs were just as effective and safe as the VKAs (i.e. non-inferior to the VKAs). This basic aim was met: within the clinical trials the medications were at least as effective and safe as the VKAs. What this means concretely is that at least as many thromboses and strokes were prevented and that the number of major (or 'clinically relevant' in the case of rivaroxaban) bleedings was no greater. There are indications that some or all of the medications are not only equal to the VKAs but somewhat more effective and safer. One important advantage of the NOACs appears to be that they result in fewer intracranial haemorrhages.

However, an important side note must be pointed out here. In the clinical trials in which medical centres in dozens of countries participated, a significant difference in the quality of the VKA treatment was evident. When the data for dabigatran (the medication about which the most information has been published so far) was re-evaluated, the apparent greater efficacy of dabigatran disappeared if data only from those centres where the quality of treatment was above average (greater than the median) was examined. If the quality of anticoagulant treatment in the Netherlands is relatively high as a result of the national system of Thrombosis Services, a system which most countries do not have, this may mean that NOACs are not more effective or safer in comparison to the anticoagulant regime in the Netherlands. However, the Committee came to the conclusion that a comparison between the quality of anticoagulant treatment in the Netherlands and the quality of treatment in the clinical studies is not possible on the basis of the available data.

As to the indication DVT, published studies are available on the use of dabigatran and rivaroxaban for acute treatment of VTE (the first three to nine months). The Committee is of the opinion that in the context of the published clinical studies, dabigatran and rivaroxaban are just as effective and safe as VKAs for this indication. An important advantage of rivaroxaban is that it is not

necessary to treat the patient initially with low-molecular-weight heparin, as is necessary with VKAs because of their insufficient effectiveness in the first few days.

Safety in everyday clinical practice

Despite the favourable results of the clinical studies, the Committee is of the opinion that there are still a number of important uncertainties regarding the effectiveness and safety of the medications in everyday clinical practice. These uncertainties have to do with the following points.

First of all, the population treated in practice differs from the participants in the clinical studies. In particular, people at higher risk of complications were excluded from the clinical studies. Secondly, there is no suitable antidote for the NOACs as there is for the VKAs. The lack of a means to reverse the effects of the anticoagulant can lead to serious problems in emergency situations such as accidents or emergency operations. Thirdly, the risk that patients take their medication too infrequently or at improper times is probably greater for the NOACs than for the VKAs because there is no regular supervision from the Thrombosis Services. Unsafe use of the medications can have serious immediate consequences. It is also important to note that the lack of supervision on the part of the Thrombosis Services also eliminates the management function which the Thrombosis Services currently has over the anticoagulant treatment.

Cost-effectiveness

In order to gain more insight into the cost-effectiveness of the NOACs, the Committee has carried out a cost-effectiveness analysis. Given the limitations in time and means, the Committee chose to focus the analysis on the prevention of stroke and systemic embolism in atrial fibrillation patients (the largest group of patients). To this end, a simulation was set up in which half of the patients were treated with 150 mg of dabigatran twice daily, and the other half received a VKA. The difference in medical costs between the two groups was divided by the difference in quality-adjusted life years (QALY) and expressed as an incremental cost-effectiveness ratio. This incremental cost-effectiveness ratio of approximately €12,000 per QALY falls within the usual limits of what is generally considered to be cost-effective. However, given the possibility of a less favourable comparative effectiveness and safety profile of NOACs versus VKAs in the Netherlands than was seen in the clinical trials, it is important to be aware that NOACs may be less cost-effective than this in the Netherlands. It must also

be pointed out that the much greater ease of use of NOACs as compared to VKAs hardly carries any weight in a cost-effectiveness analysis.

Consequences for the Thrombosis Services

Because it is not necessary to regularly monitor the use of the new medications, the Thrombosis Services will see a decrease in turnover roughly proportional to the number of people who start using NOACs. In the opinion of the Committee, it is not yet possible to reasonably predict the percentage of patients who will continue to use VKAs. For the next several years in any case, some patients will continue to rely on VKAs and the concomitant supervision. These will be patients who use VKAs for conditions for which the NOACs have not yet been tested, patients who do not tolerate NOACs, and patients for whom there are serious doubts about compliance with medical advice or who have a strong preference for continuing with VKAs. If the number of people relying on the Thrombosis Services falls below a certain critical level, it may be more efficient for outpatients' clinics or general practice surgeries to be in charge of monitoring the anticoagulant treatments and to harbour the expertise that requires. Experiences in other countries show that while it is certainly possible to organise anticoagulant treatment supervision differently, the best results are achieved with a specialised organisation, whether it is part of a hospital or not.

Conclusions and recommendations

The Committee has concluded that after more than fifty years of reliance on VKAs, the new medications offer the possibility of significantly simplifying anticoagulant treatment for both patients and health care providers. NOACs are a potentially promising new option in anticoagulant treatment for the registered medical grounds. The Committee is therefore of the opinion that these medications should be part of doctors' arsenal of treatments, and should be made available to patients. For the time being use should be restricted to patients who have undergone an elective knee or hip replacement in order to prevent deep vein thrombosis, patients with atrial fibrillation, and patients with VTE. According to the results of the clinical studies carried out so far, frequent monitoring of the treatment will no longer be necessary. As a result, this treatment will be just as “ordinary” as other forms of drug treatment.

However, doubts remain as to the safety of NOACs in everyday practice. It is also uncertain as to whether the health benefits offered by the medications and the cost-effectiveness of the medications in the context of anticoagulant

treatment in the Netherlands are sufficient to justify the extra costs. Therefore the Committee feels that introduction of the NOACs must be accompanied by more detailed research into their safety, effectiveness and cost-effectiveness. The goal of this research should be to remove the remaining uncertainties and definitively establish the added value of the new medications. In the opinion of the Committee, the manufacturers of the medications could participate in financing this research. The Committee offers proposals for the design and organisation of the research. In addition, the professional groups must adjust their guidelines in order to guarantee safe use of the new medications and promote compliance with treatment. They also need to indicate how the disappearance of the management function of the Thrombosis Services will be compensated for.

Chapter 1

Introduction

The treatment of patients with the current anticoagulants requires precision. If the dose is too low, clots can form in the bloodstream and if the dose is too high, bleeding can occur. In order to be able to monitor the patients closely, a system of Thrombosis Services has been set up in the Netherlands. In recent years a new generation of anticoagulants has been developed which have a different mechanism of action. How effective and safe are these new drugs and what requirements do they set regarding the monitoring and the supervision of patients? At the request of the Minister of Health, Welfare and Sport, the Health Council has issued some advice.

1.1 The request for advice

A scientific assessment is required of the new drugs and the role that they can play in the treatment of thrombosis, says the Minister in her request for advice. Elements which play a role here are long-term effects, patient compliance and whether or not antidotes are available.

The drugs have other requirements regarding the checking and monitoring of patients than the current anticoagulants, and the advent of these new drugs may possibly have consequences for how the monitoring of anticoagulant treatment is organised in the Netherlands. Therefore the Minister is asking the Council to look at the position of the Thrombosis Services in our country and the possible consequences of the advent of the new drugs for them.

At the Minister's request, the Health Council has consulted and exchanged information with the Health Care Insurance Board (the CVZ) regarding the therapeutic assessment of the current and new anticoagulants, and in the assessment of health economics arguments. The Council also looks at experiences with other ways in which the monitoring of anticoagulant treatment is organised in other countries. The complete request for advice can be found in Annex A.

The Health Council has set up a committee to draw up this advice. The members of the Committee are listed in Annex B. In this advice the Committee concentrates on three main questions:

- Are the new anticoagulants just as effective and safe as the current drugs (vitamin K antagonists)?
- Are the new drugs cost-effective?
- How will the way in which the monitoring of anticoagulant treatment is organised in the Netherlands change?

The advice has been reviewed by the Drugs Advisory Group.

1.2 Bookmark

In Section 2 the Committee examines the mode of action of the current anticoagulants and how they differ from the new generation of drugs. Furthermore the indications for which the new drugs can be used are looked at and the Committee assesses how the monitoring of anticoagulant treatment is organised abroad. After a description of the clinical studies into the efficacy and safety of the new anticoagulants in Section 3, in Section 4 the Committee looks at the efficacy and safety of the drugs in everyday practice. In this section it refers to a number of aspects which require closer examination before the drugs can be used on a large scale. Section 5 contains the outcomes of studies into the cost-effectiveness and, finally, in Section 6 the Committee formulates its conclusions and recommendations.

Chapter 2

The current and new generation of anticoagulants

In this section the Committee outlines the background to this advice. To start with it looks at thrombosis and embolism and their current treatment. The Committee then compares the action and use of the current anticoagulants with the new generation of anticoagulants: in which indications can these drugs be used? Finally, the Committee looks at the way in which anticoagulant treatment is organised abroad. The New Oral AntiCoagulants are hereafter abbreviated to NOACs.

2.1 Clotting, thrombosis and embolism

If a blood vessel is damaged due to an injury, the clotting process starts immediately. The result is the formation of a clot made up of blood platelets and fibrin which covers the damaged area and stops the loss of blood. The clot starts to form because platelets adhere to the damaged area, are activated by this, and then adhere to each other to form a plug. This plug is then strengthened by a network of fibrin threads. The formation of the fibrin threads is the result of what is called the coagulation cascade: a process in which the clotting factors activate each other in a chain reaction in the last step of which the soluble fibrinogen is converted into insoluble fibrin.

The clotting process can also start if a blood vessel is damaged on the inner surface without there being an injury, such as, for example, in the case of atherosclerotic plaques. Then a blood clot (a thrombus) forms in a blood vessel

which hinders or obstructs the blood flow. If that happens in an artery of the heart, it can cause a myocardial infarction. In the brain it may result in a stroke. Blood clots can form in the arteries as well as in the veins, mainly in the 'deep' veins of the legs and in the small pelvis. If a fragment of a clot breaks off from a deep vein thrombosis (DVT) of this kind, the part that has become detached (an embolus) can be carried with the bloodstream and occlude an artery in the lungs (pulmonary embolism). In people with the heart rhythm disorder atrial fibrillation, there is the risk that a clot will form in the atrium of the heart; if a piece breaks off there it can travel to the brain or other organs and there cause an infarction.

2.2 Current treatment of thrombosis and embolism or an increased risk of thrombosis

People in whom deep vein thrombosis or pulmonary embolism is diagnosed are treated with vitamin K antagonists as they are known (and briefly with heparin). Of these vitamin K antagonists (hereinafter referred to as VKAs) phenprocoumon and acenocoumarol are used in the Netherlands whereas, outside the Netherlands, mostly warfarin is used. These substances inhibit the action of vitamin K in the liver. Vitamin K is an essential component in the formation of the so-called vitamin K-dependent clotting factors. As a result of this inhibition, there are fewer functional clotting factors in the blood. As a result, the blood clots more slowly. Therefore the thrombus does not grow any larger and can be dissolved by fibrinolysis without a new thrombus forming immediately. Depending on the indication, the treatment is continued for three to six months or even longer, sometimes even lifelong. People who are at considerably increased risk of thrombosis are also treated with anticoagulants. Among others, these are people who have recently undergone a major operation on the knee or hip, people with recurring venous thrombosis or pulmonary embolism, and people with chronic atrial fibrillation. It is not unusual for people to have to use VKAs for the rest of their lives, particularly people with atrial fibrillation.

2.2.1 Monitoring blood clotting

Because of the fact that VKAs reduce the function and lower the quantity of vitamin K-dependent clotting factors in the blood, there is the risk that blood clotting is inhibited too severely. This can result in severe bleeding. During the treatment, a careful balance must be maintained between too much inhibition,

with the risk of bleeding, or too little, with the risk of thrombosis.[1] Also the effect of a given dose is difficult to predict exactly: there are large differences in dosage between individuals and in the same individual over the course of time. Furthermore, VKAs are known to have many interactions with other drugs, as a result of which concomitant use with other medication can affect the anticoagulant effect. Because vitamin K is found in food, a vitamin K-rich or vitamin-K poor diet can affect the setting of the dosage of anticoagulant medication. People who use VKAs must therefore take into account what they eat and drink, and when prescribing other medication care must be taken to ensure that the drugs can be taken together with VKAs, or that, if necessary, the dosage of the VKAs is adjusted.

There is a laboratory test which can be used to measure the anticoagulant effect anticoagulantion on the blood following the use of VKAs: this is the *International Normalised Ratio* (INR). The INR is based on the measurement of the prothrombin time: after adding calcium and thromboplastin (tissue factor) to the test tube containing the patient's blood(plasma), the time that it takes for a clot to form is measured (in seconds). When using VKAs the prothrombin time is lengthened. Among other things, because there are many different thromboplastin reagents with different 'sensitivities', a method has been devised for standardising the test, in which the value measured in the patient is expressed as a fraction of the average value in healthy people, to which a correction factor is then applied.[2,3] By regularly determining the INR measured in this way, and if necessary adjusting the dosage of VKA, the risk of deviations of the INR downwards or upwards is limited. Depending on the indication for treatment, the aim is to keep the INR within a defined range. This is called the 'therapeutic range'.

What is best depends on the indication. As far as atrial fibrillation and the treatment of venous thrombosis and/or pulmonary embolism (VTE) are concerned, in many countries, including America and England, a therapeutic range of 2-3 has been chosen. The Netherlands deviates from this slightly with a wider range of 2-3.5. In the clinical studies on the NOACs, the range of 2-3 has been adhered to.

With a defined therapeutic range, it was also possible to create a yardstick for the quality of the monitoring of the anticoagulant treatment. In general the *time in therapeutic range* (TTR) is used for this, a term which stands for the time within which a person's INR is within the range. Different methods have been developed with which the TTR can be used as a quality indicator. One example is a statistical interpolation in which it is estimated for an individual patient how much of the time his or her INR falls within the therapeutic range (Rosendaal

method).[4] Alternatively, of all the measurements at a defined time (in different patients) it is calculated which percentage of the measurements were within the range (*cross section of the files* method) or which percentage of all measurements were within the range over a defined period. In all these methods no distinction is made between an excessively high INR (over-treatment) or an excessively low INR (under-treatment). The TTR is also used as a quality mark for, for example, an individual Thrombosis Service. It is clear from various observational studies that with a low TTR, the risk of bleeding or thrombosis and embolism is greater.[5-8]

2.2.2 Role of the Thrombosis Services

Due to the need to control (monitor) anticoagulant treatment with VKAs closely by measuring the INR and adjusting the dose, intensive supervision is necessary. In the Netherlands a system of Thrombosis Services has been set up for this. People who are treated with anticoagulants come to the closest Thrombosis Service at intervals where a blood sample is taken, the INR determined and when necessary any adjustment made to the dose (number of tablets per day). For people who find it difficult to get there, somebody comes from the Thrombosis Service to take blood at home. Some of the people, estimated to be around 10%, monitor their INR independently at home, with the supervision of a Thrombosis Service, in which they can also determine their dosage themselves. A national system of Thrombosis Services of this kind is relatively unique in the world. In other countries the monitoring is mostly done by the medical specialist who prescribes the treatment, or by an outpatients department in a hospital (see too below).

Virtually all Thrombosis Services are affiliated to the Federation of Dutch Thrombosis Services (FNT). The annual reports of the FNT give an overview of the services carried out and their quality. From the last annual report on the year 2010, it can be seen that rather more than 400,000 patients were treated in that year. The annual report also gives the reasons for treatment: atrial fibrillation in 58% of the patients, and VTE in 15%. In addition, there were people under treatment with an artificial valve (6%), for prophylaxis for a medical procedure (1%) or for a small number of other reasons (‘other’ arterial reasons) such as coronary syndromes or peripheral artery disease, which in themselves account for a further 20% of the total.

At the end of 2010 63 Services were affiliated to the FNT, two of which are in Spain and one is in Curaçao.[9] Approximately a third of the services are independent; a slightly larger number are established in a hospital; finally there

are Thrombosis Services which form part of a GP's laboratory.[10] The FNT has a system of accreditation of Thrombosis Services in conjunction with the Coordinating Committee for promoting the quality assurance of the laboratory study and the Accreditation Board. In 2009 51 of the Services were accredited.[10] Accreditation is not required in order to be recognised by the Ministry. The Services keep patient data in digital files and use software programs for calculating the correct dose. A dosing doctor ultimately gives the dosing advice. The annual reports of the FNT are drawn up with the help of the computer files of the Thrombosis Services. The most important quality yardstick reported on is the TTR, referred to above.

2.2.3 IGZ and RIVM reports

After the risks of anticoagulant treatment were pointed out in a number of reports, the Health Care Inspectorate (IGZ) carried out a study in conjunction with the National Institute for Public Health and the Environment (RIVM) in 2008-2009 into the bottlenecks in anticoagulant treatment, targeted mainly at the position of the Thrombosis Services. The reports which gave cause for concern are the HARM study (2006),[11] the IPCI study (2006),[12] and the IGZ study into patient safety (2004).[13]

The main aspect dealt with in the IGZ/RIVM study was that of anticoagulant treatment as an example of multidisciplinary disease management.[10,14] In this case the multidisciplinary care team comprises the group of different carers which a patient using the VKAs may come into contact with, including medical specialists in the hospital, the general practitioner, workers in the Thrombosis Service, the nurse practitioner, the pharmacist, home care and the dentist. Risks arise when communication and coordination between the various carers is not going well. The reports from IGZ and RIVM concluded that there were considerable shortcomings here. The IGZ report was accompanied by advice to the Minister of Health, Welfare and Sport to set up a national multidisciplinary steering committee on thrombosis care. The IGZ also set a number of requirements which had to be met before July 2012. In the meantime this steering committee has been set up and has started with drawing up a guideline.

2.3 A new generation of anticoagulants

The substance on which the VKAs' action is based, coumarin, was originally isolated from spoiled clover in hay. Its activity was discovered in America when in the 1930s massive haemorrhaging occurred in cattle which had eaten spoiled

clover: *spoiled sweet clover disease*. There is a good half a century of experience with coumarin derivatives. Because of the need for monitoring and the other disadvantages of using these drugs, there has always been a need for an alternative. For a few years now a number of new anticoagulants have been under development which have arisen from the greatly increased knowledge about the clotting process. Representatives of this new generation of drugs act at specific points in the clotting process, in particular certain reaction steps in the coagulation cascade. The products which are furthest along in the clinical development process are the direct thrombin inhibitors and the direct factor Xa inhibitors. The anticoagulant action of the direct thrombin inhibitors is based on inhibition of the formation of fibrin from fibrinogen under the effect of thrombin; the action of the factor Xa inhibitors is based on inhibition of the formation of thrombin from prothrombin under the influence of factor Xa. The clinical development of what was the 'front runner ' among these drugs, the thrombin inhibitor ximelagatran, has ended prematurely on account of side-effects on the liver.[15]

There are now four NOACs which are available for use in practice or will probably be registered shortly: dabigatran, rivaroxaban, apixaban, and edoxaban. Dabigatran is a direct thrombin inhibitor; the other three are direct factor Xa inhibitors. The most obvious advantage of these new drugs is that monitoring no longer appears to be necessary: in the clinical studies they were used with fixed doses and without monitoring. Moreover, they are possibly more effective and safer than the vitamin K antagonists. Dabigatran, rivaroxaban and apixaban are registered for the prevention of VTE in people who are undergoing an elective knee or hip replacement. The dosage is lower than if the NOACs are given for the treatment of VTE. In the Netherlands they are also included in the Drugs Reimbursement System (GVS) for this indication. Recently both dabigatran and rivaroxaban have also been registered for the indication 'prevention of stroke and systemic embolus in patients with non-valvular atrial fibrillation'. Rivaroxaban is also registered for the indication treatment of DVT and secondary prevention of VTE. The manufacturers of dabigatran and rivaroxaban have submitted an application to the minister to extend reimbursement to the indication prevention of stroke and systemic embolus in patients with non-valvular atrial fibrillation (and treatment/prevention of VTE for rivaroxaban) and to this end have submitted a dossier to the Health Care Insurance Board (CVZ) for assessment. This assessment is carried out by the Pharmaceutical Care Committee (CFH) of the CVZ.

2.4 Indications for which the NOACs provide an alternative

As has been stated, dabigatran and rivaroxaban have recently obtained registration for the indications atrial fibrillation and the treatment and prevention of VTE (dabigatran only for the first indication). Two indications are central in this advice. But to start with, the Committee names below the indication for which the first registration (and reimbursement) has been obtained, namely prophylaxis in major orthopaedic operations. Then it looks at atrial fibrillation and the significance and practice of anticoagulation in atrial fibrillation. Finally, the treatment and prophylaxis of VTE, other than after major orthopaedic operations, is discussed.

2.4.1 Prophylaxis against VTE in major orthopaedic operations

The first indication for which these drugs obtained registration was prophylaxis after major orthopaedic surgery, in particular hip and knee replacement operations. In the Netherlands rivaroxaban and dabigatran were included in the insured package for this indication in 2008 and apixaban in 2011. The Committee's advice does not go into any further detail on this indication. It is, however, important to say that, at the time, on the advice of the CFH and the CVZ, the Minister placed the drugs on the so-called list 2 of reimbursed drugs. That means that for each extension of the indication a new application has to be submitted by the manufacturer to the minister. Also, on writing out a prescription the doctor has to fill in a form giving the indication.

2.4.2 Atrial fibrillation

Atrial fibrillation is a disease of the heart in which the electrical activation of the heart muscle from the atria is very irregular; instead of the regular excitation from the sinus node, impulses come from different places in the atria. Due to this uncoordinated stimulus, the chambers of the heart contract irregularly, which is reflected in an irregular pulse, while the atria are mechanically ineffective. The symptoms may be mild, such as palpitations or becoming tired more quickly during exercise, or may even be absent altogether. The consequences of atrial fibrillation can also be very serious. The most feared complication is a stroke. Atrial fibrillation is estimated to increase the risk of stroke by a factor of five.[16] The most important reason for this is that blood stagnates in the motionless atria, which is accompanied by an increased tendency to clot as a result of which a clot

can form. A fragment can detach from a clot and block a blood vessel in the brain. The risk of this complication, however, depends on a number of other factors (including age and concomitant diseases). If the risk is moderately or seriously raised, it is recommended that people with atrial fibrillation are treated with anticoagulants (see more below).

Depending on the timescale, atrial fibrillation is classified into a number of types.[17,18] This classification has been changed a few times over the years. The most common classification now is into: 1) first attack; 2) paroxysmal atrial fibrillation, i.e. that attacks last no longer than 7 days; 3) persistent atrial fibrillation; 4) permanent (chronic) atrial fibrillation.

As referred to above, in 2010 in the Netherlands more than 230,000 people with atrial fibrillation were under treatment at the Thrombosis Services. The actual number of people with atrial fibrillation and at increased risk of stroke is probably higher. First of all, atrial fibrillation frequently remains undetected. Screening has established that approximately one third of the people who turn out to have atrial fibrillation had not had the condition diagnosed before. Secondly, it appears from research in various countries, including the Netherlands, that many people with atrial fibrillation who according to the guidelines would have to be treated with VKAs, were not treated.[19]

Atrial fibrillation frequently occurs among the older population. In England, for example, it has been estimated that 7.2% of people aged 65 or over have atrial fibrillation. [20] The residual lifetime risk of a 40-year-old ever having atrial fibrillation is estimated at 25%. As far as the Netherlands are concerned, 'the Rotterdam study' is an important source of insight into the prevalence of atrial fibrillation. This showed that the prevalence of the condition in the population of 55 and over is approximately 5.5%, rising with age to almost 18% in people aged 85 or over.[21,22] A good half of the patients are over 75. In Dutch general practice the prevalence among people aged 60 and over appears to be 5.1%.[23] A comprehensive overview of studies into the epidemiology of atrial fibrillation in the Netherlands can be found in the NHG standard Atrial fibrillation (in Dutch).[17]

People with atrial fibrillation are frequently under the treatment of a cardiologist, but some of the patients are treated by their general practitioner. At an early stage of the disease an attempt can be made to return the heart to sinus rhythm by administering an electric current. For this cardioversion patients are given anticoagulants, from approximately three weeks before the procedure to one month afterwards. The INR must be monitored for this and an off target value can be the reason for the procedure having to be deferred. If cardioversion has no chance of success, the patient is usually only treated with (anti-

arrhythmic) medication. In some cases catheter ablation is used with the aim of destoying the tissue spots that generate the abnormal electrical impulses from which the rhythm disorders come. In 2010 slightly more than two thousand catheter ablations were performed for the treatment of atrial fibrillation in the Netherlands, involving less than 1% of the number of patients.[24]

In all cases care has to be paid to anticoagulant treatment. The prevention of a stroke is generally seen as one of the main aims of the treatment.[25] The use of anticoagulant treatment using VKAs by people with atrial fibrillation lowers the risk of stroke by around two thirds.[26] Because the basic risk depends on a number of risk factors,[27] in people with a very low basic risk the disadvantages of the treatment do not outweigh the risk of a stroke. In people with a slightly raised risk, aspirin can also be prescribed instead of VKAs. In order to be able to make a choice between no anticoagulant treatment, aspirin or VKAs, a number of risk scores have been developed. The one most used at the moment is the $CHADS_2$ score. Each letter stands for a risk factor: Chronic heart failure, Hypertension, Age (≥75 years), Diabetes, and 'previous Stroke'. For each of the risk factors 1 point is scored if present, while 'previous stroke' scores double. The score is therefore a whole number between 0 and 6, and the higher the score, the greater the estimated risk of a stroke.[28] The European Society of Cardiology (ESC) has recently been advising the use of the $CHADS_2$-VASc score, a refinement of the $CHADS_2$.[29] Furthermore, these guidelines emphasise that before administering anticoagulants, a carefully considered assessment is to be made of the risk of bleeding. For this it is also recommended that use is made of a score, for example the HAS-BLED score, in which the letters also stand for the different risk-increasing factors (the H for 'Hypertension', the A for 'Abnormal renal/liver function', S for 'Stroke', B for 'Bleeding history or predisposition', L for 'Labile INR (TTR<60%), E for 'Elderly (>65 years)' and D for 'Drugs/alcohol (platelet inhibitors, NSAIDs, excessive use of alcohol, etc.)').[25,30]

Because of the disadvantages of anticoagulant treatment, alternatives have been sought. One possibility that has been introduced recently concerns a procedure carried out on the left auricle, which is the main reservoir in which blood clots can form. This can involve surgical resection or ligation of the auricle, or closure using a device via a catheter. The effectiveness of such techniques is, however, not yet sufficiently known and they are little used as yet.

Virtually all available AF guidelines recommend that no account should be taken of the type of atrial fibrillation in determining the indication for anticoagulant treatment.[18,27,31] Both the NHG standard and the CBO guideline are based on the $CHADS_2$ score, in which the NHG standard uses a slightly adapted version.[17]

Most Dutch cardiologists follow the ESC's guidelines, which are largely incorporated into the CBO guideline, but each year are adjusted in line with the latest knowledge.[18] The NHG standard recommends anticoagulant treatment with VKAs where there is a score of 2 or higher (corresponding to an annual risk of stroke of 4% or higher); the ESC guidelines recommend anticoagulant treatment with VKAs where there is a $CHADS_2$ score of 1 or higher.[18] The most recent ESC guideline does, however, pay a great deal of attention to a more detailed risk assessment.[18] The crux of this is first to find the patient who has a very small risk of stroke of almost 0% who does not need treatment, and then to decide on VKA treatment in all other cases; only in patients who have a CHADS2-VASc score of 1 can a choice be made between a VKA and aspirin, preference being for VKA.

2.4.3 *Venous thrombosis and (pulmonary)embolism*

The risk of dying after venous thrombosis is high. Approximately 20% of patients die within one year.[32] After a pulmonary embolism the risk of dying within three months is also around 20%.[32] The higher mortality rate is partly due to the fact that VTE can be the first sign of malignancy. But even if the patients who die from cancer are left out of consideration, the risk of dying within a year is still always around approximately 12%.[32,33]

Due to epidemiological research a great deal is known about the risk factors for having a VTE. In general, VTE is seen as a multicausal condition.[31,34] To a large extent these factors relate to "Virchow's triad" (damage to the vessel wall, stasis of the venous blood, increased coagulability of the blood). Known risk factors are trauma, surgical procedures, in particular hip or knee-replacement operations, admissions for serious internal conditions, immobilisation, pregnancy and childbirth, use of the contraceptive pill and cancer. The high risk after major orthopaedic operations is the reason that people are given prophylaxis with anticoagulants after hip or knee-replacement operations. A great deal of interest has been generated by the discovery of hereditary factors, such as factor V Leiden and the prothrombin mutation (20210A). In addition there are a number of other non-hereditary risk factors, varying from lifestyle to comorbidity. An important risk factor is having once had a VTE.[35] In the first three months after a VTE, the risk of a new VTE is greatly raised, with an (absolute) risk higher than 10%. After three months the risk falls to 2-10%.[31] Therefore in the case of a VTE, the treatment needs to be continued for some time after the acute phase.

The risk of thrombosis among the general population has been studied in a large prospective longitudinal study in the U.S. In this LITE study the incidence of a first VTE was 1.92 per 1,000 person years, with a higher incidence in men and rising with age. That is probably an under-estimate of the actual incidence because VTE can remain undetected.[36] Also, the Leiden Thrombophilia Study (LETS and the follow-on study MEGA) have provided a great deal of epidemiological knowledge.[37,38]

In venous thrombosis or pulmonary embolism, treatment is started with anticoagulants. Because it takes some time for the VKAs to 'work', heparin is started which works immediately. Heparin, or preferably low-molecular weight heparin (LMWH) administered subcutaneously, is given for at least five days until the INR is stable and is above 2.0 for two days.[31] The treatment with VKAs is continued for a period the length of which depends on the estimated risk of a new thrombosis or embolism, and can vary from 3 months to an undefined time. How long the treatment or secondary prevention with VKAs should be continued after a VTE is still, however, a matter for discussion. From a recent meta-analysis it was concluded that 3 months of treatment was sufficient, provided that there is no indication to continue the treatment for an unlimited period.[39] The risk of death does, however, remain increased up to at least 8 years after the first VTE.[40] Difficult decisions about continuing or stopping the treatment have to be made that hinge on a choice between two evils: recurring thrombosis or bleeding. In North America there is a strong tendency to treat patients with anticoagulants for the whole of their lives after a first 'spontaneous' VTE.[41] In Europe, and certainly also in the Netherlands, the attitude is far more reserved and relatively more wary of the risks of the treatment.

2.4.4 *Possible future indications*

Various clinical trials have been started in which the NOACs are tested for other indications in which an increased tendency to blood clotting plays an important role. As far as potential patient numbers are concerned, the largest of these are acute coronary syndrome (myocardial infarction and unstable angina pectoris). Possibly one or more of these agents will obtain registration for this indication shortly.

However, there are also indications for which VKAs, in any event for the time being, remain the preferred drug. This applies in particular to people who have an artificial heart valve. Furthermore, clinical trials have shown that some of the patients stop taking the NOACs for one reason or another. Finally there are contraindications to NOACs, such as severe kidney failure. Some people will

therefore continue to have VKAs indicated, and monitoring of the anticoagulant treatment will be needed.

2.5 Anticoagulant treatment in other countries

Specialised knowledge is needed for monitoring and adjusting the dosage of anticoagulant treatment with VKAs as well as laboratory facilities for measuring the INR. There are various ways in which monitoring the anticoagulant treatment can be organised. Internationally the following ways are used in practice. Firstly, the doctor in attendance can take responsibility for it himself, with the help of a laboratory. That can take place in a primary care setting (general practitioner or family physician), with a general practitioner's laboratory, or by a medical specialist with a hospital laboratory. The laboratory measures the INR and the doctor in attendance gives dosage advice and instructions to the patient. Secondly, the doctor in attendance can refer the patient to a specialised service. That may be an outpatient clinic at a hospital or a place outside the hospital, such as a Thrombosis Service (anti-coagulation clinic). Checking anticoagulation, giving dosage and other advice is then taken over entirely by the Service. Different people are responsible for dosage advice in a service of this kind: a specialist in internal medicine, a pharmacist, or a specialised nurse. Finally, for some time the patient himself has been able to monitor the anticoagulant treatment and determine the dose; this is mostly done with the help of a support service, such as the Thrombosis Service in the Netherlands.

In most countries there is a mixed system in which a combination of these forms can be found. In the US and in the UK, for example, many patients are treated with these drugs in primary care (community based management), where there are also Thrombosis Services and anticoagulant monitoring in a hospital.[42-44] Only in the Netherlands and in Italy has it been decided to set up a national system of Thrombosis Services. This has arisen due to the desire and belief that a specialist service leads to the best results and that this be available for everyone. Whether it is actually the case that monitoring anticoagulant care in the Netherlands is on average better than in other countries has never been investigated directly. However, an observational (non-randomised) study has been carried out into the effect of the way in which anticoagulant monitoring is organised and the outcomes, in particular the TTR [measurement of time within therapeutic range]. In evaluating the role of the way in which anticoagulant monitoring is organised, account must always be taken of the fact that the TTR is also dependent on a number of patient-related characteristics.[3] The same quality of control can therefore lead to other results in different patient groups.

It has been found from different studies that people with access to a specialised service are less often under-treated, and that the TTR is better.[44-46] The TTR in specialised services appears in retrospective studies to be better than if monitoring is done by general practitioners.[3,47] A systematic review found that a specialised service (anti-coagulation clinic) produces better results than a hospital's outpatients clinic (clinic-based testing).[46] Two relatively short prospective randomised studies, however, found no difference in outcome between specialised services and monitoring conducted by the doctor in attendance.[47,48] Good results are obtained with self-testing too.[49,50] However, self-testing is only reserved for a group of motivated and relatively healthy people.

It is to be expected that different ways of organising anticoagulant monitoring is also associated with differences in costs. Thus in the UK, which has a healthcare system which is reasonably comparable to the one in the Netherlands, there are great variations in the costs of monitoring anticoagulant treatment.[51,52] A study by the English NICE Institute estimated the annual costs per patient of the anticoagulant monitoring carried out in primary care to be on average £322 (€383) and in secondary care of £565 (€672).[53] In health economic analyses, estimates of annual costs vary from $545 (€420) in America,[54] Can$405 (€308) in Canada,[55] and in the UK around £200 (€238),[56] or £415 (€494) in another study respectively.[57]

The development and introduction of the INR in the 1970s and 1980s resulted from a perceived need for international cooperation and standardisation.[58] The importance of a standardised test for the treatment of the patient and for the exchange of scientific data is self-evident. However, there appear to be not only differences between countries and within countries in how anticoagulant treatment is organised but also in the way in which anticoagulant monitoring is carried out.[59]

Of particular importance for the interpretation of the clinical studies on the NOACs are the results with anticoagulant treatment with VKAs which are conducted in the circumstances under which such studies are carried out. These phase 3 randomised clinical studies are designed and carried out according to a strict protocol. It may be expected that the quality of the treatment, as evaluated according to the TTR, will be better than what is seen in daily practice. This expectation is confirmed by a meta-analysis which revealed that the TTRs in clinical studies were comparable with those obtained in specialist centres (*anti-coagulation clinics*).[46] It has also been found, however, that there can be a great

difference within clinical studies in the TTR between participating centres and countries. An analysis of the INR data of a study in which a VKA was compared with clopidogrel plus aspirin in atrial fibrillation showed, for example, that the TTR per centre varied from less than 50% to more than 75%.[60] Furthermore, it was inferred from the data that the TTR must be at least between 58% and 65% before the VKA treatment shows better results than the comparative treatment with clopidogrel and aspirin. This also shows that the added value of a new treatment such as that with a NOAC compared with a VKA depends on the quality of the monitoring of the anticoagulant treatment.

This great variation in the quality of the anticoagulant treatment between centres and countries was also seen in the clinical studies with the NOACs. Thus, in the RE-LY trial, which will be examined in greater detail in Section 3.3.1, the TTR proved to vary from 44% in Taiwan to 77% in Sweden. These figures are not, however, by definition, representative of the monitoring of anticoagulant treatment in the various countries. For centres are selected for participation in clinical trials. Moreover, strict quality control is carried out. The differences between countries which are seen in clinical studies are therefore not intrinsically representative of the clinical practice in those countries.

To summarise, the following conclusions can be drawn. First of all there are different ways in which the monitoring of anticoagulant treatment can be organised. Countries, and regions within countries, differ in the degrees to which these ways are represented and in the costs of monitoring the anticoagulant treatment. From a number of studies it can be seen that a service specialising in anticoagulant treatment leads to the best results. Secondly, the quality of the monitoring of anticoagulant treatment as measured with the TTR is an important factor which determines what the added value of an alternative to the VKA treatment is. Clinical studies have shown that there was a great difference in the quality of the VKA treatment. The randomised clinical trial situation is, however, not representative of the quality of treatment in a country or region.

Chapter 3

The clinical studies into the NOACs

This section describes the clinical experience with the NOACs. It deals with the clinical trials which were conducted in order to obtain market authorisation: the phase 3 randomised clinical trials. To begin with, the Committee deals in brief with the design of the studies and then describes the clinical experiences in the indication atrial fibrillation and the indication VTE. Annex C contains a comprehensive overview of the studies.

3.1 Registrations

Registration for a new medicine is obtained after approval by the competent agencies. In America it is the FDA (Food and Drug Administration) and in Europe it is the EMA (European Medicines Agency). Registration is mainly for a clearly defined indication for which the drug can be prescribed. After registration a drug can be eligible for reimbursement. In the Netherlands, after a request submitted for the purpose, the Minister decides whether to include a drug in the GVS (which implies that the drug is reimbursed), and the way in which it is reimbursed. The Minister decides on this on the basis of advice from the CFH of the CVZ. An overview of the current registration status and the reimbursement status in the Netherlands for the different drugs is given in Table 1.

Table 1 Overview of registrations and reimbursement status

Drug (Manufacturer)	FDA (USA)	EMA (EU)	CFH (NL)
Dabigatran (Boehringer Ingelheim)	Prevention of stroke and systemic embolism in atrial fibrillation (since October 2010) [61,62]	Indication: VTE Prevention after hip or knee operation [63] Indication: atrial fibrillation [64]	Included in Medicines Reimbursement System (GVS) in Annex 2 for indication: Prevention of VTE after hip or knee operation[65,66] [a]
Rivaroxaban (Bayer)	Prevention of VTE after hip or knee replacement operations (July 2011) [67] Indication: atrial fibrillation (November 2011) [68]	Indication: VTE Prevention after hip or knee operation (September 2008) [69] Indication: atrial fibrillation (December 2011) [64,69,70] Treatment of DVT and prevention of recurrence of VTE and PE (December 2011) [64,69,71]	Included in GVS in Annex 2 for indication: hip or knee operation (February 2009) [72] [a]
Apixaban (Pfizer/Bristol-Myers Squibb)	b	Indication: hip or knee operation (May 2011) [73,74]	Included in Annex 2 for indication: Prevention VTE after hip or knee operation (October 2011) [75]
Edoxaban (Daiichi-Sankyo)	None yet	None yet [c]	

a Initially put on list (Annex) 1B but because of the risk of 'off-label' use was transferred to list 2.
b Given the status "priority review" by the FDA for the indication atrial fibrillation. Decision is expected in spring 2012.
c Only still registered in Japan for the indication: knee and hip.

3.2 The design of the clinical trials

In general the phase 3 clinical trials are planned, designed and conducted in a standardised way. In the case of the NOACs there are, however, a number of aspects which merit attention.

First of all dabigatran and rivaroxaban have been registered for the indication prevention of stroke and embolism in atrial fibrillation. In both cases this was on the basis of one large, international, randomised trial. Mostly the registration authorities require two large trials per indication, but the international registration authorities use criteria according to which, under certain circumstances, one large study can also be sufficient. Furthermore, the studies on dabigatran in atrial fibrillation and that on rivaroxaban in the acute treatment of VTE were not designed to be 'double-blind'. A blind trial was difficult to carry out because the control group was treated with VKAs and therefore had to be regularly monitored. A solution to this problem was found by carrying out sham INR

controls and a number of studies were indeed double-blind. Furthermore, the studies were carried out with a control group which received an 'active' treatment. The people in the control group were given the treatment which was regarded as the best option at the time. In the case of atrial fibrillation, in cases where there, treatment with VKAs is the standard treatment when there is a moderate to seriously raised risk of stroke. Because of the comparison with active treatment, and the expectation that the efficacy of the new drug would not be greater but that there could perhaps be a benefit to health due to greater safety and greater ease of use, the statistical analysis was directed at demonstrating equivalence. Hence it did not need to be shown that the new drug was better. According to this study design (*non-inferiority design*), the results of the comparison may be less favourable for the new drug, but not more than a limit given beforehand (the '*non-inferiority margin* of the 95% confidence interval').[76-78]

3.3 Atrial fibrillation

This section gives an overview of the studies published so far for the indication atrial fibrillation. All trials included patients with non-valvular atrial fibrillation at increased risk ($CHADS_2$ score of at least 1). Only the most important results are listed. A more extensive overview of the results can be found in Annex C.

3.3.1 Dabigatran: RE-LY

The study with which dabigatran obtained registration in Europe is the RE-LY study, as it is known. In all, 18,113 patients in 44 countries were included in the study in which the patients received, after randomisation, a dose of 2 x 150 mg per day dabigatran, dabigatran at a dose of 2 x 110 mg per day, or warfarin.[79] The three groups were monitored for two years (median) and after this period the outcomes were compared. Two types of outcomes were defined beforehand to serve as a yardstick for comparison, the aim of which was to show that dabigatran is not inferior to VKAs. The criterion for efficacy was how many people suffered a stroke or an embolism; the criterion for safety was how many people suffered a serious haemorrhage (for an overview of the outcomes, see Table 7 in Annex C). From the statistical analysis of the outcomes the authors of the article in which the results were published concluded that dabigatran 2 x 150 mg was superior in terms of efficacy, with a relative risk of 0.66 (confidence interval (CI): 0.53-0.82); as far as safety was concerned, there was no significant difference: 0.93 (0.81-1.07).[79] Also fewer people died, but that difference was not statistically significant. Furthermore, it is important that the number of

cerebral haemorrhages in the dabigatran users was a good half less (0.30% per year versus 0.74% per year; relative risk 0.40 (0.27-0.60)) than in the VKA users. On the other hand, more gastro-intestinal haemorrhaging was seen (1.51% per year versus 1.02% per year, relative risk 1.50 (1.19-1.89). Also there were significantly more myocardial infarctions among dabigatran users (0.74% per year versus 0.53% per year; p=0.049). In a later update of the follow-up this was no longer statistically significant.[80] Furthermore, there was no difference if all cardiac events (including unstable angina pectoris, procedures such as PCI and sudden death) were considered together.[86] A recent meta-analysis by Uchino et al. concluded, however, that there are clear signs of a higher incidence of myocardial infarction in dabigatran users than in VKA users.[81] This may therefore indicate that dabigatran offers less protection against myocardial infarction than VKAs, for which this protection is known.[82]

The results for the lower dose (2 x 110 mg daily) were between those of the higher dosage and VKAs and led to the conclusion that, at this dose, dabigatran was not inferior to VKAs. The FDA decided to only register the 150 mg dosage because analyses of the RE-LY study did not identify any subgroup which would benefit from the lower dosage compared with the higher dosage. Moreover, the FDA recommended the marketing of 75 mg tablets, for dosage of 75 mg twice daily to people with severe renal function disorders, a group which was excluded from participation in the study.[83]

In addition to this main publication, a more detailed analysis of the same data was also published by Wallentin et al.[84] A central question in this was whether there was a difference in the results if the quality of care was looked at, measured by the TTR. The mean TTR per patient was 64.4%. The outcomes were connected with the TTR quartile: more strokes and embolisms, the lower the TTR was, but as far as bleeding was concerned there was no clear connection. However, because the TTR depends not only on the quality of care but also on a number of the patient's characteristics, which in turn also influence the effect of dabigatran, no valid comparison can be made on the basis of individual TTR values (iTTR). Wallentin et al therefore calculated the mean TTRs per participating centre (cTTRs), which was the basic unit for the randomisation procedure. If it is assumed that, centre by centre, patient groups do not differ very much one from the other in terms of distribution of patient characteristics, the cTTR would be a good measure of the quality of care. There proved to be a great difference in the average TTRs per centre and per country, varying from 44% in Taiwan to 77% in Sweden. The analysis revealed that the efficacy varied according to the cTTR. Proceeding per quartile from 'poorer' to 'better', the *hazard ratios* for the primary end point (stroke or systemic embolus) were: 0.57

(0.37-0.88), 0.50 (0.33-0.77), 0.69 (0.44-1.09), 0.95 (0.61-1.48). In the best half of the centres there was therefore no evident superiority. The authors concluded that the quality of care has an effect on the extent to which the NOACs offer advantages: 'these results show that local standards of care affect the benefits of use of new treatment alternatives'.

A sub-group which deserves special attention concerns the patients who had had an earlier stroke or a TIA, which is the case in approximately 30% of all strokes.[85] Not only is the risk of a (new) stroke greater in these patients, as is apparent in the $CHADS_2$ score, but they are also at increased risk of intracranial haemorrhaging and in general the strokes are more severe than earlier strokes. Moreover, in some of these patients the use of VKAs is difficult because of the damage resulting from the stroke. A separate analysis in the group of patients in the RE-LY study with an earlier stroke or TIA (3,623 of the 18,113 participants) showed results which were comparable with the results in people without an earlier stroke or TIA.[86] However, patients who had had a TIA or a stroke in the previous two weeks were excluded from participating, so that the study only offered limited insight into the effectiveness in the acute phase after a stroke (defined as the first 90 days after a stroke[85]).

The American College of Chest Physicians 2012 guideline recommends dabigatran above VKAs, with a recommendation level of 2B.[27] This means a weak recommendation with moderate-quality evidence.

3.3.2 Rivaroxaban: ROCKET-AF

ROCKET-AF was a double-blind study involving 14,264 patients in 45 countries, in which the patients who were given rivaroxaban (20 mg per day) were also 'monitored', with sham controls. The primary end point for efficacy was the same as in the RE-LY study. The 'non-inferiority condition' was amply met. However, superiority was not demonstrated: the hazard ratio in the people who were given rivaroxaban, calculated on the basis of 'intention-to-treat', was 0.88 (0.74-1.03). As far as safety was concerned there was no difference in the occurrence of bleeding (severe bleeding or clinically relevant minor bleeding): the hazard ratio was 1.03 (0.96-1.11). With rivaroxaban too, however, significantly less intracranial haemorrhaging was seen (0.5% versus 0.7%; hazard ratio 0.67 (0.47-0.93), p=0.02).

At 55% the mean TTR in ROCKET-AF was considerably lower than the 64.4% in the RE-LY study.[87]

A separate analysis was also carried out with the data of this study for the patients who had already had a stroke or TIA.[85,88] In accordance with the on average far higher $CHADS_2$ score among the participants of this study compared with the RE-LY study (and the ARISTOTLE study, discussed below), the group witha previous stroke or TIA was far larger than the group in the RE-LY trial. In this case too the results were comparable with those in patients without a history of stroke or TIA.

3.3.3 *Apixaban: ARISTOTLE*

Apixaban too was compared with VKAs in a double-blind phase 3 clinical trial, the ARISTOTLE study, in a dose of 5 mg twice a day.[89] 18,201 patients were included who were monitored for 1.8 years (median). The primary efficacy end point of stroke (ischaemic or haemorrhagic) or systemic embolism, occurred significantly less frequently in the group of people who were treated with apixaban than in the group treated with VKAs, with a hazard ratio of 0.79 (0.66-0.95). The safety endpoint of major bleeding too occurred significantly less in the group treated with apixaban, with a hazard ratio of 0.69 (0.60-0.80). Finally a significantly lower mortality rate was also seen, with a hazard ratio of 0.89 (0.80-0.99).

In the publication on the results of the study a subgroup analysis was also presented in which, among other things, it was investigated whether there was a difference in effects in people without or with a history of earlier stroke or TIA. The statistical test for this was negative (no difference). In another clinical study, the AVERROES trial, efficacy and safety of apixaban was also investigated in patients with a history of stroke or TIA.[79,85] This involved people who were regarded as being unsuitable for treatment with VKAs, which is a different (but not yet less important) indication than that for which dabigatran and rivaroxaban have obtained registration.

3.3.4 *Edoxaban: ENGAGE AF-TIMI 48*

Efficacy and safety of edoxaban are investigated in the ENGAGE AF-TIMI 48 study.[90] The results of this have not yet been published.

3.3.5 *Overview*

Table 2 gives a brief overview of the results of the clinical studies. A more extensive overview can be found in Table 7 of Annex C.

Table 2 Efficacy and safety compared with VKAs in atrial fibrillation.

Drug	Study	Efficacy[a]	Safety[a]
dabigatran [b]	RE-LY	0.66 (0.53-0.82)	0.93 (0.81-1.07)
rivaroxaban	ROCKET-AF	0.88 (0.74-1.03)	1.03 (0,96-1.11)
apixaban	ARISTOTLE	0.79 (0.66-0.95)	0.69 (0.60-0.80)
edoxaban	ENGAGE AF-TIMI 48	-	-

[a] Efficacy and safety are shown as relative risks (hazard ratios, with 95% confidence intervals) of the new drug versus VKAs for the primary endpoints of the clinical studies.
[b] For dabigatran only the results for the dosage of 150 mg twice a day are given.

3.4 Venous thrombosis and pulmonary embolism

In this section only the studies published results are summarised. The studies for which the results have to date been exclusively presented at conferences are referred to but not discussed further. A distinction is made between the 'acute' treatment of VTE, the first months, and a treatment continuing after this period. Most clinical studies consist of a part which evaluates the acute treatment and a follow-up study relating to the continuing treatment. The studies on the acute treatment were designed according to a *non-inferiority design* in comparison with VKAs; the studies into continuing treatment were designed either as superiority studies compared with placebo, or as non-inferiority study compared with VKAs.

3.4.1 Dabigatran: RE-COVER, RE-COVER2, RE-MEDY and RE-SONATE

The value of dabigatran for the acute treatment of VTE compared with VKAs was investigated in the RE-COVER study.[91] In the double-blind study involving 2,539 patients with acute VTE the patients were treated for six months with 2 x 150 mg dabigatran daily, after first being treated with enoxaparin for five to ten days. The primary end point as regards efficacy was the onset of VTE or death related to it. This occurred in 2.4% of the patients who were treated with dabigatran, versus 2.1% in the control group, a hazard ratio of 1.10 (0.65-1.84), in which dabigatran was found to be non-inferior. The primary end point for safety, major bleeding, occurred in 1.6% of the dabigatran users versus 1.9% in the control group, a hazard ratio of 0.82 (0.4-1.48). There was no significant difference in the mortality rate.

Although it was shown with this study that dabigatran was non-inferior to VKAs for this indication, a second study was started at the request of the FDA.[92] The reason for this was that due to the low number of observed events, it was not

feasible to carry out subgroup analyses. Furthermore, it is not unlikely that the FDA questioned the high upper limits of the confidence intervals (1.84 and 1.48 respectively) and regarded the risk of a possibly poorer result as too high. The RE-COVER 2 study was of an identical design. The results were recently presented at the annual conference of the American Society of Hematology in December 2011.[93] The efficacy end point occurred in 2.4% in the dabigatran group, versus 2.2% in the control group, a non-inferior hazard ratio again of 1.08 (0.64-1.80); the hazard ratio for the safety end point was 0.69 (0.36-1.32). However, the study has not yet been published.

The efficacy and safety of dabigatran in continued treatment were investigated in the RE-SONATE and the RE-MEDY study. In the RE-SONATE study, after six to eighteen months of 'usual treatment', almost 1,500 patients were randomised to six months of follow-up treatment with placebo or dabigatran (2 x 150 mg). In the RE-MEDY study, after three to twelve months of 'usual' treatment, almost 3,000 patients were randomised to six to thirty- six months of follow-up treatment with dabigatran (2 x 150 mg) or VKAs. Provisional results for these studies were presented recently (end of July 2011) in Kyoto at the biennial conference of the International Society on Thrombosis and Haemostasis. The comparison with placebo (RE-SONATE) revealed a strong efficacy of treatment: the primary end point of a recurring VTE occurred in 0.4% in the dabigatran arm, versus 5.6% in the control group, which corresponded to a hazard ratio of 0.08 (0.02-0.25), or a reduction in risk of 92%. The risk of major bleeding was greater (0.39% versus 0%; confidence interval hazard ratio: 0.04-1.05).[94] The comparison with warfarin in the RE-MEDY study resulted in the occurrence of the primary end point of a recurring VTE in 1.8% in the dabigatran group versus 1.3% in the warfarin group, which corresponded to a hazard ratio of 1.44 (0.78-2.64), which fell within the statistical limits for non-inferiority. Major bleeding occurred in 0.9% of the people who used dabigatran, versus 1.8% in the warfarin users, a hazard ratio of 0.52 (0.27-1.01). Statistically significantly more myocardial infarctions were seen in the group treated with dabigatran.[95] For these two studies as well, official publications have not appeared yet.

3.4.2 Rivaroxaban: EINSTEIN-DVT, EINSTEIN-PE and EINSTEIN Extension

With rivaroxaban too phase 3 clinical studies have been carried out into efficacy and safety in both acute and in continued treatment. The EINSTEIN-DVT trial was a non-blinded (open label) study in which 3,449 patients with acute DVT (no symptomatic pulmonary embolism) were randomised to rivaroxaban (15 mg

2 dd for 3 weeks, followed by 20 mg 1 dd) or VKAs (with subcutaneous enoxaparin for the first days), for three months, six months, or twelve months.[96] A particular feature of the study was that the people who were treated with rivaroxaban in the initial phase were not treated with enoxaparin, as in the dabigatran studies. The primary end point for efficacy, recurring VTE, occurred in 2.1% in the rivaroxaban group versus 3.0% in the control group. The hazard ratio of 0.68 (0.44-1.04) clearly qualified as non-inferior. The primary end point for safety was the occurrence of major bleeding or minor bleeding considered to be clinically relevant. This end point was seen just as frequently in both groups (8.1%), corresponding to a hazard ratio of 0.97 (0.76-1.22).

The EINSTEIN-PE trial was designed in a virtually identical way to the EINSTEIN-DVT trial, but with the difference that the criterion for participation was pulmonary embolism (with symptoms) instead of a DVT. There were 4,832 participants, 2,419 of which were given rivaroxaban (also again without temporary enoxaparin), and 1,413 VKAs, the first days in combination with enoxaparin. The primary efficacy end point of 'first recurring VTE' occurred in 2.1% in the rivaroxaban group versus 1.8% in the control group, a hazard ratio of 1.12 (0.75-1.68). The primary safety end point of the occurrence of major or clinically relevant bleeding occurred in 10.3% of the rivaroxaban users versus 11.4% in the control group, a hazard ratio of 0.90 (0.76-1.07).

The double-blind designed EINSTEIN-Extension study included 1,196 patients, some of which participated in the EINSTEIN-DVT study and had been treated for DVT for six to twelve months with rivaroxaban or VKAs. The patients were randomised to thirty-six months of continued treatment or placebo.[96] The end points for efficacy were the same as in the EINSTEIN-DVT and EINSTEIN-PE study, but for safety only the occurrence of major bleeding was a primary end point. The efficacy end point occurred in 1.3% in the rivaroxaban group versus 7.1% in the placebo group, a hazard ratio of 0.18 (0.09-0.39) clearly to the advantage of rivaroxaban. There were more bleedings among the rivaroxaban users (4 in total (0.7%) compared with 0 in the placebo group).

In the study into continued treatment in which a comparison was made with placebo, a combined end point was of particular interest, defined as *net clinical benefit*: the occurrence of either the primary end point of efficacy, or the primary end point of safety. After all, with continued treatment, the most important question at the moment is whether the risks of treatment outweigh the risks of no anticoagulant treatment; in America there is a tendency to continue anticoagulant treatment for a long time, while in Europe there is less of an inclination to do so. In the EINSTEIN Extension study, the hazard ratio for the occurrence of the 'net

health benefit end point' was 0.28 (0.15-0.53). In other words: the treatment offered clear advantages in this study.

3.4.3 *Apixaban and edoxaban*

The studies for apixaban and edoxaban have not yet been completed. These are the AMPLIFY and AMPLIFY-extension studies for apixaban, and the Hokusai study for edoxaban.

3.4.4 *Overview*

The results for the clinical studies into acute treatment of VTE are summarised in Table 3 below.

Table 3 Efficacy and safety in acute treatment of VTE.

Drug	Study	Efficacy [a]	Safety [a]
dabigatran	RECOVER	1.10 (0.65-1.84)	0.82 (0.45-1.48)
	RECOVER 2	-	-
rivaroxaban	EINSTEIN-DVT	0.68 (0.44-1.04)	0.97 (0.76-1.22)
	EINSTEIN-PE	1.12 (0.75-1.68)	0.90 (0.76-1.07)
apixaban	AMPLIFY	-	-
edoxaban	Hokusai	-	-

[a] Efficacy and safety are shown as relative risks (hazard ratios, with 95% confidence intervals) of the new drug versus VKAs for the primary end points of the clinical studies.

3.5 Conclusions on the efficacy and safety of the NOACs

As regards the indication atrial fibrillation, the Committee considers that dabigatran, in the dosage of 150 mg 2 dd, rivaroxaban and apixaban are at least as effective and safe as VKAs in the context of the published studies. Dabigatran is possibly even more effective than VKA treatment – a judgement on this is, however, made difficult by the difference in the quality of the VKA monitoring and VKA dosing in the control group. Apixaban appears to be more effective and safer than VKAs. It is also important that the NOACs lead to fewer intracranial haemorrhages. Gastrointestinal haemorrhages do, however, occur more often. The risk of myocardial infarction appears to be raised with the use of dabigatran compared with the use of VKAs.

There is still a lack of clarity about the efficacy and safety in patients who have recently had a stroke or TIA. On the one hand, the numbers of patients in whom this was the case were relatively small in the clinical studies; on the other,

this category of patients were partially excluded from participation, and both the relevant clinical events (TIA/stroke), and the time between event and start of the treatment, were not defined sharply enough for this clinical question.

As regards the indication VTE, the Committee judges that in the context of the published clinical studies, dabigatran and rivaroxaban are just as effective and safe in the acute treatment of VTE as VKAs. An important advantage of rivaroxaban is that the patient does not need to be treated initially with low-molecular-weight heparins (LMWH).

Chapter 4

Efficacy and safety in everyday clinical practice

Experience with the NOACs in practice is limited compared with the half a century of experience with VKAs. Also, a controlled clinical trial can never automatically be seen as being representative of everyday clinical practice, and that is certainly also true for this risky type of medication. In addition, there are still a number of problems concerning safety that are inherent to the NOACs. In this section the Committee looks in further detail at aspects of the NOACs that need to be carefully assessedl before they can be used on a large scale.

4.1 How representative were the clinical trials?

Clinical trials differ from 'ordinary' everyday practice in important respects. The group of patients in a phase III randomised clinical trial (RCT) is never entirely representative of the target group for which the treatment is intended. Firstly this is because participation in a clinical trial requires a certain 'motivation', and secondly because for participation in a trial stricter exclusion criteria are applied than for use in practice. In the case of anticoagulants this means in particular that patients with an increased tendency to bleeding are excluded from taking part, i.e. precisely those patients who are at the greatest risk of complications from the medication.[97]

Experience in other countries where the NOACs have already been introduced shows that there are concerns about safety in everyday prescribing practice. For example there have been many reports of bleeding in countries

where the drugs have already been on the market for quite a long time.[98] Because VKAs also cause bleeding, it is difficult to assess whether the number of cases of bleeding is a cause for concern.[98] In any event the American FDA has announced that extra caution should be exercised.[99] Also, a number of cases have been reported in the specialist literature that have led to questions about safety. Among other things the lack of an antidote in emergency situations plays a part in this.[100] Not knowing the effects of the NOACs in specific clinical situations, such as the acute treatment of a stroke, is also a reason for doubts.[101-103]

A second important reason for looking critically at the representativeness of the clinical trials is particularly relevant for the situation in the Netherlands. In the description of the RCTs it has already been pointed out that there was a great difference in TTR percentages between centres and countries. A better quality of the control of the anticoagulant treatment means that 'the bar is higher' for a new drug to be as good or better. If it is assumed that in the Netherlands the monitoring of the anticoagulant treatment is of good quality as a result of the system of Thrombosis Services covering the whole of the country, this could mean that the comparison in the Netherlands ends up as being less favourable for the NOACs, measured both by clinical end points and by cost-effectiveness. Extrapolation to the specific situation in the Netherlands would therefore be desirable. A direct comparison of the quality of the monitoring of the anticoagulant treatment between the clinical trials and the Dutch Thrombosis Services is difficult however.

The Committee considered the ways in which an extrapolation could be made to the specific situation in the Netherlands. This exercise led to the following considerations.

- The VKA regimen in the clinical studies was different to what is usual in the Netherlands. Apart from the use of phenprocoumon or acenocoumarol instead of warfarin, the defined therapeutic range in the Netherlands is wider (2-3.5 versus 2-3 in the RCTs). This makes it difficult to compare TTRs in the Netherlands, as an approximation for the quality of the treatment, with those in the RCTs. To analyse the Dutch data again with the 2-3 range as the target is not valid, because the monitoring itself was aimed at a different target range. An alternative is to look at outcomes of the treatment, in particular the occurrence of serious bleeding or strokes. The incidence estimates derived from this could then be compared with those in the warfarin group in the RCTs. There is a study available that provides an insight into the outcomes with anticoagulant treatment in the Netherlands.[7] A comparison of the incidence figures in this study with those of the VKA arms in the RCTs suggests that the Dutch VKA regimen is better than that of the

RCTs and that the difference in favour of the NOACs could be less, or could disappear. For example, in the Dutch study the incidence of serious bleeding in people with atrial fibrillation treated with VKA was 2.9 (2.3-3.5) per 100 patient-years.[7] That is low even in comparison with the estimate of 3.11 for the best (fourth) cTTR quartile in the RE-LY-study.[84] For the efficacy end point in the Dutch study this was 1.4 (1.0-1.9) (including myocardial infarction), corresponding to a value between that for the third (1.51) and the fourth (1.34) best quartile (excluding myocardial infarction) in the RE-LY-study.

- However, against this comparison there are important objections to be made regarding the methodology. The outcomes depend not only on the TTR, but also on the basic risk of the treated population. Conversely, the latter is also a determinant of the TTR.

The Committee concludes that in the context of the clinical studies the drugs have proved their added value. However, there continues to be uncertainty about their added value in relation to the treatment with VKAs in Dutch practice at the present time.

4.2 Reversal of the anticoagulation

In the event of an emergency, such as an accident or the need for an emergency operation, the action of VKAs can be stopped by the administration of vitamin K (acts slowly) or Prothrombin Complex Concentrate (PCC, acts immediately).

At the moment there are no registered drugs for which it has been established that they can stop the action of the NOACs quickly and satisfactorily. The only options available now are stopping the medication, or in the case of dabigatran possibly dialysis, but these methods are not sufficient in all cases.

Research is, however, being carried out into possible antidotes. PCC that is also used to stop the anticoagulant action of VKAs is a serious candidate. PCC contains high concentrations of four clotting factors – factor II, factor VII, factor IX and factor X. In theory the concentrate could ‘competitively inhibit’ the inhibitors of the coagulation (dabigatran, rivaroxaban, and others). In a small study with healthy test subjects it was seen that the effect of rivaroxaban as measured with coagulation tests can be reversed immediately with PCC, but not that of dabigatran.[104] The fact that the result of the coagulation test returns to within normal values does not mean, however, that a haemorrhage also stops, or that the clotting in the body is normal again. More research is needed in order to establish whether treatment with PCC in a clinical setting is beneficial.

Apart from the problem of reversal of the anticoagulation it can also happen that for one or a number of reasons a patient is unable to tolerate dabigatran or rivaroxaban and has to switch to VKAs. Because it takes about five days for the effect of VKAs to be sufficient and in the meantime the NOAC has to leave the body, there needs to be a strategy for enabling this transition to take place smoothly. There is no consensus on this yet, although recommendations have indeed been made.[105] In any event, expertise is needed for this. Conversely, the switch from VKAs to NOACs also has to be made carefully.

4.3 Testing of the effect

A properly validated test that can be used routinely to measure the anticoagulant effect of the NOACs, such as the INR with the use of VKAs, is not available at the moment. Tests are available, however, that do provide an insight into the anticoagulant effect.

Examples of tests with which the effect of dabigatran can be measured are the ecarin clotting time, the thrombin time, and a commercial test, The Hemoclot® diluted Thrombin Inhibitor assay (Hyphen BioMed, Neuville-s ur-Oise, France). The routinely used activated partial thromboplastin time (aPTT) is also an option. In patients who take therapeutic doses of dabigatran the aPTT is prolonged one and a half to two times. At higher dosages however, this test becomes insensitive and no longer correlates with the dabigatran plasma levels.[106,107] With the use of rivaroxaban the prothrombin time is extended. There is even a linear dose-response relationship. Its coefficient depends, however, on the specific reagent that is used and therefore has to be calibrated first, in a similar manner to that in which the INR is calculated from the effect of VKAs on the prothrombin time.[105,108] Also an adjusted anti-factor Xa test can be used like that with which the activity of heparin is measured. However, for an accurate estimate of the amount of rivaroxaban in the blood a test developed (calibrated) specially for rivaroxaban is needed. Finally, the concentrations of rivaroxaban and dabigatran can be measured directly in the plasma. Commercial tests are already available for this.[105]

So there are tests that can measure the effect of the NOACs, but they are not (yet) common in the current point of care setting. Furthermore, there is no test that is suitable for all NOACs and each agent needs a test of its own. This means that (at the moment)it is not practicable to monitor the treatment. Even though it appears that routine monitoring is not necessary with the NOACs, there are enough possible situations in which it would be desirable to measure the haemostatic status, for example in the event of failure of the treatment, with

bleeding, before surgical procedures, or if the patient is confused and does not know whether he has taken his medication properly.

As referred to above, it is indeed possible to measure the concentration of the agent in the blood. If there was sufficient data on the precise connection between concentration and the effect on clotting, in theory it would be possible to determine whether someone's anticoagulation is appropiate. But for this it has to be shown what connection these concentrations have with the degree of anticoagulation and how these are related to relevant clinical end points, such as recurrent thrombosis or bleeding. For the time being such data does not exist or is not made available by the manufacturer.

Further research is being carried out into methods of quantifying the effects of the NOACs in a standardised way.

4.4 No monitoring of anticoagulation: compliance and responsible prescribing

A number of studies have shown that many of the people who for example have been prescribed drugs to reduce cholesterol or antihypertensives stop taking the tablets quite quickly. For example, it has been seen that six months after starting treatment with statins, over a third to half of the people already stopped taking the medication.[58,109] In a Dutch study it was found that of the people who started with a statin, after two years 47% of the people were still taking the medication.[110] Even of the people who were prescribed statins after a stroke, after a year 40% stopped.[111] Also it appears that only 50-70% of the people take antihypertensives adequately in the long term.[112,113] A Dutch study shows that of the people who were prescribed an antihypertensive, after a year over 40% had stopped taking the medication.[114]

In the case of antihypertensives and statins, the consequences of not taking medication correctly will not be immediately apparent in greatly increased mortality figures. But it is different with anticoagulant medication. In view of the serious and direct consequences perhaps it can be assumed that 'spontaneous' compliance will be better than with the classes of drugs discussed above. It is about both continuing with the treatment (persistence) and taking the medication with the correct frequency and at the right times (adherence). But with some users of VKAs adherence to the medication is not optimal either. This has become apparent from some studies in which an 'electronic pill box' was used which records each time the box is opened. A count of the number of days that the tablets were not taken shows that on average 21% of the days were

missed.[115,116] Lack of adherence was also associated with many variations in the INR values.[115,117]

Up to now going to the Thrombosis Service has always helped and been a stimulus in encouraging compliance. Not only do the measured INR values show whether the patient has been taking his medication properly, but also the feeling of being supervised is a good motivation for many patients. Moreover, Thrombosis Services have a role in ensuring that a solution is found for problems that may stand in the way of persistence and adherence to the medication. So no longer having to go to the Thrombosis Service for a check when using NOACs, brings with it the considerable disadvantage that there is no longer any way of knowing whether the patient is complying with the treatment. The Committee believes that this absence of supervision in the proper use of anticoagulants is an important point for attention.

Also, the greater ease of prescribing by the doctor can lead to adverse situations. There is the risk that the doctor prescribes the drugs and then loses sight of the patient. On the other hand, certainly with atrial fibrillation this is a patient group that in general needs a great deal of care and as a result in most cases has regular check-ups with a GP or specialist. Particularly with an older patient with multimorbidity, or the patient with a mild kidney function disorder, besides regularly seeing the patient, for example kidney function will have to be checked as well in order to prevent plasma levels of the NOAC being too high.[98,118] If there are changes in the use of medication, it will have to be checked that no adverse interactions occur with the NOACs. Also, a proper explanation about the correct use of the medication is essential. Not only will agreement have to be reached with the patient about the importance of taking the medication at the right times; he or she also has to know what signs have to be looked out for and with which events (such as dental procedures) special measures have to be taken.

After half a century, the risks associated with VKAs are well known. The fact that VKAs are responsible for an estimated 10% of medication-related hospital admissions was what gave rise to the Health Care Inspectorate's study, referred to above, into bottlenecks in anticoagulant treatment.[10] As stated earlier, in that report the Health Care Inspectorate found that in various treatment situations the cooperation and communication in the 'chain' of caregivers who are involved in the treatment of patients who use VKAs fell short. Above all, the report highlighted 'the lack of structural arrangements between the various links in the chain, the poor communication and coordination and the lack of supervision'. The report made a number of proposals for improvement, in which the role of supervision was placed with the Thrombosis Services and advice was given to

the Minister to set up a national steering group on Thrombosis care. This steering group was created and also on behalf of the Ministry the CBO (Dutch Institute for Healthcare Improvement) has started with the development of Guidelines for Thrombosis Care in which it is to be set out 'what good thrombosis care must satisfy in terms of content, organisation and process'.

The question is what will change from this 'managed care perspective' with the advent of the NOACs? It is not expected that the NOACs will make anticoagulant treatment substantially safer. After all, as regards the primary safety end points the drugs were not superior to VKAs. But it is perhaps true that for the patients who use NOACs the management of thrombosis care has become simpler through the absence of one pivot (the Thrombosis Service). But it is precisely this that can cause problems because there is no oversight (supervision) of the treatment. The gap that is created gives practitioners who prescribe the NOACs the task of making proper provision for the supervision and instruction of the patient and making arrangements between themselves concerning responsibility and the transfer of information.

4.5 Consequences for the Thrombosis Services

If the NOACs are reimbursed and are used in clinical practice, fewer people will be assigned to a Thrombosis Service than is currently the case. If the favourable results of the clinical studies in which the dosage of the NOACs was not adjusted on the basis of clotting tests are confirmed in everyday clinical practice, a large part of the work of the Thrombosis Services will no longer be required. The core of the activities of the Thrombosis Services consists of taking blood samples for the INR determinations, 40% of which are carried out in the patients' homes, the INR determinations themselves and giving advice on dosage. The Thrombosis Services also provide information and advice and there is a monitoring system with the pharmacies in order to prevent problems with interacting medication. For the over 10% of patients who carry out the checks themselves and/or dose themselves (self-management), the Thrombosis Services make measuring equipment available and offer instruction, training and supervision. The number of INR determinations carried out forms the basis for the financing of the Thrombosis Services. For each determination an amount of about €10 can be declared (policy rule of the Dutch Health Care Authority (Nza)).[119] This sum includes all costs, including staff costs, housing costs and other costs. There is a separate tariff for supervising the self-management patients which also includes the costs of the self-measuring equipment. In 2010 about 6 million INR determinations were carried out. For each patient who switches to a NOAC, the

number of determinations carried out and that are to be declared falls by on average 20 per year. The services requested of the Thrombosis Services regarding the monitoring of the anticoagulant treatment will fall proportionally with the number of patients who switch to NOACs. In the hypothetically most extreme case that all patients switch to the NOACs, the Thrombosis Services will cease to exist. If the number of determinations falls below a certain 'critical mass', it may perhaps be more efficient to organise the remaining activities differently and for example make them part of a GP's laboratory or an outpatients clinic of a hospital, as has already happened to some extent.

It is difficult to say to what extent and how quickly the NOACs will replace the VKAs.

The Committee expects that certainly for the next few years there will continue to be a need for the services of the Thrombosis Services, at least, for the following groups of patients.

- People who use VKAs for indications for which the NOACs have not yet been investigated, such as a heart valve prosthesis. In 2010 this group accounted for 6% of the total number of patients treated, over 25,000 people.[9] It is expected that it will be another four years at least before the drugs have been investigated for this indication. At the moment the central registry of clinical studies (clinicaltrials.gov) reports only one phase 2 study with dabigatran for this indication (NCT01452347). In 2010 the group 'other arterial indications' represented 20% of the total. In the interim too this group will not have switched entirely to NOACs.
- Some patients do not tolerate the NOACs, or have a contra-indication. In the clinical trials it was seen that some of the patients stop the NOACs and then have to be treated with VKAs. In the case of dabigatran, for example, this was the case with 21% of the people. Examples of a contra-indication are seriously impaired kidney function, or having a heart valve defect.
- Preference will be given to VKAs rather than the NOACs if there are serious doubts concerning compliance.

Finally, it is likely that some of the patients who are now using VKAs will prefer to have regular checks carried out by a Thrombosis Service. New patients who are eligible for anticoagulant treatment will probably start with NOACs except if any of the points referred to above apply. The most likely scenario with reimbursement and fulfilment of the expectations of the NOACs is that all new patients with atrial fibrillation who do not have any contra-indications and meet the treatment criteria will start with a NOAC. Also for the treatment of VTE the preference may be for the NOACs, certainly in view of the advantage that with

rivaroxaban it is not necessary to start treatment first with heparin or LMWH. People who are already under treatment with a Thrombosis Service for the indication atrial fibrillation will be given the option of switching, either by the doctor in attendance (GP or cardiologist), or on the initiative of the Thrombosis Service. It is difficult to predict how many will respond positively to this. Finally, it is likely that those people who test themselves will in general tend to prefer NOACs.

According to the FNT's (Federation of Dutch Thrombosis Services) latest annual report, in 2010 58% of the patients were being treated for the indication atrial fibrillation (about 225,000 people) and 15% (58,000 people) for VTE. If in the next few years the latter group largely disappears and for example half of the first group, this means that about 45% of the turnover of the Thrombosis Services will disappear.

In summary, it is expected that the capacity needed of the Thrombosis Services will fall. It is difficult to make an estimate of the speed with which this will happen and of the level that will ultimately be reached.

However, the possibility must also be taken into account that in practice the NOACs may cause more problems than expected and that for at least some of the patients treated it will be evident that some form of monitoring or supervision will be desirable. In that case VKAs may continue to play an important role. Then the Thrombosis Services will contract less and may perhaps continue to play a part in the limited monitoring and supervision of people who use NOACs.

4.6 Conclusion: measures needed to monitor safety and promote proper use

Although in the context of the clinical studies the NOACs have provided evidence of their added value, there is uncertainty about the added value of the drugs in clinical practice in the Netherlands, compared with the current treatment with VKAs. The Committee therefore considers it to be necessary to gain some understanding of the efficacy and safety of the NOACs in everyday clinical practice. Continued collection of data and following how the patients fare are therefore essential. Secondly, ways need to be found for monitoring and promoting compliance, and for guaranteeing proper prescribing.

In order to be able to advise on this, the Committee has surveyed existing models that could offer starting points for one or both aspects. Possibilities considered were placement on List 2 of the Medicines Reimbursement System; making the policy rule 'expensive drugs' applicable; the establishing of registration systems (*registries*); research sponsored by the manufacturer; the use

of linked large anonymous databases to follow the outcomes with the patients; the developing of guidelines by the professional groups; and the managed care model.

On the basis of considerations on the possibilities and the limitations of these methods the Committee advises the following:

- The setting up of comparative research on the basis of a registration system in which a sufficiently large number of unselected patients are included who are prescribed a NOAC. The health condition of these patients is followed and compared with patients who are given VKAs. The Committee asks that only that data is collected that is needed in order to answer the questions concerning safety and cost-effectiveness, so that a clear answer can be expected within a few years. In order to enable a comparison to be made between the NOACs and the current anticoagulant policy in the Netherlands, it considers the gradual introduction of the NOACs with a *stepped wedge design* to be the most appropriate method.[120,121] With this, a new intervention at group level is introduced at different times. This offers the great advantage that it remains possible to make a comparison with a 'control group' while ultimately everyone gets access to the intervention. Because in the Netherlands everyone who uses VKAs is registered with a Thrombosis Service, the Thrombosis Services should be a suitable 'clustering unit'. The Committee is of the opinion that the manufacturers should pay for some of the costs of this research.
- The development of guidelines by the professional groups in which it is clearly defined who is responsible and when for the anticoagulant treatment. Following on from this it should be seen whether promoting compliance with the help of specialist nurses or practice support staff is useful, in the same way as the example of the outpatients clinics for heart failure and, more recently, the outpatients clinics for atrial fibrillation.[122] If the doctor in attendance does not have the time to devote sufficient attention to supervising the patient, a referral to a Thrombosis Service may be considered for an instruction discussion and a follow-up visit for an evaluation after six months, for example.

Chapter 5

Cost: cost-effectiveness and impact on the budget

It is rare that a new drug is less expensive than the treatment it is replacing. So in the case of these NOACs as well it can be expected that their introduction will increase the cost of healthcare. The price that is now being asked for the NOACs that can be obtained in the pharmacy is many times greater than the price of the VKAs. The difference is so great that it appears to be unlikely that the saving in the cost of monitoring will outweigh it. A more favourable picture can arise if costs due to strokes and bleedings fall because the NOACs are better and safer. Because it is probable that the introduction of the NOACs will bring cost increases with it, the Committee has had a cost-effectiveness analysis carried out. This section discusses this analysis. In view of the relatively short time available for this advisory report, it was chosen to limit the analysis to the cost-effectiveness of dabigatran for the indication atrial fibrillation. The prevention of stroke with atrial fibrillation is the main indication in numbers of patients treated, and it is likely that the cost-effectiveness of the other drugs will not differ significantly from that of dabigatran. The consequences of any differences in price between the drugs can be evaluated simply in the modelled calculations.

The VKA treatment of patients with atrial fibrillation with a moderately to severely raised risk of stroke is not only an effective treatment but has also proved to be cost-effective. For a comparison between treatment with VKA and no treatment, only relatively old studies are available. In most of these studies it was found that the health benefits from preventing stroke and systemic embolism lead to net cost savings. In other words: the cost including the treatment and

monitoring is lower, through 'savings' in sickness costs as a result of, among other things, strokes, with more years lived, and in terms of quality-adjusted life years (QALYs).[123,124] VKAs are also still very cost-effective compared with aspirin; even if in most studies there is no longer any question of there being net cost savings, the additional costs per QALY gained are small.[123,124]

An evaluation of the cost-effectiveness of a NOAC therefore involves a comparison with a treatment that compared with no treatment is very cost-effective.

Annex D contains a more extensive discussion of the study.

5.1 Overview of published cost-effectiveness studies

All the cost-effectiveness studies that have been carried out and published so far on the NOACs are about dabigatran in the treatment of atrial fibrillation. An overview of the results of these studies is given in Table 4. All these studies were computer simulations and were based on the results of the RE-LY trial, in particular the frequencies found in it for the occurrence of the relevant clinical events (event rates) in the various arms of the trial. The calculated incremental cost-effectiveness ratios vary from less than €6,000 per QALY to more than €60,000. At least two of the studies were sponsored by the manufacturer.

As well as these studies, a cost-effectiveness analysis has also been published in which the cost-effectiveness of dabigatran was investigated in patients who had already had a stroke or a TIA. This study was also based on the RE-LY trial.[125] The calculated incremental cost-effectiveness ratio of this study was $25,000 per QALY. A sensitivity analysis showed that the cost-effectiveness ratio was strongly influenced by the quality of the VKA treatment (TTR).

The quality of the VKA treatment was also an important point for consideration in the critical evaluation of the cost-effectiveness analysis that was submitted by the manufacturer to the NICE institute in the United Kingdom. NICE is responsible for deciding whether new drugs in the UK are reimbursed. A model submitted by the manufacturer is a fixed element of the application procedure. The manufacturer's model was critically analysed, on behalf of NICE, by a team of researchers at the University of York.[126] Instead of the cost-effectiveness ratio of about £9,000 calculated by the applicant, an estimate of about £19,000 was considered likely, which fell just within the limit of what is regarded by NICE as being cost-effective. The researchers came to the conclusion that the cost-effectiveness ratio depended not only very strongly on the quality of the anticoagulant treatment, but also on the cost of monitoring.

Table 4 Published cost-effectiveness studies.

Study	(Incremental) cost-effectiveness ratio [a]	Special features
Pink et al.[56]	£23,082/QALY (€26,700 /QALY) In centres with good control: £42,386 (€50,863)	As well as cost-effectiveness, the study also looked at the 'net benefit' (only difference in QALYs) Based on RE-LY cohort
Shah & Gage [54]	$86,000/QALY (€66,220/QALY)	Based on a cohort of 70-year-olds Also looked at other treatments: aspirin and aspirin plus clopidogrel Also carried out analyses stratified by $CHADS_2$ score and risk of haemorrhage.
Freeman et al.[127]	$45,372/QALY (€34,936/QALY)	Based on RE-LY cohort
Sorensen et al.[55]	Can $10,440 (€7934/QALY)	Sponsored by the manufacturer
Kansal et al. (Heart 98;573)	£4,831/QALY (€5,749) when starting treatment before the age of 80 years. £7,090/QALY (€8,437) when starting treatment at or after the age of 80 years.	Sponsored by the manufacturer

[a] Prices converted at current exchange rates: 1$=0.77 €; 1 Canadian$= 0.76€; 1£= 1.19€.

5.2 Design and starting points of the cost-effectiveness study

Within the tight time frame of the request for advice, the Committee chose to have a cost-effectiveness study carried out that was limited in size but which did, however, include the main determinants for cost-effectiveness. In particular it was decided to focus on a comparison between dabigatran and VKAs for the indication atrial fibrillation on the basis of the results of the RE-LY study. This choice was also made because of the fact that this was the indication and the drug about which most information was available.

A Markov model was designed to carry out this comparison, in which a virtual patient population is created, half of which is treated with dabigatran and the other half with a VKA. These treatments are continued for the rest of the patients' lives. The two groups are 'followed' over time, at intervals of one month, in which at each time each 'individual' is in a certain health state. At each period of time there is a chance that the state changes: apart from increasing age, the patient may have had a stroke, or a myocardial infarction, or any of the other events that are described in the clinical studies. Each state is associated with costs and with a change in quality of life. The two groups differ from each other in the risks that they have of events and in the cost of the treatment. When everyone in the simulation has died, it is calculated what the difference was in the total number of QALYs 'lived' between the two groups, and what the difference in total cost was. Dividing the cost by the QALYs produces the

incremental cost-effectiveness ratio (ICER); these costs can be seen as the extra costs to gain a QALY.

This approach corresponded largely to the studies referred to in Table 4. The main objective was to adapt the main parameters as much as possible to the situation in the Netherlands.

5.3 Model and input parameters

At the start of the simulation there were 10,000 patients with atrial fibrillation, with a distribution according to the $CHADS_2$ score. It was based on a patient population whose relevant characteristics were the same as those in the RE-LY trial, the exception being that it was a group of 70-year-olds at the beginning with a distribution according to the $CHADS_2$ score that is comparable to that of the Dutch population.[128] When the age of 75 was reached, the score was increased by 1 point. Half the patients were treated with dabigatran 2 x 150 mg; the other half with acenocoumarol (apart from the costs, regarded in this study as equivalent to warfarin).

At any time during a period of one month a change in the patient's health state could occur due to any of the following clinical events: a stroke (ischaemic or haemorrhagic), intracranial haemorrhage (excluding a haemorrhagic stroke), a myocardial infarction, a TIA (Transient Ischaemic Attack), a pulmonary embolism, serious extracranial bleeding, or minor bleeding. With this, the patient falls into one of the following health states: atrial fibrillation but otherwise healthy, dead, status post stroke, status post intracranial haemorrhage, status post myocardial infarction, or status post a TIA. In turn, new events could occur from these conditions. It was assumed that extracranial bleeding and minor bleeding cause only temporary damage. Also, the simplified assumption was made that the health state depended only on the most serious event, in decreasing order of stroke, intracranial haemorrhage, myocardial infarction, TIA. So someone with a stroke who suffers a myocardial infarction stays in the condition of 'status post stroke', while someone who after a myocardial infarction suffers a stroke moves from the condition of 'status post myocardial infarction' to 'status post stroke'. Also, anyone from any state could stop the medication and switch to VKAs or aspirin. Annex D contains a diagram of the health states and transitions.

5.3.1 Transition probabilities

Estimates of the likelihood of a certain event occurring in a period of a month (the 'transition probablity') were taken from the RE-LY study, or, if not given in

this study, from other studies. The likelihood of a stroke depended on the $CHADS_2$ score (0-1, 2, 3 or higher); after a stroke or TIA the likelihood of a following event increased. In the model the likelihood of death also depended on the health state. For patients with just a TIA or minor bleeding (and atrial fibrillation), the age-specific mortality rates for the general Dutch population are taken. A greater likelihood of death was associated with all other states. For stroke and myocardial infarction, these were based on Dutch mortality rates that take into account the time after the event,[129] adjusted by a 'correction factor' for atrial fibrillation.[130,131] Annex D contains a complete list of the transition probabilities and the sources for the estimates.

5.3.2 *Quality of life and costs*

The distribution of the patients by the health states and the changes in them form the basis for calculating the costs and the health outcomes (effects). The latter are expressed in the number of QALYs: the quality-adjusted life year, in which a weight of 1 stands for optimum health. According to whether the health condition is felt to be worse, the weight is less than 1. The weight that is associated with a certain health condition is called the 'utility', or the disutility if on the other hand the loss of quality of life is expressed. For a list of the values used and for the sources on which the estimates are based, see Annex D.

For the costs too, as much as possible values have been taken from Dutch studies or that apply specifically for the Netherlands, such as the costs for monitoring anticoagulant treatment. It was calculated that the annual costs for the treatment with VKAs, including the cost of the drug (acenocoumarol) and the INR controls, are just over €225. The annual cost of dabigatran, based on the current price of €1.33 per capsule, was calculated at almost €1,000, i.e. about four times as much (see also Annex D).

As regards the costs as a result of medical events, only the various events that could occur in the model were taken into account. As well as costs for acute events, stroke and myocardial infarction involved life-long costs. This means that the costs per unit of time (month) for stroke and myocardial infarction varied depending on the time that had elapsed after the event: one month, two to six months, seven to twelve months, and following years. All amounts were adjusted for inflation and converted to 2010 prices. A list of the values used and sources for these estimates is given in Annex D.

The costs were estimated from the perspective of health care: only the medical costs and cost of care were included, and not for example the costs of reduced labour productivity as a result of a stroke.

Finally, in accordance with the Dutch guideline for economic evaluations, the costs and the effects (QALYs) were discounted at rates of 4% and 1.5% respectively.[132]

5.3.3 *Sensitivity analyses*

To set out the uncertainty margins in the outcomes and to investigate which factors have a great influence on cost-effectiveness, a number of sensitivity analyses have been carried out. An important point that has already been referred to above is that the difference in effectiveness between dabigatran and VKA treatment depends on the quality of the anticoagulant treatment in the group treated with a VKA. Based on the analysis by Wallentin et al., two scenarios have been investigated, one with a TTR of less than 65.5% (the median cTTR calculated by Wallentin et al.) and one with a TTR of 65.5% or more. Also, univariate and multivariate sensitivity analyses have been carried out in which alternative values for the following parameters were inputted: the likelihood of stroke in the different treatment arms, the likelihood of dying after a stroke, the life-long costs of stroke and the treatment of a myocardial infarction, and the costs of monitoring the anticoagulant treatment. Finally, what is known as a probabilistic sensitivity analysis was carried out, which is described in further detail in Annex D. Also a cost-effectiveness acceptability curve was produced, which for different threshold values for cost-effectiveness (willingness to pay) shows what the likelihood is that at this threshold value the intervention is cost-effective.

5.4 Results

Table 5 shows the outcomes for the starting scenario (base case). Treatment with dabigatran leads both to higher total costs and also more health compared with treatment with a VKA (acenocoumarol). If the difference in total costs is divided by the difference in QALYs, the number that results shows how much more money it would cost to gain a QALY by using dabigatran rather than a VKA. The result, an incremental cost-effectiveness ratio (ICER) of €11,758, can be seen as relatively cost-effective compared with other interventions in healthcare. In the Netherlands there is no fixed threshold for cost-effectiveness. So in the absolute sense it is not possible to talk about ‘cost-effective’, but this ICER falls within the limits of what is still generally regarded as cost-effective.

Table 5 Cost-effectiveness of dabigatran 150 mg bd versus VKA for patients with atrial fibrillation based on a model with different sets of input values.

	Model NL [a]	Model RE-LY [b]	Model RE-LY/Pink [c]	Pink et al
ICER (€ /QALY)	€11,758	€11,846	€20,375	€23,082
Total costs				
Dabigatran	€16,931	€16,774	€10,256	€9,850
VKA	€13,874	€13,694	€5,855	€6,480
QALYs				
Dabigatran	7.73	7.75	6.77	6.54
VKA	7.47	7.49	6.55	6.39

[a] This model was based on a distribution of patients by CHADS2 score based on Dutch data.
[b] The relevant input parameters of the RE-LY trial were used here (i.e. not likelihood of transition adjusted for the Netherlands).
[c] The input parameters of the model of Pink et al. were used for this.

ICER: Incremental cost-effectiveness ratio

The results of the sensitivity analyses are given in Annex D. A better quality of the monitoring of the INR as measured with the TTR had the strongest effect. This led to estimates that ranged from €7,046 with a quality of monitoring below the median, to a point estimate of €30,133 per QALY with a quality of monitoring above the median.

5.5 Conclusions regarding cost-effectiveness

The use of dabigatran rather than VKAs produces a health benefit, but it is associated with higher costs. The incremental cost-effectiveness ratio is favourable in the base case and suggests that the intervention is more cost-effective than many other interventions that are regarded as being cost-effective. The incremental cost-effectiveness ratio will, however, be much higher if dabigatran is compared with a VKA treatment with good quality monitoring.

Chapter 6

Conclusions and recommendations

Finally, the Committee presents its conclusions and recommendations. With this it also answers the Minister's questions.

6.1 The Committee's findings and conclusions

6.1.1 Efficacy and safety of the NOACs compared with the old drugs

After more than 50 years the NOACs open up the possibility of improved care for the patient who has been diagnosed as needing anticoagulant treatment. For the time being these are patients who have had an elective knee or hip replacement to prevent venous thrombosis, and patients with atrial fibrillation, or with VTE. The improvement in treatment consists in particular of a considerable simplification for the patient and care providers: regular monitoring of the effect of the treatment will, according to the results of the clinical studies that have been carried out so far, no longer be necessary. As a result, it will become a treatment that is just as 'ordinary' as treatment with other drugs.

In the clinical trials that have been carried out in order to have the drugs registered, they have proved to be at least as effective and safe as the VKAs. This means that at least as many thromboses and strokes were prevented, and that no more major bleeding occurred. There have even been indications that some of the drugs, or all, are not only equivalent to the VKAs, but also rather more effective

and safer. An important advantage of the NOACs appears to be that they may lead to less cranial haemorrhaging.

Whether the added value that has been seen in clinical studies also applies to the same extent in Dutch clinical practice is uncertain.

- In view of the particular organisation of anticoagulant treatment with VKAs in the Netherlands it is possible that the number of haemorrhages and thrombotic complications among VKA users is lower here than in the VKA arms of the trials. The health benefit that can be obtained with the NOACs will in that case also be less. As a result, it remains unclear whether any therapeutic added value of the NOACs in the trials (other than equivalence and ease of use) also applies for the Dutch situation.
- With the introduction of the NOACs in everyday clinical practice, patients will also be given the drug who were not represented, or only to a limited extent, in the clinical trials. In particular these are people with a higher risk of bleeding or thrombosis. The question is whether the NOACs will be just as safe with this group as VKAs.
- Also, unlike with the VKAs, there is no antidote available for emergency situations in which the anticoagulant effect of the NOACs has to be reversed immediately, such as with accidents or emergency operations. A first paper on the effectiveness of prothrombin complex concentrate as an antidote appeared recently.
- Doubts still remain about the safety of the NOACs in everyday clinical practice, as can be seen from reports from registering authorities and analyses in the scientific journals.
- An important point for consideration is compliance. With the NOACs it is no longer established regularly whether someone is using the drugs properly. With this indication and this type of medication, a lack of compliance can already have serious consequences in the short term.

6.1.2 Cost-effectiveness of the NOACs

It is evident from the cost-effectiveness analysis that has been carried out that the NOACs are expensive, both in terms of the costs per life-year gained and also the total effect on expenditure in healthcare. The estimated incremental cost-effectiveness ratio is just below €12,000 per QALY, which falls within the limits of what is generally seen as being acceptable. The greatest uncertainty issue remains however whether the therapeutic added value from the clinical studies also applies regarding the quality of the monitoring of anticoagulant treatment in

the Netherlands. The less this added value is, the greater will be the incremental cost-effectiveness ratio.

6.1.3 Consequences for the Thrombosis Services

For the time being there will still be a need for the current care provided by the Thrombosis Services: for indications for which the NOACs are not registered; for people for which there are serious doubts about compliance; for people who do not tolerate the NOACs; and for people who have not yet switched over to the NOACs or do not wish to do so. It is expected that the capacity needed for this will decrease. The fall in turnover of the Thrombosis Services (and the costs that can be declared) is roughly proportional to the proportion of patients who switch to a NOAC. The rate at which patients will switch to the NOACs and the ultimate proportion of patients that will be treated with NOACs is still difficult to estimate at the present time.

6.2 Recommendations

The Committee recommends the NOACs as a new option in anticoagulant treatment in the registered indications. After 50 years of treatment with VKAs this is an important innovation. These drugs should therefore become part of the treatment arsenal of the doctor and be available to the patient.

It is essential that the introduction of the NOACs be accompanied by a number of conditions that guarantee the continued collecting of data and the proper use of drugs so that after a few years the uncertainties that exist at the moment can be dispelled and the added value can be determined definitively.

Research

The Committee recommends that at the same time as the introduction of the NOACs comparative research should be started. The aim of this research is firstly to collect more information on the efficacy and safety of the drugs in less selected populations than those in the randomised clinical studies; and secondly to obtain a better picture of their cost-effectiveness compared with the current anticoagulant treatment with VKAs in the Netherlands.

- A suitable framework within which these recommendations could be put into effect is provided by the recently started GGG (Good Use of Drugs)

programme of ZonMW (the Netherlands Organisation for Health Research and Development).

- The data collection for this research should be limited solely to that data that within a period of a few years can help to answer the two questions set out above.
- In order to enable a comparison to be made with the current VKA policy, the Committee recommends introducing the drugs gradually using a 'stepped wedge design'.
- It is clear that manufacturers too must accept their responsibility and make a financial contribution to the proposed research, while guaranteeing the objectivity and scientific accessibility of the data.
- The scientific leadership of the research and details of how it is organised would have to be established under the direction of ZonMW. The expertise of the Thrombosis Services could be used in carrying out the research.

Responsibilities of the professional groups

The professional groups are considered to adapt their guidelines in the area of the treatment and prevention of thrombosis and in doing so pay ample attention to the issue of patient guidance so that compliance is supported and sufficient care is given to the precautions and warnings in the use of the NOACs. It must also be made clear who is responsible for the treatment and when. It must also be ensured that the guidelines are revised regularly.

The consequences for clinical practice must be considered.

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A The request for advice

B The Committee

C Overview of the NOACs

D Cost-effectiveness analysis

E List of abbreviations

Annexes

Annex **A**

The request for advice

The President of the Health Council received the following letter (reference GMT/MVG-3081054) from the Minister of Health, Welfare and Sport on 4 October 2011:

Dear Mrs Gunning,

Further to my previous discussion with your secretary, Dr. C. Postema, on the care of thrombosis, I would ask for your attention on the following.

In your schedule for 2012 you included the care of thrombosis as a subject on which the Health Council will publish an advisory report in 2012. The reason for doing so is the advent of a new generation of anticoagulants. The stakeholders involved need a scientific assessment of the position of these new drugs in the care of thrombosis. Elements such as the long-term effects, compliance and whether there is an antidote available play a part in this.

As can be seen, the drugs set requirements in respect of monitoring of patients that are different to those of the current drugs for thrombosis, and the advent of these NOACs may perhaps have consequences for the organisation of thrombosis care in the Netherlands. In the light of this, in your advice I would also ask you to consider the position of the Thrombosis Services in our country and the possible consequences of the advent of the new drugs for the Thrombosis Services.

In addition, when drawing up your advice I would also ask you to take the following into account:

- The Health Care Insurance Board (CVZ) assesses anticoagulants within the framework of whether they are permitted in the health care package that is insured. I understand that the CVZ will advise the Ministry of Health, Welfare and Sport on this probably at the earliest in November 2011. In its assessment the CVZ will concentrate on the individual drug in relation to the standard treatment. The pharmacotherapeutic treatment arsenal will also be one of the subjects in your advice. The effect and the side effects of the current anticoagulants are an important reason why the Thrombosis Services were created. I would also you to work together with the CVZ in the therapeutic assessment of the current and the new anticoagulants.
- Health-economics arguments will also play a part in your advice. In the assessment by the CVZ too, pharmaco-economic considerations will play a part in the final package advice to the minister. Please keep in close contact with the CVZ on this point as well.
- Finally, I would ask you to expressly include in your advice experience with other forms of thrombosis care in other countries.

Following on from this, I would ask you to submit your advice to me by March 2012 at the latest so that in good time I can make a balanced integral decision on the package.

Yours sincerely,
(signed)

The Director of Medicinal Products and Medical Technology,
drs. H.R. Hurts

Annex **B**

The Committee

- Prof. dr. E. Briët, *Chairman*
  Emeritus Professor of Internal Medicine, Amsterdam
- Prof. dr. A. Algra
  Professor in the Clinical Epidemiology of Thrombosis Treatment and Prevention, University Medical Centre Utrecht and Leiden University Medical Centre
- Prof. dr. Ph.G. de Groot
  Professor in Thrombosis and Haemostasis, University Medical Centre Utrecht
- H. van Laarhoven
  De Hart & Vaatgroep, The Hague
- Dr. K. Meijer
  Haematologist, University Medical Centre Groningen
- Prof. dr. J.C.M. Meijers
  Professor in Experimental Vascular Medicine, Academic Medical Centre Amsterdam
- Prof. dr. S. Middeldorp
  Professor in Internal Medicine, in Particular Thrombosis and Haemostasis, Academic Medical Centre Amsterdam
- Dr. K. Redekop
  Clinical Epidemiologist and Health Economist, Erasmus University Rotterdam

- Prof. dr. P. H. Reitsma
  Professor in Experimental Molecular Medicine, Leiden University Medical Centre
- Prof. dr. P.A.B.M. Smits
  Professor in Pharmacology, University Medical Centre St. Radboud, Nijmegen
- Prof. dr. H.J.G.M. Crijns, *advisor*
  Professor in Cardiology, University Medical Centre Maastricht
- Prof. dr. A.W. Hoes, *advisor*
  Professor in Clinical Epidemiology/General Practice, University Medical Centre Utrecht
- Prof. dr. F.W.G. Leebeek, *advisor*
  Special Professor in Haematology, in Particular Haemostasis and Thrombosis, Erasmus Medical Centre
- Dr. F.J.M. van der Meer, *advisor*
  Specialist in Internal Medicine, Leiden University Medical Centre
- Prof. dr. M.J. Postma, *advisor*
  Professor in Pharmacy/Health Economist, Rijksuniversiteit Groningen
- Drs. P.P. Kruger, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Dr. P.M. Engelfriet, *scientific secretary*
  Health Council, The Hague
- Dr. C.A. Postema, *scientific secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the

expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Overview of the NOACs

There follows an overview of the pharmacological properties of the NOACs, and then a summary of the results of the clinical studies that have been published.

Pharmacology

Detailed documentation on the pharmacological properties of the NOACs is contained in the latest version of the guidelines of the American College of Chest Physicians.[3]

Unlike the VKAs, the NOACs inhibit coagulation at a specific point in the coagulation chain. The main mechanism on which the anticoagulant action of dabigatran rests is the competitive inhibition of the reaction in which thrombin converts fibrinogen to fibrin; that of the other three drugs is the inhibition of the reaction in which factor Xa converts prothrombin to thrombin. The most commonly cited advantages of the NOACs relate mainly to the pharmacokinetic and pharmacodynamic properties. The most important properties are shown in Table 6 below. Dabigatran is administered as a *prodrug* which after absorption from the intestine is converted by esterases in plasma, erythrocytes and the liver into the active form. Despite the manufacturers' claim that the NOACs have much more 'predictable' kinetics with much less interindividual and intraindividual variation than the VKAs, a population study has shown that considerable differences in plasma levels are seen.[133] The NOACs are

metabolised by the cytochrome P450 enzyme complex to a much lesser extent, as a result of which there is less of a chance of the interactions with other medication that cause so many problems with the VKAs. It is important that 80% of dabigatran is cleared by the kidneys. Serious kidney function disorders (*glomerular filtration rate* <30 ml/min) also constitute a contraindication for use, which is not the case with VKAs. Another disadvantage is that the dosage is twice a day, which can have a negative effect on compliance.

Rivaroxaban and apixaban bind quite strongly to plasma proteins. Furthermore, they are partly metabolised by cytochrome P450 enzymes (cP450 3A4). Therefore there is a chance of interactions with drugs with strong protein binding or cP50-dependent metabolism. The use of azole antimycotics (such as ketoconazole) is not advised. Dabigatran should not be combined with quinidine and amiodarone, due to competition for the P-glycoprotein transport system.

Table 6 Overview of pharmacological properties.

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trade name (EU)	Pradaxa	Xarelto	Eliquis	-
Dosages	tablets 110 mg and 150 mg	10 mg, 15 mg, 20 mg	2.5 mg, 5 mg	30 mg, 60 mg
Action	thrombin inhibitor, with reversible binding to thrombin administered as dabigatran etexilate, converted to dabigatran mainly in the liver	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
T ½ (hours)	12-14	9-13	8-15	8-10
Time to Cmax (hours)	2	2-4	1-3	1-2
Bioavailability (%)	6.5	80	66	>45
Interaction mechanisms	P-glycoprotein transport system in the intestine	32% metabolism by YP3A4 and P-gp	15% metabolism by CYP3A4	P-glycoprotein transport system in the intestine [a]
Protein binding (%)	35	>90	87	55
Renal clearance (%)	80	66	25	35
Linear pharmacokinetics	Yes	No	Yes	Yes

[a] According to a recent publication.

Results of clinical studies

Table 7 Overview of clinical studies on atrial fibrillation.

Study	RE-LY			ROCKET-AF		ARISTOTLE	
Comparison	Dabigatran 2 x 110 mg	Dabigatran 2 x 150 mg	VKA	Rivaroxaban 20 mg	VKA	Apixaban 2 x 5 mg	VKA
Number of patients	6.015	6.076	6.022	7.081	7.090	9.120	9.081
OUTCOMES							
Stroke (all types) or systemic embolism (N)	182 [183] [a]	134 [134]	199 [202]	269	306	212	265
Incidence (%/year; or/100 py)	1,53 [1,54]	1,11 [1,11]	1,69 [1,71]	2,1	2,4	1,27	1,60
Difference in risk with KAs	0,16 [0,17]	0,58 [0,58]		0,3		0,33	
Relative risk compared with VKAs	0,91 (0,74-1,11) [0,90 (0,74-1,10)]	0,66 (0,53-0,82) [0,65 (0,52-0,81)]		0,88 (0,75 - 1,03)		0,79 (0,66-0,95)	
Major bleeding	322 [342]	375 [399]	397 [421]	395	386	327	462
Incidence	2,71 [2,87]	3,11 [3,32]	3,36 [3,57]	3,6	3,4	2,13	3,09
Difference in risk	0,65 [0,70]	0,25 [0,25]		0,2		0,96	
Relative risk	0,80 (0,69-0,93) [0,80 (0,70-0,93)]	0,93 (0,81-1,07) [0,93 (0,81-1,07]		1,04 (0,90-1,20)		0,69 (0,60-0,80)	
Death (N)	446 [ongewij-	438	487	582	632	603	669
	zigd]						
Incidence	3,75	3,64	4,13	4,5	4,9	3,52	3,94
Difference in risk	0,38	0,49		0,4		0,42	
Relative risk	0,91 (0,80 -1,03)	0,88 (0,77-1,00)		0,92 (0,82-1,03)		0,89 (0,80-0,998)	
Intracranial haemorrhage (N), *including haemorrhagic stroke* (n)	27 [27] [b]	36 [38] (12 [12])	87 [90] (45 [45])	55 (n=29)	84 (50)	52 (n=40)	122 (78)
Incidence	0,23 [0,23]	0,30 [0,32]	0,74 [0,76]	0,5	0,7	0,33	0,80
Difference in risk	0,51 [0,53]	0,44 [0,44]		0,2		0,47	
Relative risk	0,31 (0,20-0,47) [0,30 (0,19-0,45)]	0,40 (0,27-0,60) [0,41 (0,27-0,60)]		0,67 (0,47-0,93)		0,42 (0,30-0,58)	

Gastrointestinal *bleeding* (N)	133 [137]	182 [188]	120 [126]	224	154	105	119
Incidence	1,12 [1,15]	1,51 [1,56]	1,02 [1,07]	3,2 (%)	2,2 (%)	0,76	0,86
Difference in risk	+ 0,10 [0,08]	+ 0,49 [0,49]				0,10	
Relative risk	1,10(0,86-1,41) [1,08 (0,85-1,38)]	1,50 (1,19-1,89) [1,48 (1,18-1,85)]		1,46 (1,19-1,78) [c] P < 0,001		0,89 (0,70-1,15)	
Myocardial infarction (N)	86 [98]	89 [97]	63 [75]	101	126	90	102
Incidence	0,72 [0,82]	0,74 [0,81]	0,53 [0,64]	0,9	1,1	0,53	0,61
Difference in risk	+ 0,19 [0,18]	+ 0,21 [0,17]		0,2		0,08	
Relative risk	1,35 (0,98-1,87) [1,29 (0,96-1,75)]	1,38 (1,00-1,91) [1,27 (0,94-1,71)]		0,81 (0,63-1,06)		0,88 (0,66-1,17)	

a The numbers between square brackets are the revised numbers as reported in an update of the outcomes in the patients after completing the RCT.[80]

b In the report on the RE-LY study, subdural haemorrhage (no stroke) and subarachnoid haemorrhage (with stroke) are included with intracranial haemorrhage. The same applies for the ROCKET-AF study, in which epidural haemorrhage was also included (n=0 in the rivaroxaban arm and n=1 in the VKA arm).

Annex **D**

Cost-effectiveness analysis

The design of the cost-effectiveness analysis is described in the main text. The table below shows the various Markov conditions with a list of the input data.

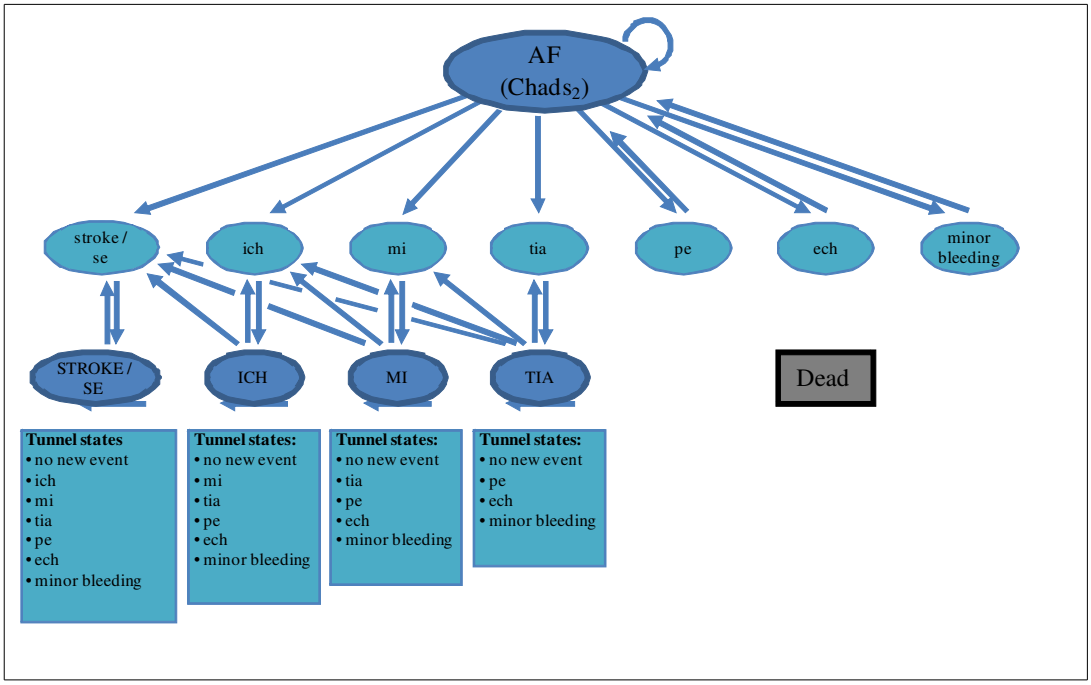

Figure 1 Markov model for a population of patients with atrial fibrillation. In the starting condition someone has only atrial fibrillation with a certain $CHADS_2$ score. In each interval of time (1 month) an event can occur, shown in small letters: stroke or systemic embolism, intracranial haemorrhage (ich), myocardial infarction (mi), Transient Ischaemic Attack (tia), pulmonary embolism (pe), extracranial haemorrhage (ech), or minor bleeding. As a result, someone enters a temporary, or 'tunnel' condition. From there, someone can then enter any of the following permanent conditions, given in capital letters and ranked in order or seriousness: status post stroke, status post intracranial haemorrhage (ICH), status post a myocardial infarction (MI), status post a TIA.

Table 8 Chances of clinical events.

'Event' (per 100 patient years)	Dabigatran	VKA	aspirin	source
Stroke or systemic embolism (primary end point)				
$CHADS_2$ score ≤1	0.0068	0.0109	0.0177	RE-LY
$CHADS_2$ score = 2	0.0084	0.0138	0.0222	RE-LY
$CHADS_2$ score ≥ 3	0.0189	0.0273	0.0441	RE-LY
Stroke or systemic embolism				
cTTR < 65.5%	0.0107	0.0199	0.0326	RE-LY
cTTR ≥ 65.5%	0.0115	0.0143	0.0233	RE-LY
Recurrent stroke	From an increased $CHADS_2$			RE-LY
Intracranial haemorrhage (excluding haemorrhagic bleeding)	0.0022	0.0038	0.0013	RE-LY
Myocardial infarction	0.0081	0.0064	0.0064	RE-LY
TIA	0.0072	0.0084	0.0135	RE-LY
Pulmonary embolism	0.0015	0.0010	0.0016	RE-LY
Extracranial haemorrhage	0.0284	0.0267	0.0145	RE-LY
Minor bleeding	0.1484	0.1637	0.0718	RE-LY
Death				
Post stroke (month 1, months 2-12, following years)	Age-specific, based on the sources cited			129,130
Post Intracranial haemorrhage [a]	*Case fatality* 25%			134
Post Myocardial infarction (month1, following months)	Age-specific, based on the sources cited			129,130
Pulmonary embolism	0.1591	0.1591	0.1591	RE-LY
Extracranial haemorrhage	*Case fatality* 6%			135,136
Atrial fibrillation, without other events	Age-specific death, min cardiovascular causes			CBS.nl
TIA and minor bleeding	Age-specific death, min cardiovascular causes			CBS.nl
Chances after stopping medication				
Post major bleeding	0.213	0.143	-	137
Stopping first year	0.412	0.091	-	137
Stopping 2nd year	0.043	0.046	-	137

a Intracranial haemorrhage (excluding haemorrhagic stroke) includes subdural and subarachnoid haemorrhage; the case fatality is calculated as a weighted average.

Table 9 Quality of life weights.

(Dis)utility health conditions	Value	Distribution	Source
Atrial fibrillation (67-year-olds)	0.774	Gamma (43.06 0.0052)	[138]
Stroke			
Permanent disability (disutility)	0.233	Normal (0.233 0.0032)	[139]
Temporary disability (disutility)	0.1385	Normal (0.1385 0.01)	[137,138]
Temporary duration	3 months	Uniform (0 0.183)	[137]
TIA			
Temporary disability	0.1032	Normal (0.1032 0.01)	[137,138]
Duration of temporary disability	5 days	Uniform (0 0.027)	[139]
Pulmonary embolism			
Temporary disability	0.1385	Normal (0.1385 0.01)	[137,138]
Duration	1 month	Uniform (0 0.183)	[139]
Myocardial infarction			
Permanent disability	0.0409	Normal (0.0409 0.002)	[138]
Temporary disability	0.1247	Normal (0.1247 0.01)	[137,138]
Duration	1 month	Uniform (0 0.183)	[139]
Intracranial haemorrhage			
Permanent disability	0.081	Normal (0.0524 0.001)	[134,138]
Temporary disability	0.3715		
Duration	1 month		
Extracranial haemorrhage			
Temporary disability (disutility)	0.1385	Normal (0.1385 0.01)	[137,138]
Duration	1 month	Uniform (0 0.183)	[139]
Minor bleeding			
Temporary disability (disutility)	0.06	Normal (0.06 0.01)	[139]
Duration	5 days	Uniform (0 0.183)	[139]
VKA use	0.013	Gamma (1.3 0.01)	[139]
Dabigatran use	0.002	Gamma (0.2 0.01)	[56]

Table 10 Costs.

Cost item	Value	Distribution	Source
Drugs			
Dabigatran	€970.90	-	www.fk.cvz.nl
Acenocoumarol			
Drug	€25.55	-	FNT; www.medicijnkosten.nl
Control	€202.00	Triangular ± 25%	FNT (F vd M)
Clinical Events			
Stroke			[140]
Month 1	€8,179.00	Triangular ± 25%	
Months 2-6	€3,157.10	Triangular ± 25%	
Months 7-12	€1,775.40	Triangular ± 25%	
Following years	€684.20	Triangular ± 25%	
Intracranial haemorrhage	€28,704.65	Triangular ± 25%	[141]
Myocardial infarction			[142]
Year 1	€17,342.00	Triangular ± 25%	
Following years	€1,054.00	Triangular ± 25%	
TIA	€6,066.83	Triangular ± 25%	Nza.2010
Pulmonary embolism	€4,593.74	Triangular ± 25%	[143]
Extracranial haemorrhage	€4,594.83	Triangular ± 25%	[143]
Minor bleeding	€28.24	Triangular ± 25%	[132] (1 GP visit)

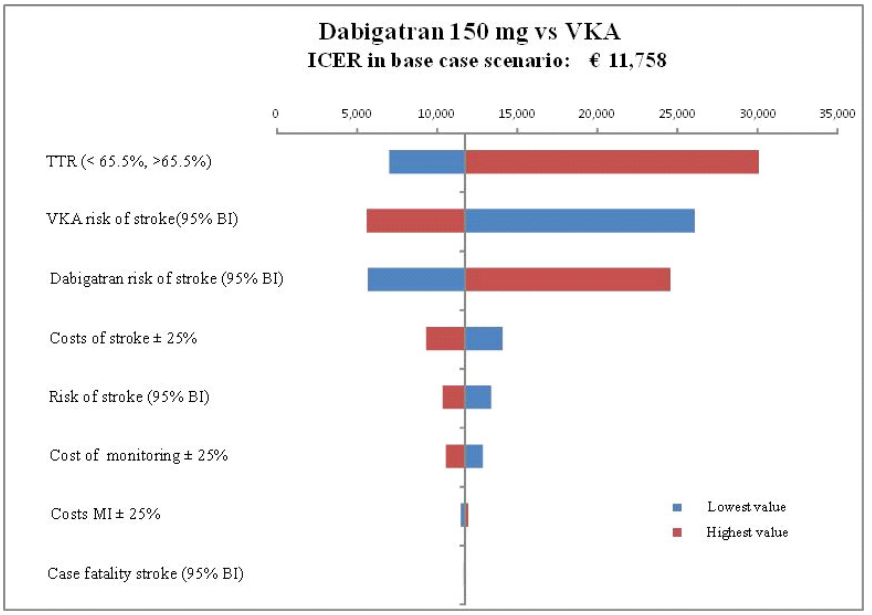

Figure 2 "Tornado plot". This graph shows how sensitive the outcome (the ICER) is to changes in a number of variables. At the bottom left are the variables for which other values have been taken. On the right it is shown with a bar what the effect on the ICER is if the lowest value for the variable is used for the input in the model (blue), for example the lower limit of the 95% CI, and if the highest value (red) is taken, for example the upper limit of the 95% CI. It can be read from the graph that variation in the TTR has the greatest effect: from cost saving to an ICER of more than €30,000.

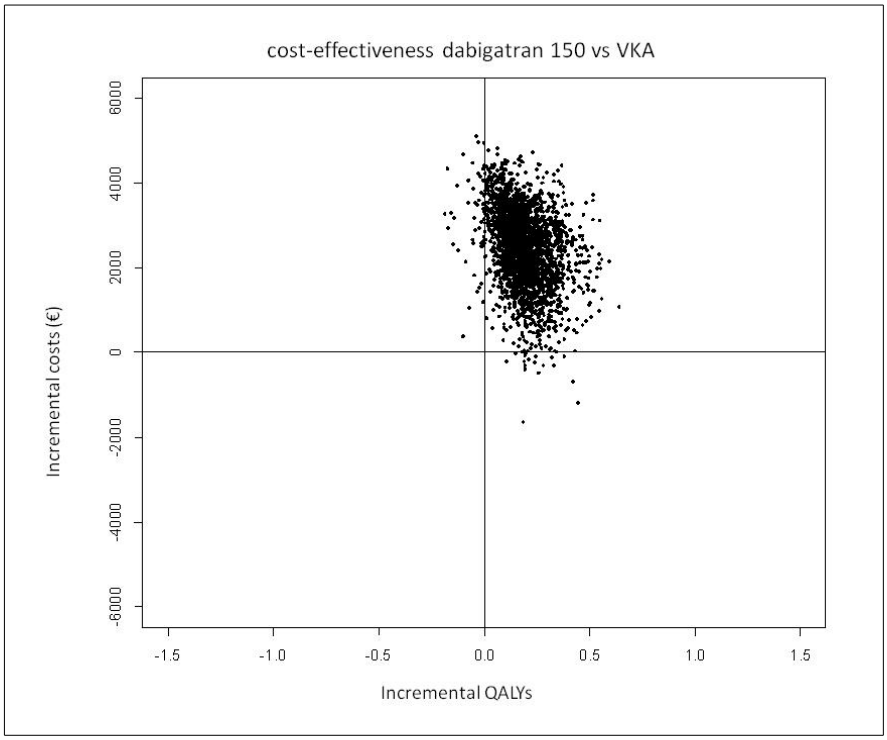

Figure 3 Result of the probabilistic sensitivity analysis. Each point represents the outcome of a simulation: QALYs gained as the x-value and the difference in costs as the y-value.
Most of the points lie in the top right quadrant, which means that the costs with the use of dabigatran are consistently higher, compared with the health benefit.

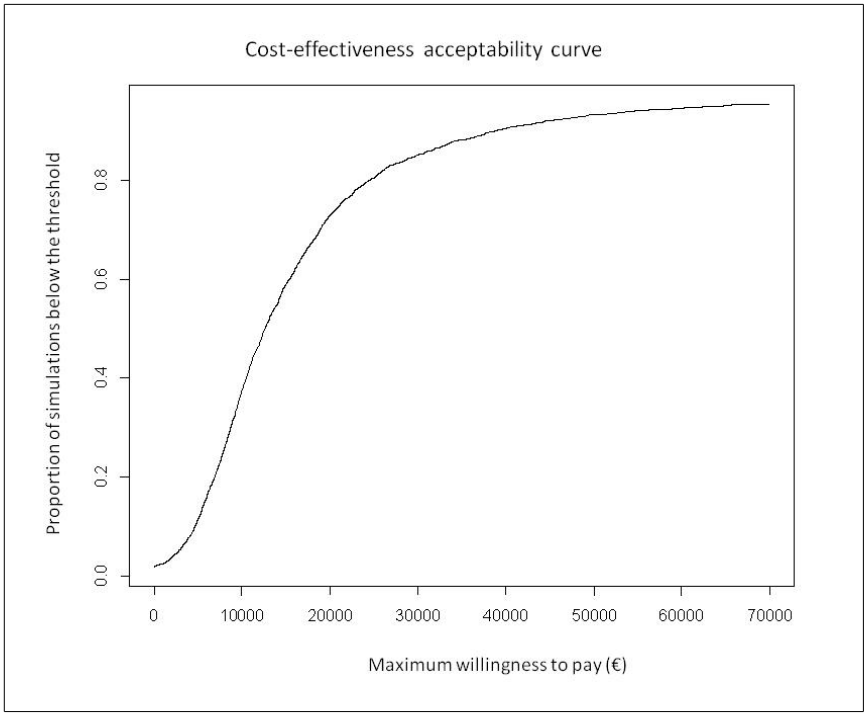

Figure 4 Cost-effectiveness acceptability curve. The x-axis shows the maximum value that someone (society or an insurance company or another 'decider') is prepared to pay for a QALY gained. The y-axis shows for each value the part of the simulations that come out below this value: the greater the preparedness to pay, the greater is the proportion of simulations that fall under this, and how greater the probability is that the new drug is cost-effective.

Annex **E**

List of abbreviations

ACCP	American College of Chest Physicians
CI	Confidence interval
CFH	Commissie Farmaceutische Hulp (Pharmaceutical Care Committee)
CHADS2	Score that gives the estimated risk of a stroke in people with atrial fibrillation. Explained in the text
CVZ	College voor zorgverzekeringen (Health Care Insurance Board)
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FNT	Federatie van Nederlandse Trombosediensten (Federation of Dutch Thrombosis Services)
GVS	Geneesmiddelen Vergoedingssysteem (Medicinal Products Reimbursement System)
IGZ	Inspectie voor de Gezondheidszorg (Health Care Inspectorate)
INR	International Normalised Ratio
LMWH	Low Molecular Weight Heparin
NHG	Nederlands Huisartsen Genootschap (Dutch College of General Practitioners)
NICE	National Institute for Health and Clinical Excellence
NOAC	New Oral Anticoagulants

RCT	Randomised Clinical Trials
TIA	Transient Ischaemic Attack
TTR	Time in Therapeutic Range
VKA	Vitamin K antagonist
VTE	Venous thromboembolism