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.