



**Universiteit  
Leiden**  
The Netherlands

## **Towards improvement of oral anticoagulant therapy**

Leeuwen, Y. van

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## **CHAPTER 8**

### **General Discussion & Summary**



## General Discussion & Summary

Although the quality of oral anticoagulant treatment has improved over time, there still is considerable risk to experience a thrombotic and haemorrhagic complication. The risk for complications increases when patients are either under- or overanticoagulated. Improvement in dosing strategies is warranted. The studies included in this thesis aim to optimise dosing of vitamin K antagonists and control of oral anticoagulant treatment.

### *Strategies for improvement of dosing of oral anticoagulants.*

In our double-blind controlled trial comparing a simple dosing algorithm to an algorithm which incorporated the patients' sensitivity for vitamin K antagonists, we showed that there was no increase in quality of treatment, expressed as time spent within the therapeutic range (**chapter 2**). Also, the time between two visits was similar in both groups, although the interquartile range was broader for the new algorithm. However, the new algorithm was more efficient, as more dosage proposals were generated and accepted. For all visits combined, the standard algorithm generated an acceptable proposal in 55.3% of cases, which was 77.4% for the new algorithm. Finally, in almost all cases in which the standard algorithm did not result in a dosage proposal, a proposal was generated by the new algorithm. In these cases, the new algorithm performed as well as an unassisted physician.

In **chapter 3** we investigated the 'transition factors' between the maintenance dosages of three frequently used vitamin K antagonists for oral anticoagulant treatment. We observed that the maintenance dose of warfarin was 0.41 (95%CI 0.39- 0.43) times the maintenance dose of phenprocoumon. The transition factor between acenocoumarol and phenprocoumon was 0.84 (95%CI 0.79- 0.89) and between acenocoumarol and warfarin 1.85 (95%CI 1.78- 1.92).

In the prospective cohort study consisting of 220 Italian patients initiating oral anticoagulant treatment with acenocoumarol described in **chapter 4**, we showed that CYP2C9\*3 was associated with a 25% dose reduction and an increased risk of over-anticoagulation (INR>6) on day 4. Two copies of the VKORC1\*2 alleles were associated with a 45% dose reduction and an increased risk of over-anticoagulation. Both VKORC1\*3 and VKORC1\*4 homozygosity was associated with an increased dose requirement and a reduced risk of over-anticoagulation. The VKORC1\*3 or \*4 + CYP2C9\*1 genotype combination was associated with the highest dose requirement and the lowest INR on day 4; VKORC1\*2 + CYP2C9\*3 with the lowest dose requirement, the highest INR and an increased risk of over-anticoagulation. Even though they spent approximately 50% of the time within the target therapeutic range, VKORC1\*3 or \*4 + CYP2C9\*1 carriers spent a large percentage of the remaining time above and carriers of VKORC1\*2 + CYP2C9\*3 below the target range.

### ***Relevance of improved dosing strategies for clinical practice***

In recent years, interest in individualised dosing of pharmaceuticals based on a genetic profile has increased. For some drugs, genetic factors can be responsible for the majority of patient variability. Variability in response to vitamin K antagonists is in part mediated by genetic variability. In accordance with the results presented in chapter 4, several studies have reported variants in CYP2C9 and VKORC1 genes to be important for patients using warfarin or phenprocoumon, although there are some conflicting results [1-6]. Individualised dosing which incorporates the specific genotype of a particular patient could result in more appropriate dosages and less frequent over-anticoagulation in the initial phase of treatment. As we showed in chapter 4, patients who have a genotype which makes them more sensitive to vitamin K antagonists need lower maintenance dosages and

are at increased risk for overanticoagulation in the initial phase of treatment. It is likely that reducing the starting dosages of these patients results in a reduction of overanticoagulation, and thus a decreased risk for bleeding complications. However, knowledge of the specific genotype of a patient in the maintenance phase of treatment is less likely to result in an improvement of therapy as reflected by the time spent within the therapeutic range. As demonstrated in chapter 2, dosing during the maintenance phase assisted by a computerised algorithm which incorporated the sensitivity of a patient for the anticoagulant did not result in an increased quality of treatment. The sensitivity factor used by the algorithm was based on the patients' response to previous dosages. This response partly depends on the genotype of a particular patient, and therefore the effect of the genotype is already reflected in the calculated sensitivity factor.

Using one single algorithm for generation of dosage proposals is most efficient for daily clinical practice. An algorithm which incorporates the genotype of the patient may be beneficial compared to an algorithm without this information, due to a possible advantage in the initial phase of treatment. But, the response to vitamin K antagonists is not entirely dependent from a patient's genetic profile. Removing the variability due to the genetic profile still leaves a substantial variability in response to vitamin K antagonists and the effect on clinical endpoints may not outweigh the costs for genetic testing. A prerequisite for genotype-based dosing is the availability of bedside genotype tests, since the genotype is already required for the first dosing proposal. To investigate the potential benefit of genotype-based dosing a randomised controlled trial should be performed.

Using the calculated transition factors reported in chapter 3 physicians are able to estimate the new maintenance dosage in case a patient needs to switch from one vitamin K antagonist to another. However, two important limitations for the use of

these transition factors require attention. First, the genotype may also influence these transition factors, as from other studies it is known that sensitivity for different vitamin K antagonists varies per genotype. In theory, in a patient who has a genotype which results in an extreme sensitivity for warfarin but not for phenprocoumon, switching may result in either under- or over-coagulation depending on the direction of the switch. In our study described in chapter 3, we could not investigate this since DNA was not available. Second, we only determined the transition factor between maintenance dosages. Since switching from one vitamin K antagonist to another also requires a transition scheme, it remains unknown what dosages are needed in the initial days after switching for optimal safety. Only one other study investigated a dosage scheme for transition from phenprocoumon to warfarin in patients treated in an outpatient clinic [7]. Because of these two important limitations, patients who switch from one vitamin K antagonist to another require frequent monitoring during the initial phase after transition.

Future studies that investigate switching between different types of vitamin K antagonists should address the potential influence of genotype on the transition factors, as well as the optimal dosing scheme for transition.

### ***Stability of oral anticoagulant treatment.***

Besides improving dosing of oral anticoagulants, monitoring of patients is also important. If one could identify patients at high risk for complications, precautions can be taken to avoid these complications.

In a study of 630 subjects with mechanical heart valve prostheses we found that unstable anticoagulation was associated with an increased risk of haemorrhagic and thrombotic complications (**chapter 5**). Both variability and time spent outside the target range affected risk. The variance growth rate described by Fihn, method

A, incorporates both aspects of instability, and was therefore most clearly associated with complications of anticoagulant therapy, especially haemorrhagic episodes. Thrombotic events were most clearly predicted with variability calculated with method B1 and B2, which only concerns variability of the INR and not the time within range. The optimal time window to determine these measures was three months. In **chapter 6** we showed that unstable anticoagulation is observed more frequently with the use of acenocoumarol versus phenprocoumon, in individuals with daily strenuous physical activity, and less frequently in obese patients. Patients who are obese, have daily strenuous physical activity, or are frequent alcohol users have a higher risk of being more frequently out of range. Furthermore, increased anticoagulant dosage substantially reduced the risk of being frequently out of range.

Finally, in **chapter 7** we described the study design of our trial of which the primary aim is to compare the quality of a treatment with warfarin to the quality of a treatment with phenprocoumon. In addition we gave an overview of the overall quality of anticoagulant treatment, without giving the results for the two treatment groups separately since the trial is ongoing. The overall quality of anticoagulant treatment was high, with a median time spent within the therapeutic range of 74.7% (IQR 58.8-87.0).

The quality of oral anticoagulant treatment depends on a combination of the percentage of time spent within the therapeutic range and instability of anticoagulation. Both factors have their own risk factors and may require their own management.

The achieved intensity of anticoagulation was less important in predicting thrombotic events than haemorrhagic events. Variability, however, seems to be most predictive for thrombotic complications. This may be because time spent



outside the therapeutic range for the greater part consists of overanticoagulation rather than underanticoagulation. Highly variable INRs result in a disturbed balance between procoagulant and anticoagulant factors which may lead to a procoagulant state, although there is no clear explanatory mechanism. Initiation of oral anticoagulant treatment is associated with a temporary hypercoagulable state due to the difference in half life between pro- and anticoagulant factors. Each time the INR rises again in a patient who is unstably anticoagulated, a hypercoagulable state may be temporarily present as a result of a similar mechanism.

Other studies have also shown that variability is a risk factor for complications of anticoagulant treatment [8-10]. For daily clinical practice this means that physicians should not interpret an INR within the therapeutic range for a patient with highly variable INRs the same as an INR within range of a patient whose INRs are always within range.

Several studies have compared the quality of treatment with acenocoumarol to a treatment with warfarin or phenprocoumon. The results with respect to stability are mostly, but not always in favour of the longer acting vitamin K antagonists [11-19]. In our study described in chapter 6 acenocoumarol was shown to be a risk factor for unstable anticoagulation, which is also in accordance with an earlier study investigating risk factors for unstable anticoagulation [20]. Acenocoumarol should therefore only be used in patients in whom short acting drugs are preferred, such as women trying to get pregnant. In all other patients a longer acting vitamin K antagonist should be used, either warfarin or phenprocoumon. Which one of these two vitamin K antagonists results in the highest quality of treatment can be answered with the results of the trial described in chapter 7.

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