Management of antithrombotic therapy in venous and arterial thromboembolism
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Chapter 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

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The clinical effectiveness of vitamin K antagonists (VKA) has been established in a variety of conditions, based on well-designed clinical trials. VKA has been widely used for the primary and secondary prevention of arterial and venous thromboembolism. It is the therapy of first choice in long-term treatment of deep vein thrombosis and pulmonary embolism, the prevention of systemic and valve thrombosis in patients with mechanical heart valves and the prevention of systemic and cerebral embolism in atrial fibrillation (AF)\(^1\). In addition, there are other widely accepted indications for VKA therapy that have not been evaluated in rigorously designed clinical trials. These indications include valvular heart disease associated with AF, mitral stenosis, dilated cardiomyopathy and prevention of graft occlusion after peripheral bypass grafting\(^4\).6.

The mechanism of action of VKA relies on the interference with the action of vitamin K, a cofactor essential for converting precursor proteins into the mature coagulation factors II, VII, IX and X\(^7\). As a result, vitamin K-dependent factors that have been affected by VKA during synthesis are dysfunctional. VKA does not affect the activity of coagulation factors in which synthesis was complete before exposure to VKA. Thus, depletion of these mature factors through normal catabolism must occur before therapeutic effects of VKA are seen. Each factor differs in its degradation half-life, ranging from 5 hours (factor VII) to as long as 60 hours (factor II). As a result, several days of therapy are required before a complete clinical response is seen. VKA prolongs both the prothrombin time (PT) and thromboplastin time (aPTT), but the PT is used clinically to guide therapy. Because of the considerable variation in PT among laboratories using different reagents, in 1983 the World Health Organization (WHO) adopted a system of normalization of the PT to allow for standardization of reporting the results. With the use of this method every PT can be converted into an INR (International Normalized Ratio), according to the formula:

\[
\text{INR} = \frac{\text{patient's PT}}{\text{normal patient average PT}} \times \text{ISI}
\]

where the ISI (International Sensitivity Index) is the calibration factor dependent on the reagent used and is provided by the manufacturer. The ISI is used to characterize the sensitivity of the reagent, which can variably affect PT. Sensitive reagents have a low ISI. The ISI is both instrument-dependent and reagent-dependent. Because the INR is dependent on the ISI, it is critical for each laboratory to calibrate the ISI for their own instruments and reagents.

There is a wide variability in the required dose of VKA among patients\(^8\). Since even the required dose in an individual patient may vary over time, frequent INR monitoring is necessary to ensure a stable level of anticoagulation and dose-adjustments have to be
made to maintain the INR in the therapeutic range. The notion of the "therapeutic range" is defined as the range that provides maximal antithrombotic effect with minimal risk of bleeding. Ideally, the INR should be kept in the therapeutic range most of the time, but many factors influence this goal. These include pharmacologic factors, such as interacting drugs or illnesses that affect the metabolism of VKA, such as fever or hepatic dysfunction. In addition, important fluctuations in vitamin K intake can also affect the INR, occurring in both apparently healthy and sick patients. Increased intake of vitamin K leading to a reduction of the response to VKA, occurs in patients consuming green vegetables and in patients treated with supplements containing vitamin K. Reduced vitamin K intake potentiates the effect of VKA in sick patients treated with antibiotics and intravenous fluids without vitamin K supplementation and in states of fat malabsorption.

Besides the need for frequent monitoring, the major drawback of treatment with VKA is the risk for bleeding complications. Annual bleeding incidences of 0-4.8% for fatal bleeding and 2.4-8.1% for major bleeds have been reported. Minor bleedings occur more often, with an incidence of approximately 15% per year. Although intracranial bleeding is rare, it is the most frequent cause of fatal bleeding, with mortality rates ranging from 10 to 68%. There is a strong relationship between the intensity of anticoagulant therapy and the risk of bleeding complications. Since most of the bleeding events occur in the period of overcoagulation, it is plausible to assume that the risk for bleeding will decrease with a more stable level of anticoagulation. However, even with a therapeutic INR, patients are still at risk for bleeding. Age is the most important patient characteristic that increases the risk for bleeding. One study showed a 46% increase in major bleeding for every 10 year increase above the age of 40. Other conditions that have been associated with bleeding during VKA therapy include (treated) hypertension, malignancy and a previous bleeding episode.

Although the effectiveness of VKA has been clearly demonstrated in a number of trials for several conditions, there are a number of aspects of this therapy that remain a matter of debate. One of these unresolved issues comprises the optimal intensity of VKA therapy in patients with mechanical heart valves. The first ACCP guidelines published in 1986 recommended an INR between 3.0 and 4.5, regardless of the type and location of the valve. However, the risk for thromboembolism appears to vary with the position of the valve. Patients with a prosthesis in the mitral position have a significantly higher risk of thromboembolic complications than those with an aortic valve prosthesis, whereas the bleeding risk is similar. Based on this discrepancy, a minor discrimination in anticoagulation intensity was recommended between aortic and mitral valves and the target range was lowered to 2.0 and 3.5, depending on the position and type of the valve. However, these latest guidelines are based on only a few studies and are in contrast to a landmark trial by Cannegieter et al. The authors
described, based on a discrepancy between the target and achieved INR, that the optimal intensity of anticoagulation, resulting in the fewest adverse events, lies between INR levels of 2.5 to 4.9.

Another important unresolved question is the optimal intensity and duration of treatment with VKA in patients with venous thromboembolism (VTE). At present, standard treatment of VTE consists of an initial course of (low molecular weight) heparin for at least five days, followed by VKA with a target INR between 2.0 and 3.0\textsuperscript{15,16}. Target INR's above 3.0 has been shown to result in more bleeding, without any benefit in the prevention of recurrences\textsuperscript{17}. Recently, it was hypothesised that extended secondary prophylaxis with low intensity VKA therapy (INR 1.5-1.9) might be as effective as conventional intensity VKA therapy (INR 2.0-3.0) but associated with a lower bleeding risk. In a double-blind study involving patients with unprovoked VTE who had completed three months conventional intensity VKA therapy, two intensities of VKA therapy were compared\textsuperscript{21}. The study showed that the risk for recurrent thromboembolic disease was higher in the low intensity group, without significant differences in the bleeding risk, and therefore is no treatment option for the secondary prophylaxis after a first episode of VTE.

The optimal duration of treatment with VKA reflects a balance between the risk of recurrent disease when the treatment is discontinued and the risk of bleeding resulting from continued therapy. The risk of recurrence depends on patient specific risk factors. This risk is greater among patients who have a persistent risk factor (thrombophilia or cancer) and those whose initial episode occurred in the absence of an apparent risk factor than it is among patients in whom VTE develops in association with a transient risk factor, such as surgery or plaster immobilisation\textsuperscript{18}. In addition, the cumulative risk of bleeding complications is also determined by various risk factors. Major determinants are the length of therapy and various patient characteristics (increasing age and the presence of cancer)\textsuperscript{19,20}. Ideally, treatment should be continued until the benefits of treatment (i.e. prevention of recurrent VTE events) are offset by the risks (i.e. major bleeding). However, rational decisions on the optimal duration of anticoagulant therapy for the individual patient require knowledge of the risk of recurrence after discontinuation of treatment and the risk of bleeding during anticoagulant therapy.

In the debate about the optimal duration of treatment with VKA it is also reasonable to take the burden of treatment, as experienced by the patient, into account. Stopping treatment may affect quality of life negatively because of a strong fear of a recurrent episode, whereas others experience anticoagulant treatment and its monitoring as a burden. This subjective estimation of quality of life will probably have a considerable impact on the patient appreciation of the duration of treatment.

Patients with atrial fibrillation or mechanical heart valves receiving chronic VKA therapy pose a clinical challenge when they need to undergo invasive procedures.
Temporary discontinuation of anticoagulants increases the risk for valve thrombosis and embolism. Since arterial embolism often results in death or major disability it is important to minimize this risk. However, perioperative thromboembolic risk is unknown because there are no reliable data from patients without long-term anticoagulation, but may be higher than expected since the prothrombotic effect of the surgery itself could increase the risk of thromboembolic complications. On the other hand, continuation of anticoagulants perioperatively can cause life-threatening bleeding. In the absence of clinical evidence, several anticoagulant strategies have been developed, but are mainly based on quantification of thromboembolic risk during discontinuation of anticoagulation and the risk estimates for bleeding associated with reinitiation of the anticoagulation. The guidelines are diverse, varying from discontinuation of VKA a few days before surgery and reinstitution after surgery to complete coverage with intravenous unfractionated heparin (UFH) only shortly interrupted during the surgical procedure. Recently, low molecular weight heparin (LMWH) was considered as a potential alternative for unfractionated heparin, because it results in stable anticoagulation without the need for monitoring and dose adjustments. Another potential benefit is avoiding hospitalization solely for anticoagulation with intravenous unfractionated heparin. However, the half-life of LMWH is prolonged as compared to UFH and the clearance is not always predictable. This makes it difficult to precisely time the last preoperative injection and therefore this strategy carries a certain risk for perioperative bleeding.

Outline of the thesis
More research is necessary to improve the management of anticoagulant therapy in patients with venous and arterial disease. Aim of this thesis is to contribute to this research. The first part of this thesis concerns anticoagulant strategies in patients with mechanical heart valves. Chapter 2 gives an overview of various aspects of anticoagulant therapy in patients with mechanical and bioprosthetic heart valves as well as for patients with atrial fibrillation. Chapter 3 describes the results of a meta-analysis comparing two intensities of VKA for patients with mechanical heart valves. In Chapter 4 we studied a cohort of patients with prosthetic heart valves who underwent non-cardiac surgical interventions. The incidence of thromboembolic and bleeding complications were evaluated according to the different periprocedural anticoagulant strategies.

The second part of the thesis focus on patients with atrial fibrillation. The design and the results of the PIANO study are described in Chapter 5. In more detail, the PIANO-study (perioperative interruption of anticoagulant treatment in patients with atrial fibrillation) is a randomised study comparing two different anticoagulation regimens in the perioperative period. Chapter 6 gives insight in the risk of perioperative thromboembolism and bleeding in patients with AF who undergo a surgical procedure. A
A dataset of a large clinical trial of patients with AF was used to evaluate all non-cardiac surgical interventions.

The third part of this thesis deals with patients with venous thromboembolic disease. In Chapter 7 we discuss the findings of a meta-analysis concerning the natural course following a first episode of symptomatic venous thromboembolism, in particular after cessation of treatment with VKA. A decision model for the optimal duration of treatment for patients with deep vein thrombosis is presented in Chapter 8. The influence of co-medication on the stability on VKA treatment is described in Chapter 9. Finally, in Chapter 10 we studied whether the anticoagulant activity of pentasaccharide can be corrected by the prohemostatic agent recombinant factor VIIa.

**REFERENCE LIST**


