Determinants of effective, safe and convenient vitamin K antagonist use
Kooistra, Hilde Afra Margareth
Chapter 1

Introduction
INTRODUCTION

Anticoagulants are very effective for the treatment and prevention of several thrombotic diseases, but this comes at the cost of bleeds. The efficacy and safety of anticoagulants are inversely related: a higher efficacy comes at the cost of more bleeding events. There are several types of anticoagulants, of which vitamin K antagonists (VKA) are most commonly used. Unfortunately, an optimal balance between efficacy and safety cannot be achieved constantly in every patient on VKA.

The aim of this thesis is to identify predictors and determinants of the efficacy, safety and convenience of VKA treatment for the individual patient. To illustrate the problems of too little and too much coagulation, the hemostatic balance and the effect of interfering diseases are first described. Secondly, the clinical impact of atrial fibrillation (AF) and venous thrombosis (VTE) on survival and quality of life are discussed, as these diseases are the main indications for anticoagulants. Subsequently, an overview of anticoagulants and their working mechanism will be provided. Lastly, the relevance of individualized care will be outlined, as well as the advantages and disadvantages of an observational research design.

Haemostasis and thrombosis

Under normal circumstances, blood circulates through the veins without clotting and without hemorrhage. This is the result of the mechanisms toward clot formation, counterbalanced by inhibition of the coagulation cascade and degradation of the clot (fibrinolysis). There are extensive feedback mechanisms to prevent disturbance of this delicate balance, as this would have serious consequences for survival.

For the formation of a clot, basically all coagulation factors have to be present at a sufficient level. Diseases such as hemophilia A and B, which are caused by a deficiency of a coagulation factor, lead to impaired clot formation. This does not only worsen the clinical outcome of bleeds that would have occurred anyway such as after a trauma, but also causes severe bleeding problems without any provocation. Supplementation of the missing coagulation factor can prevent and treat these bleeds.

On the other hand, a prothrombotic state can also be life threatening. Virchow was the first to describe the three factors involved: abnormalities in the composition of blood, the flow of blood and the vessel wall. The first includes a deficiency of inhibitors of the coagulation cascade such as protein S or C or antithrombin. The second can occur during immobilization and in patients with atrial fibrillation for instance. Vessel wall abnormalities play mainly a role in atherosclerotic thrombosis, but evidence is growing that this is also relevant for the development of venous thrombosis. The mechanisms leading to morbidity and mortality differ between arterial and venous thrombosis. Occlusion of an arterial vessel stops the oxygen supply downstream, causing ischemia and in the end necrosis. Venous thrombosis causes upstream congestion of blood and less blood return to the heart.

The treatment of thrombosis depends on the primary underlying mechanism. Atherosclerotic
thrombosis, mainly caused by alterations of the vessel wall, can be treated with platelet aggregation inhibitors such as aspirin. Anticoagulants are indicated if the main underlying mechanisms are alterations in the composition of the blood and/or blood stasis, like in VTE and AF. In this thesis we will focus on the anticoagulant treatment of AF and VTE.

Clinical impact of AF and VTE

AF is a common health problem with a high prevalence (1.5-2.0%) that increases with age. The main complication is a stroke, which occurs four to five times more often in patients with than without AF. This is caused by embolism of stasis-precipitated thrombi formed in the left atrial appendage. Not only the prevalence of AF increases with age, but age is also an important risk factor for stroke within the group of AF patients. Other risk factors are congestive heart failure, hypertension, diabetes, previous stroke, vascular disease, and female sex.

Strokes and transient ischemic attacks (TIAs) due to AF are more severe than emboli from carotid disease, possibly due to larger clot particles. A quarter of the patients die of stroke, which is almost twice as many as in stroke patients without AF. Long-term disabilities have potentially an even larger clinical impact as they occur more frequently than death, and can be devastating for the quality of life. In addition, 23% of patients suffer a recurrent stroke within one year.

The incidence of venous thrombosis is about 0.15% per year and also increases with age. It usually presents as a deep vein thrombosis (DVT) in the leg or as pulmonary embolism (PE). Risk factors for VTE are amongst others inflammation, estrogen use, pregnancy and puerperium, inherited thrombophilia, malignancy, immobilization and surgery.

Approximately 4% of patients without cancer and 20% of patients with cancer die within 30 days after VTE diagnosis, a quarter of these deaths are directly related to PE. In addition, half of the DVT patients have a decreased quality of life because of a post-thrombotic syndrome. This is characterized by pain, edema, pigmentation, and sometimes even venous ulcers. The majority of PE patients have persistent complaints of dyspnea at long-term follow-up. The most severe form is caused by chronic thrombotic pulmonary hypertension with progressive right heart failure, resulting from increased vascular resistance. This is characterized by progressive dyspnea on exertion, edema, palpitation and/or hemoptysis. The risk of recurrent VTE following cessation of anticoagulation in patients without a removable causal factor is about 10% in the first year and 30% at five years.

As AF-related stroke and VTE have a large clinical impact, there is much to gain from an effective treatment. Moreover, prevention can be worthwhile in patients at high risk for an event. As mentioned before, both patient groups strongly benefit from the hypocoagulability that can be induced by anticoagulants.

Anticoagulants

Platelets and fibrin are essential to form a firm clot. Fibrin is generated by the configuration of fibrinogen, and this process is initiated by thrombin formed via the coagulation cascade. All
anticoagulants inhibit fibrin formation by interfering with the coagulation cascade.

There are three main types of commonly used anticoagulants: heparins, vitamin k antagonists (VKA) and non-VKA oral anticoagulants (NOACs). The first can only be administered intravenously or subcutaneously, and promote the working mechanism of the natural coagulation inhibitor antithrombin. As many patients have to use anticoagulants for a long period or even for life, the use of an oral drug is commonly preferred over the more invasive treatment with heparins. For decades, VKA were the only oral anticoagulants. Vitamin K is needed for the production of coagulation factors II, VII, IX and X. During this production process vitamin K is oxidized into an inactive form. As vitamin K is only limited available, the vitamin K epoxide reductase complex (VKOR) reduces vitamin K to its active form again. VKA block the VKOR enzyme, and in this way limit the production of factors II, VII, IX and X (Figure 1). More recently, the NOACs have been introduced. Instead of interfering with the production of coagulation factors, they inhibit the activated factors II (e.g. dabigatran) or X (e.g. rivaroxaban, apixaban, edoxaban).

Figure 1. Points of action for oral anticoagulants on the coagulation cascade, adapted from Grottke et al.24.
With the introduction of the NOACs, a good oral alternative for VKA has become available. Physicians now have the option to choose the type of anticoagulant that is best for the individual patient. For this, it is essential to know the advantages and disadvantages of VKA and NOACs.

**Vitamin K antagonists**

VKA are very effective in preventing thromboembolic events, e.g. patients with AF have 64% less strokes while on VKA, and the risk of recurrent disease is reduced from 25% to 3% in the first 6-12 months after VTE. However, it can be challenging to achieve a stable anticoagulation level that protects well against thrombosis, but does not increase the bleeding risk disproportionally. This is because the dose response may vary remarkably between but also within patients. The variation can be partly explained by genetic differences determining the VKOR production, other patients characteristics such as age and comorbidity, and external factors such as the vitamin K content of the diet and interactions with comedication. Therefore, frequent blood measurements are required to adjust the dosing scheme.

The level leading to the desired therapeutic effect of a drug is called the therapeutic range. Initially, the anticoagulant effect was measured by a prothrombin time (PT). However, proper VKA management remained difficult because the PT results from different laboratories were not directly comparable, thus no uniform therapeutic range could be used. This problem was solved by the introduction of the International Normalized Ratio (INR). This is the ratio of the PT of the patient and the normal PT of that laboratory, adjusted for the type of reagent used in the test by the International Sensitivity Index: \( \frac{PT_{\text{patient}}}{PT_{\text{normal}}} \). Consequently, in every laboratory the INR is 1.0 (range 0.8 - 1.3) in patients without anticoagulants. A higher INR indicates more time needed to form a clot, thus ‘thinner’ blood. In patients with AF and VTE, the balance between the bleeding and thrombotic risk is optimal within the therapeutic range of INR 2.0 to 3.5. Above INR 3.5 the bleeding risk is disproportionally high, and below INR 2.0 patients are not well protected against thromboses.

In The Netherlands, VKA management is provided by dedicated thrombosis services. This results in service-oriented care, as they are easily accessible for questions from patients and even visit patients at home for INR-measurements. They register any complication of treatment as a mandatory part of the Dutch quality system, which is also very valuable for research purposes. By performing frequent INR measurements and dose adjustments, they aim to keep the INR within the therapeutic range during the whole treatment period.

The most commonly used measure for VKA control is the time in the therapeutic range, which was first introduced by Rosendaal. It is based on linear interpolation and reflects the proportion of days that the INR is within the therapeutic range. More recently, it has become clear that also the degree to which one INR differs from the next INR is independently related to clinical outcome. Fortunately, VKA perform still well if the INR is during a limited time above or under the range. Only the quarter of patients with poorest VKA control, who spend approximately 35% of the time out
of the therapeutic range, have significantly more bleeding events and are less protected against thromboses.

VKA-associated bleeds

Major bleeds are the most important complication of VKA, and the incidence is approximately 1-2% per year. The risk is among other things highest during the first three months of treatment, at higher age, during malignancy, in patients with a history of bleeding, in patients using platelet aggregation inhibitors, and in patients with poor VKA control. However, the safety of VKA does not only depend on the bleeding incidence, but also on the treatment options in case of bleeding. Local hemostasis can be achieved through surgery, endoscopy or compression for example. However, it is often necessary to antagonize the anticoagulant effect as well. Also, for safe surgery in an emergency setting, rapid correction of the INR may be indicated. If reversal can be awaited for three to five days, this can be achieved by withholding anticoagulants. If a more rapid reversal is needed, an excess of vitamin K can be administered that will directly restore the production of coagulation factors, but will take at least eight hours to normalize hemostasis.

In urgent situations, where an immediate and complete correction of the anticoagulant effect is required, supplementation of factors II, VII, IX and X is indicated. One treatment option could be fresh frozen plasma. Although plasma contains all vitamin K-dependent coagulation factors, it needs ABO typing and thawing before use, and is associated with long infusion times. The second option is plasma-derived prothrombin complex concentrates (PCC), which contain factor II, IX and X, and a variable dose of factor VII. It can be administered in smaller volumes with shorter infusion times than plasma. A recent clinical trial has shown that PCC administration results in a better clinical outcome than the use of plasma. However, there is still no consensus regarding the optimal dosing strategy of PCC. Infusion of too much PCC might increase the thrombotic risk, and is more expensive. However, if hemostasis is delayed because of an insufficient first dose, this can also lead to more severe bleeding and extra costs. The administered dose can be based on patient characteristics, the target INR, and/or the INR at presentation. However, there are also promising studies from our group, suggesting that rapid administration of a fixed dose could be as effective and less expensive.

NOACs

NOACs are direct inhibitors of activated factor II or X (Figure 1). Large worldwide clinical trials have shown that they are at least as effective and safe as VKA, and meta-analyses even identified a favorable risk-benefit ratio for NOACs. NOACs reduced significantly the risk of stroke, intracranial hemorrhage, and mortality, with comparable major bleeding as for VKA. Another important advantage of NOACs is that they can be used in a fixed dose without the need for monitoring, as they have fewer food and drug interactions than VKA. However, these advantages come with higher costs, limited experience of the physicians, the lack of control on therapy compliance, requirement
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of adequate renal clearance, and finally more gastrointestinal complaints and bleeds.\textsuperscript{51}

In contrast to the well-known real-life efficacy and safety of VKA, for the NOACs only limited real-life data are available. These are urgently needed, as trial data may not readily translate into clinical practice. Vulnerable subpopulations are often underrepresented, such as cancer patients, patients with poor adherence, elderly and patients with multiple comorbidities. Hopefully, ongoing large phase IV registry studies will provide the real-life data in the near future.\textsuperscript{52-54}

Clinical decision making

Clinical decision making starts with the choice whether the patient should receive any anticoagulant at all. Subsequently, the preferred type of treatment should be determined. If patients are taking interacting drugs, VKA or NOACs might be contraindicated. Also, some thrombotic indications such as a prosthetic valve require VKA.

However, most patients do not have a contraindication for any anticoagulant. In that case, the optimal treatment choice depends on the bleeding risk, thrombotic risk, convenience of treatment and costs. These factors can differ between patients and within patients over time, and therefore require individual decision making and regular evaluation. Although it is impossible to know what the future will bring, epidemiological research can help to make the decision with the highest chance of a favorable outcome.

Observational research

The two main types of studies are observational and experimental studies. The very complete, and prospectively collected data of the thrombosis services contain a wealth of information. The high prevalence of AF and VTE make it possible to perform subgroup analyses. Therefore, observational research is an attractive option in the field of anticoagulation, but it is essential to be aware of its advantages and disadvantages.

An important advantage is the better generalizability, because vulnerable patients are commonly underrepresented in experimental studies. On the other hand, an observational design makes it more difficult to differentiate between an association and a causal relationship. For instance, breast feeding and the intelligence of the child are strongly associated. However, mothers with a higher intelligence more often breast feed their children, and the intelligence of offspring partly results from the intelligence of the mother. Therefore, the mother’s intelligence is considered a confounder. Confounding is a problem because it leads to misinterpretation: ‘Low intelligence can be prevented by breast feeding.’ Such a spurious association can be eliminated by adjustment or stratification by the common cause. Research confirms that breast feeding is not related with the intelligence of the child if the intelligence of the mother is taken into account.\textsuperscript{55} However, one can only control for known confounders.

If causality is the primary interest, experimental research provides the strongest evidence. It can minimize confounding by random allocating of patients to an intervention and non-intervention
group. This results, probably, in an equal distribution of all known and unknown factors. Consequently, any difference between the two groups results from an alteration of the ‘natural course’ due to the intervention. Thus in our example, this would be random allocation to breast feeding. However, interventions can be dangerous, unethical, expensive, unpractical or even impossible. Of course, no medical ethical committee would allow us to tell patients to refrain from breast feeding, because it has many other advantages for mother and child. Therefore, observational research may be the best option to analyze causality but requires substantial knowledge of the subject. Confounding is not an issue for the identification of predictors.

Another important cause of misinterpretation results from a systematical error in the data, which is called bias. Smoking women with a low birth weight baby may feel ashamed and deny smoking during their pregnancy more often than smoking mothers of healthy babies, for example. This would lead to the wrong conclusion that smoking protects against low birth weight. Another kind of bias is selection bias. If a study would analyze the effect of four meetings to help pregnant women to quit smoking, it is likely that at the fourth session only patients show up who think it is helpful. Consequently, the success-rate measured at the fourth meeting would be too optimistic, as patients who did not appreciate the meetings are underrepresented. Survivor bias also occurs frequently in medical research. It would occur if we would select all babies from smoking mothers who were born alive to determine the impact of smoking. Stillbirth babies would not be included, which would lead to an underestimation of the negative impact of smoking. Including all mothers with confirmed pregnancies (an inception cohort) would solve this problem.

If observational research is applied in the right way, it provides a great opportunity to learn from ‘the natural course of things’. Without any harm during the study, it can be beneficial for future decision making.

Scope of this thesis
The efficacy and safety of VKA are directly related to the degree of VKA control. Therefore, it is important to be able to predict which patients are at high risk of poor VKA control, as they might need extra medical attention. Moreover, alternative treatment options could be considered, such as switching to a VKA with a longer half-life or to one of the NOACs. In chapter 2, we present a prediction model of poor VKA control in VTE patients. In addition, we determined whether predictors of VKA control were also predictors for clinical outcome. For this, we used a prospective cohort of patients allocated to VKA in two randomized trials (EINSTEIN DVT and PE studies).

Unfortunately, even patients with initially stable VKA therapy can develop extreme overanticoagulation later on. This could be the temporary result of a transient distorting factor, resulting in rapid restabilization. However, it could also be a prelude of subsequent long-lasting inferior quality of VKA control, accompanied by poor clinical outcome. In chapter 3, we analyzed the difference in quality of VKA control, thrombotic risk and bleeding risk before and after overanticoagulation. Subsequently, the patients with overanticoagulation were compared with
patients without overanticoagulation.

The bleeding risk does not only depend on the degree of VKA control, but evidence is growing that age above 75 is also an independent risk factor for major bleeding. Interestingly, previous studies showed that these patients still benefit from anticoagulant therapy. However, it is unknown whether the bleeding and thrombotic risks keep increasing after the age of 75 years. In chapter 4, we analyzed in a matched cohort study the bleeding and thrombotic risk in septuagenarians, octogenarians and nonagenarians. In addition, we compared the incidence of thrombotic and major bleeding events within age groups.

The clinical outcome of a VKA-related bleed depends on the treatment options. Death, blood loss and the need for blood transfusion might be preventable if early hemostasis can be achieved. PCC can lead to immediate normalization of the coagulation cascade. Dosing can be based on patient and treatment factors, but a fast fixed dose might be even better. In chapter 5, a systematic review of the literature was performed to identify the optimal dosing strategy of PCC for emergency VKA reversal.

Previous chapters focused on the efficacy and safety of VKA. Another important aspect is the impact of VKA use on quality of life. This is in particular relevant for AF patients, because they are treated for life, and their treatment goal concerns prevention of possible future events instead of symptom relieve of a current disease. Moreover, most ischemic strokes cause long-term disabilities but are not fatal, therefore VKA improve quality of life (QoL) rather than survival. This makes patients and physicians reluctant to start VKA, as they fear a negative impact of VKA on QoL due to the frequent INR measurements, common minor bleeding and complex dosing. However, this assumed negative impact of VKA on QoL is insufficiently supported by evidence. In chapter 6, in a prospective cohort study of newly referred AF patients we determined whether the introduction of VKA lowered quality of life. In addition, we identified patient and treatment characteristics that were determinants of intra-individual changes in VKA perception.

In the final chapter (chapter 7), the results of this thesis are summarized and future perspectives discussed.
REFERENCES

43. Goldstein JN. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist


