An evidence based approach to optimizing anticoagulant strategies
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Chapter 1

General Introduction
Etiology of venous thromboembolism

It is only since a few years that deep venous thrombosis and pulmonary embolism are no longer considered as two different diseases but as two manifestations of a single clinical entity: venous thromboembolism. The etiology of venous thromboembolism has been well described by Virchow (1856). Based on pathological observations and thinking he developed the concept that the etiology of venous thromboembolism could be traced back to the triad of venous stasis, vessel wall damage and changes in the clotting capacity of the blood. The occurrence of one or more of these events could provoke venous thromboembolism. Currently, bed rest and immobilization (increased venous stasis), orthopedic surgery, trauma and cancer (vessel wall damage) thrombophilic disorders and cancer (disturbed clotting capacity) are all well recognized risk factors for venous thromboembolism.

The first written account of venous thromboembolism was reported in the 13th century. The manuscript describes a young man from Normandy, who developed unilateral edema in the right ankle that extended up to the thigh, without any symptoms in the contralateral leg. During the course of his illness he developed ulcers and fistulae. A surgeon advised him to wait and see. This conservative approach was rather uncommon in those days. The young man’s condition worsened and manifestations of gangrene appeared. Completely desperate he visited the tomb of Saint Louis in the church of Saint Denis. Soon thereafter his skin healed and a few months later he was cured.

Development of anticoagulants

Despite the long history of the disease, major improvements with respect to the development of pharmacotherapy for thrombotic disorders were only reported in the first half of the 20th century.

It were Jay McLean, L. Emmett Holt, Jr. and William Henry Howell who isolated an extract from the liver (hepar) of a dog and discovered that this substance had very strong anticoagulant properties. Around 1939 relatively large amounts of heparin could be produced and soon thereafter the drug was used for the treatment of thrombosis that occurred as a complication following surgical interventions. It was demonstrated that the administration of heparin prevents further thrombus growth, since it inhibits the production of fibrin via factor Xa and thrombin.

Unfractionated heparin for the initial therapy of venous thromboembolism is administered intravenously and requires hospitalization. In the last two decades of the 20th century research was focused on improving the effectiveness of heparins and finding more convenient routes of administration. This resulted in the development of heparins with a lower molecular weight with the advantages of higher bioavailability, a longer half-life and therefore a more predictable anticoagulant response. As a result
of these pharmacokinetic properties, a stable and sustained anticoagulant effect can be achieved when low-molecular-weight heparin is administered subcutaneously, once or twice daily, without laboratory monitoring.

Vitamin K antagonists were originally used as a very effective rat poison and its discovery was rather a coincidence. In 1920 a farmer in Wisconsin visited the chemical laboratory of Karl Paul Link because his cattle died of a mysterious hemorrhagic disorder at the end of the winter season. Link discovered that ingestion of spoiled sweet clover caused a hypocoaguable state that increased the risk of bleeding. He isolated dicoumarol from the clover and proved that this was the hazardous component. The Wisconsin Alumni Research Foundation (WARF) patented his findings. Ingestion of the substance, then named warfarin, caused fatal internal hemorrhages. Only in 1955 warfarin was used for the first time in humans as an anticoagulant. The underlying mechanism of anticoagulation was firstly described by the Danish scientist Henrik Dam. He and his colleagues proved that the absence of a certain vitamin caused a hemorrhagic disease in chickens. He named it vitamin K after the Danish word “Koagulation”. Vitamin K antagonists inhibit the formation of the vitamin K dependent clotting factors II, VII, IX and X in the liver.

**Treatment with anticoagulants**

In a landmark study published in 1960 by Barritt and Jordan the efficacy of the combination of heparin and orally administered vitamin K antagonists for the treatment of venous thromboembolism was demonstrated. They observed a convincing decrease in recurrences and mortality in patients with pulmonary embolism who were randomized to treatment with heparin and vitamin K antagonists compared to those who received no treatment.

Heparin as the initial treatment in combination with vitamin K antagonists for the long term is still the therapy of choice in patients with venous thromboembolism. Heparin is very effective for the prevention of further thrombus growth and starts functioning immediately after administration to the patient, while the optimal effect of vitamin K antagonists may take several days.

Another indication for the use of vitamin K antagonists is the prevention of thromboembolic complications in patients with atrial fibrillation or mechanical heart valves. Treatment with vitamin K antagonists presents a problem when these patients need surgery, because the risk for anticoagulant related bleeding is significant. On the other hand, temporary interruption of vitamin K antagonist therapy carries a thromboembolic risk, especially during surgical procedures, because of the prothrombotic effect of the intervention and the rebound hypercoagulability-phenomenon. There is not much consensus about the appropriate perioperative management of anticoagulation for patients who have been on long-term vitamin K antagonist therapy.
An evidence based approach

The past few decades many randomized clinical trials and observational studies about the treatment with anticoagulants have been published. Despite this significant amount of scientific evidence, there are still a number of issues that remain unresolved. In many clinical situations for which no sufficient data are available, a conventional trial or observational study is a first step to obtain evidence and give an answer to the question whether current clinical practice is good for the patient or not. A systematic review summarizes the evidence of published trials that investigate the efficacy and safety of a therapy in a specific clinical setting. It encompasses a systematic search of literature, which is subsequently critically appraised by means of predefined criteria and results in more precise estimates for efficacy and safety of therapeutic strategies.

In many situations a randomized clinical trial or a systematic review is sufficient to provide evidence for clinical decisions. However, in many situations clinical trials and systematic reviews can not give the answers we need. For example, when the decisions involve events occurring over longer periods than the scope of a clinical trial. In these situations decision analytic models can be helpful for clinicians to make decisions about the best treatment strategy. In some settings the patient’s valuations of the therapy and possible outcomes can be incorporated in the decision model together with the risks and benefits of the therapy. In the end, such decision analytic models can help clinicians to make tailored decisions with respect to the treatment of individual patients.

Outline of this thesis

Since the introduction of low-molecular-weight heparins a large number of randomized clinical trials have been published in which the effectiveness and safety of low-molecular-weight heparin is compared to unfractionated heparin for the initial treatment of patients with symptomatic venous thromboembolism. A pooled analysis of these studies is described in chapter 2. When a once daily treatment regimen with low-molecular-weight heparin is as effective and safe as a twice daily regimen, once daily administration can be recommended as the standard therapy in patients with a first episode of venous thromboembolism. In chapter 3 the results of a systematic review of studies in which once and twice daily regimens of low-molecular-weight heparin are compared is reported.

Together with the initiation of heparin therapy, treatment with vitamin K antagonists is started in patients with venous thromboembolism. Intensity of therapy with vitamin K antagonists has to be monitored to obtain a therapeutic INR (International Normalized Ratio) between 2.0 and 3.0. Intensity below this range is sub-optimal and results in less effective therapy and above this range increases the risk
of iatrogenic bleeding. It is known that patients spend on average less than 60% of their time in this therapeutic range. In chapter 4 it is hypothesized that adequate dissolution of the thrombus might lead to reduced venous obstruction and valve damage and therefore that a poor quality of treatment with vitamin K antagonists increases the risk for the post-thrombotic syndrome. In a cohort of patients with an episode of deep venous thrombosis the relation between the time spent beneath the therapeutic range and the occurrence of the post-thrombotic syndrome was investigated.

The usual duration of therapy with vitamin K antagonists in patients with a first episode of venous thromboembolism is three to six months. However, there is a debate about the length of this treatment period. It has been shown that a longer duration of treatment with vitamin K antagonists compared to a short duration results in a decrease of the risk of recurrent thromboembolic events. Prolongation of treatment results in an increased risk for vitamin K antagonists related bleeding, which has to be balanced against the efficacy of prolonged treatment. Chapter 5 contains a description of a meta-analysis, which quantifies the risk for recurrent venous thromboembolism in relation to the time since the index event. This quantification of the risk for recurrence is important for the determination of the optimal duration of treatment with vitamin K antagonists.

Therapy with vitamin K antagonists can be a real burden for the patients because the treatment requires regular visits of thrombosis units and patients may be prone to develop serious bleedings as well as minor hemorrhages, for example of the gingiva. Consequently, some patients prefer a shorter duration of treatment. To determine the optimal duration of treatment with vitamin K antagonists, the efficacy of treatment has to be balanced not only against the risk of bleeding but also against the burden of treatment as perceived by the patient. In chapter 6 valuations of several health states related to venous thromboembolic disease are presented. These data were obtained in more than 120 patients who were treated or had been treated with vitamin K antagonists.

It is clear that the efficacy of prolongation of treatment is highly dependent on the risk for recurrence and therefore on patients’ individual risk profiles. It is questionable whether the absolute risk reduction under prolongation of vitamin K antagonist treatment can counterbalance the cumulative burden of treatment and the continued risk of bleeding, which may affect the quality of life of the patient. In chapter 7 the results of a decision analytic Markov model for determining the optimal duration of treatment with vitamin K antagonists are described. In the model the benefits and disadvantages of continued treatment in several subgroups of patients with a first episode of venous thromboembolism are weighed in a quantitative way. Chapter 8 focuses on patients with mechanical heart valves who are at increased risk for thromboembolic events and therefore need long-term treatment with vitamin K
antagonists. In case of non-cardiac surgery anticoagulation should be interrupted, because of the risk of bleeding. This chapter is a description of the frequency and methods of the interruption used in a number of Dutch hospitals. In addition, the relation between the perioperative anticoagulation strategies and the risk for thromboembolic and bleeding complications is explored. In chapter 9 the results of this thesis are summarized and directions for future research to improve the evidence-base for anticoagulant therapy are proposed.

References