An evidence based approach to optimizing anticoagulant strategies
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Chapter 9

Summary
In this thesis several aspects of treatment with anticoagulants are discussed. Chapter 1 constitutes a short description of the etiology of thrombotic disorders, a brief history of the development of the antithrombotic drugs: heparins and vitamin K antagonists, followed by an outline of the thesis.

Low-molecular-weight heparins have been shown to be effective and safe for the prevention of venous thromboembolism. There is accumulating evidence that these anticoagulants are also effective and safe for treatment of venous thromboembolism. In chapter 2, the results of a systematic review are presented on the effect of fixed-dose, subcutaneous low-molecular-weight heparins compared with adjusted-dose, intravenous or subcutaneous, unfractionated heparin for the initial treatment of acute deep venous thrombosis or pulmonary embolism. A systematic search was performed to identify all randomized trials comparing fixed-dose, subcutaneous low-molecular-weight heparin with adjusted-dose, intravenous or subcutaneous administered unfractionated heparin in patients with venous thromboembolism. Two reviewers assessed trials for inclusion and quality, and extracted data independently. Twenty-two studies with a total of 8867 patients were included. In eighteen trials, the risk of recurrent venous thromboembolism at the end of follow-up was evaluated. A statistically significant difference in recurrence was observed in favour of low-molecular-weight heparin (odds ratio (OR) 0.68, 95% confidence intervals (CI) 0.55 to 0.84). At the end of the initial treatment period, in nineteen trials, major haemorrhages were evaluated. A statistically significant difference of the risk of major haemorrhagic events was observed in favour of low-molecular-weight heparin (OR 0.57, 95% CI 0.39 to 0.83). Also the mortality at the end of follow-up (eighteen trials) was statistically lower in those treated with low-molecular-weight heparin compared to unfractionated heparin (OR 0.76, 95% CI 0.62 to 0.92). Low-molecular-weight heparin is more effective than unfractionated heparin in preventing recurrent venous thromboembolism, and significantly reduces the occurrence of major haemorrhage during initial treatment and overall mortality at the end of follow-up.

In the initial treatment of venous thromboembolism low-molecular-weight heparin is administered once or twice daily. A once daily treatment regimen is more convenient for the patient and may optimize home treatment. But it is uncertain whether a once daily treatment regimen is as safe and effective as a twice-daily treatment regimen. The objective of the review presented in chapter 3 was to compare the efficacy and safety of once daily administration to a twice-daily administration of low-molecular-weight heparin. A systematic search of the literature was performed. Randomized clinical trials in which a once daily treatment regimen with low-molecular-weight heparin was compared to a twice-daily regimen in the initial treatment of patients with venous thromboembolism were identified. Two reviewers independently assessed trials on criteria for inclusion and extracted the data. Five studies were included with a total of 1508 patients. The pooled data showed a
statistically non-significant difference in recurrent venous thromboembolism between the two treatment regimens in favour of a once daily treatment regimen (OR 0.82; 95%CI 0.49 to 1.39). A comparison of major haemorrhagic events (OR 0.77; 95%CI 0.40 to 1.45) and mortality (OR 1.14; 95%CI 0.62 to 2.08) also showed non-significant differences between the two treatment regimens in favour of once daily treatment with low-molecular-weight heparin. These results show that once daily treatment with low-molecular-weight heparin is as effective and safe as twice-daily treatment with low-molecular-weight heparin.

About 30% of patients with an episode of adequately treated deep venous thrombosis develop the post-thrombotic syndrome within two years. During treatment with vitamin K antagonists patients spend sometimes only 60% of time in the target range. In Chapter 4 it was hypothesized that poor quality of treatment with vitamin K antagonists results in inadequate dissolution of the thrombus, which can lead to increased venous obstruction and valve damage. If so, patients who spend a large amount of their time beneath the therapeutic range are at an increased risk for the post-thrombotic syndrome. In a retrospective observational study the time spent beneath the therapeutic range was calculated for patients with a first episode of deep venous thrombosis who were treated with vitamin K antagonists for at least three months. At follow-up assessments for a maximum of five years, presence and severity of signs and symptoms of the post-thrombotic syndrome were recorded. A total of 244 patients were included for analysis. Of these, 81 (33%) had developed the post-thrombotic syndrome. The multivariate analysis showed that patients who spend more than 50% of their time beneath an INR level of 2.0 are at higher risk for the post-thrombotic syndrome (OR: 2.6, 95%CI 1.4 to 4.7). We conclude that low quality treatment with vitamin K antagonists, is related to the occurrence of the post-thrombotic syndrome in patients with deep venous thrombosis.

After a first episode of venous thromboembolism patients are usually treated with vitamin K antagonists for three to six months. Prolongation of treatment beyond six months reduces the risk of recurrent venous thromboembolism but increases the risk of treatment related hemorrhage and may be a burden for the patient. There are indications that the risk of recurrence after treatment with vitamin K antagonists decreases relative to the time since the first event. The possibility of a decreasing risk over time has important implications for decision-making about the optimal duration of treatment with vitamin K antagonists. The aim of the meta-analysis described in Chapter 5 was to quantify the risk of recurrent venous thromboembolism after treatment with vitamin K antagonists in relation to the time since the index event. An extensive literature search was performed to find randomized clinical trials and cohort studies in which patients with venous thromboembolism had been treated with vitamin K antagonists. Per treatment arm, two reviewers independently extracted data on the number of recurrent events and the duration of follow-up per time period of
three months. A total of 135 potentially eligible studies were identified. Of which, eighteen studies could be included, comprising 25 treatment arms that could be analyzed. Treatment arms were divided into three groups based on treatment duration (short, medium, and long). For each group, the monthly incidence immediately after discontinuation of treatment was high and declined rapidly thereafter. The monthly incidence after nine months seemed independent of the treatment duration. We concluded that there is a diminishing risk of recurrent venous thromboembolism over time, which stabilizes after nine months independently of the duration of the initial treatment with vitamin K antagonists.

Determining the optimal duration of vitamin K antagonist therapy for patients with venous thromboembolism requires a weighing of the benefits and risks of treatment. Quantitative expressions of patients’ valuations of outcomes after venous thromboembolism can help in making decisions on treatment duration. One can also ask patients directly for their treatment preferences. In chapter 6 patients’ valuations for health states associated with venous thromboembolism and its treatment with vitamin K antagonists are reported, along with patients’ treatment preferences. Valuations of outcomes after venous thromboembolism scaled from 0 (tantamount to death) to 1 (tantamount to perfect health) were elicited from 53 patients who had experienced venous thromboembolism, 23 patients who had experienced major bleeding during treatment and 48 patients with the post-thrombotic syndrome. In addition, patients’ treatment preferences were evaluated using treatment trade-off questions. Median health state valuations ranged from 0.33 for ‘non-fatal haemorrhagic stroke’ to 0.96 for ‘no vitamin K antagonist treatment’. Variability between patients was substantial. Patients’ treatment preferences also varied: 23% of patients chose for cessation of treatment, regardless the probability of recurrent venous thromboembolism presented, whereas 25% of patients were not willing to opt for cessation of treatment at all. Differences in valuations and treatment preferences were not associated with type of event experienced. Due to the substantial and unpredictable variability in valuations and treatment preferences, recommendations regarding treatment duration should be tailored to patients’ specific values and concerns.

To determine the optimal duration of treatment with vitamin K antagonists in patients with a first episode of venous thromboembolism a decision analytic model was developed of which the results are described in chapter 7. In a Markov decision analytic model, the risk of thromboembolic and treatment related complications as well as patients’ valuations of health states were incorporated. Risk estimates were derived from the literature. Valuations of relevant health states were obtained in a group of 124 patients. Life expectancy and quality-adjusted life expectancy were calculated for different durations of treatment and a number of subgroups of patients. For patients with an increased risk of recurrence (idiopathic first episode), there is an
almost nonexistent increase in quality adjusted life expectancy of +0.03 years when treatment duration is prolonged after six months up to one year and an increase of +0.20 years in case of lifelong treatment. For patients presenting with idiopathic pulmonary embolism the changes are +0.14 and +2.54 years, respectively. Sensitivity analysis showed the optimal duration of treatment to be sensitive to the patients’ perceived burden of treatment. Although prolongation of vitamin K antagonist treatment can be expected to increase longevity, the changes in life expectancy do not always outweigh the downsides of treatment, in particular the burden of therapy. As most changes in quality-adjusted life expectancy will be small and dependent on the patients’ valuations of health states, there is room for individually tailoring the duration of treatment with vitamin K antagonists.

Patients with mechanical heart valves are at increased risk for thromboembolism and should receive lifelong anticoagulation. However, there is no consensus about the optimal management of anticoagulation in these patients during surgery or other invasive procedures. The aim of the study described in chapter 8 was to analyze the anticoagulant strategies and to evaluate the incidence of thromboembolic and bleeding complications according to the different periprocedural anticoagulant strategies in a large series of patients with mechanical heart valves who had undergone non-cardiac surgical interventions. All patients who underwent heart valve replacement between January 1997 and December 1999 were included and followed during a four to six year period. A total of 567 patients had had heart valve replacement between 1997 and 1999. Of which 124 patients underwent 171 non-cardiac surgical procedures. Data were available from 153 interventions. Unfractionated heparin was the most frequently used anticoagulant in the perioperative period. Fifteen bleeding complications occurred during 153 interventions (10%). There was an increased risk for bleeding when the administration of unfractionated heparin was restarted within six hours after the end of surgery (relative risk 1.86, 95%CI 0.42 to 8.10). No thromboembolic event was observed in the perioperative period. We conclude that therapeutic dose of unfractionated heparin are frequently used to bridge interruption with vitamin K antagonists. Overall this strategy seems safe to prevent thromboembolic complications. The risk for bleeding complications is increased when the unfractionated heparin is reinitiated within six hours. The overall safest strategy seems to restart unfractionated heparin 12 to 24 hours after surgery.

In this thesis it is shown that low-molecular-weight heparin can be adopted safely as the initial treatment of patients with deep venous thrombosis but large studies comparing individual low-molecular-weight heparins are warranted. In addition more studies have to be performed to evaluate the efficacy and safety of low-molecular-weight heparin in patients with pulmonary embolism before low-molecular-weight heparin can be adopted as the standard therapy in these patients. It was also shown that an once-daily treatment regimen is as safe and effective as a twice-daily treatment
regimen. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent venous thromboembolism might be higher when patients are treated once daily. Hence the decision to treat the patient with a once daily regimen will depend on the evaluated balance between increased convenience and the potential for a lower efficacy.

In patients treated for an episode of venous thromboembolism, a good quality of therapy with vitamin K antagonists is associated with a lower risk for the development of the post-thrombotic syndrome. Therefore, adequate monitoring and compliance should be stimulated to reduce the risk for this invalidating chronic complication of deep venous thrombosis. The development of devices for self-monitoring of vitamin K antagonist therapy can result in increased patient responsibility and better compliance and can be helpful to achieve more stable and predictable levels of anticoagulation. Self-management at home will reduce the need for regular visits of thrombotic clinics and therefore may results in more convenient therapy as perceived by the patient. A more convenient therapy can have consequences for the optimal duration of therapy, since in decisions about duration of therapy individual risk profiles and patients’ treatment preferences have to be balanced. The model proposed in this thesis can be used to individual tailor the duration of therapy with vitamin K antagonists. Since there is a large interindividual variability in patients’ valuations, the perceived burden of treatment should be obtained in the individual patient. Therefore, further research should focus on the development of simple and accurate instruments to assess patients’ treatment preferences. For that purpose treatment trade-off questions are preferred since these offer a more realistic and simple reflection of the actual decision dilemma and are less time consuming than the assessment of health states values for the important outcomes. These new tools cannot only be used in decision-making on duration of therapy with vitamin K antagonists to avoid over and under treatment but may also be an important aid in individual decision-making in other clinical situations.

Agents with a fast onset of action and a more predictable and reproducible pharmacokinetic response and sometimes more convenient routes of administration are now being tested in clinical situations. Special attention has to be paid to the direct thrombin inhibitors, which can be administrated orally and Factor Xa inhibitors. Recent publications show promising results but the potential downsides and long-term use of these drugs requires further investigation. In the long run these drugs may become the drugs of choice for the treatment of venous thromboembolism because of their potential advantages over vitamin K antagonists and unfractionated heparin and even low-molecular-weight heparin. Decision analytic models can then be used to incorporate the efficacy and safety of therapy, the higher costs of the new drugs as well as patients’ preferences with respect to therapy and outcomes. Collecting more high quality evidence and tailoring it for specific patient groups or even
individual patients, will lead to rational decision-making and, ultimately, better healthcare.

References


