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Chapter 10

Aim of this thesis

Although a long list of risk factors has been described for a first venous thrombotic event, the risk profile for recurrent venous thrombosis is not that well known. Also, data on factors able to predict the risk of recurrence are scarce. The aim of this thesis was to study several (modifiable) risk factors and predictors for their relation with recurrent venous thrombosis. In this chapter I provide an overview of the main findings. Furthermore, I will consider the clinical implications of this work and discuss directions for future research.

Overview of main findings

Incidence of recurrent venous thrombosis and known risk factors for recurrence

In Chapter 2 the design and the first results from the MEGA follow-up study were described. Information on recurrent events from several sources of information was combined to obtain a valid estimate of the incidence of recurrent venous thrombosis. The overall incidence of recurrence in a group of patients with a first deep vein thrombosis of the leg or pulmonary embolism was 27.9 per 1000 person-years, with a 5-year cumulative incidence of 11%. These incidences were somewhat lower than reported in previous literature. This probably has to do with our use of a strict definition of a true recurrent event, to distinguish recurrence from an extension of the first. Men had about a two-fold increased risk of recurrent venous thrombosis as compared with women and a first idiopathic event was associated with a one and a half- to two-fold increased risk as compared with a first provoked event. Age did not affect recurrence risk. For deciding on the duration of anticoagulant treatment in patients with a first venous thrombotic event this information should be taken into account.

Cancer and (recurrent) venous thrombosis

A strong relation between cancer and venous thrombosis was identified already in the early 19th century. Chapter 3 presented an overview of all knowledge gained on the incidence of and risk factors for cancer-associated venous thrombosis over the years. About 20-30 percent of all venous thrombotic events is cancer-associated and cancer increases the risk of thrombosis about four- to seven-fold. The risk of venous thrombosis in patients with cancer depends on several factors, e.g., cancer type and stage, treatment measures and patient-related factors. This information provides a basis for the identification of high-risk patients who could benefit from thromboprophylaxis and for further development and refinement of prediction models.

The risk of recurrent venous thrombosis in patients with cancer has not been studied extensively. In Chapter 4 the risk of recurrent venous thrombosis in patients with cancer was evaluated, also in relation to time of diagnosis of the malignancy and in several types of cancer patients. Patients with cancer and thrombosis had an increased risk of recurrent venous thrombosis compared with patients without cancer. Participants with cancer diagnosed before the first venous thrombotic event who died or had metastases had a two- to three-fold increased risk of recurrent thrombosis compared with patients without cancer, while patients with non-metastasized cancer or who did not die of cancer did not have an increased recurrence risk. Participants with cancer diagnosed after the first thrombosis had an increased recurrence risk, which was especially high in the first three months after cancer diagnosis (about five-fold compared with patients without cancer). Risk of recurrent venous thrombosis differed for different types of cancer, for different stages of cancer and for different time periods after cancer diagnosis. Currently, guidelines provide treatment recommendations for the group of patients with cancer and venous thrombosis as a whole. Our study supports current thought that risk of recurrent venous thrombosis is not the same for all patients with cancer and that stratification of patients with cancer-associated venous thrombosis according to their recurrence risk is of relevance to offer these patients a better tailored treatment approach.

The pathophysiology underlying the association between cancer and venous thrombosis is largely unknown. Furthermore, it is not known in what way patients with cancer who develop thrombosis are different from those who do not. In Chapter 5 several plasma coagulation factor levels (procoagulant, anticoagulant and fibrinolytic) were studied in four groups of individuals with and without cancer and with and without venous thrombosis. Increased levels of procoagulant coagulation factors in participants with thrombosis without cancer and even higher levels of these factors in participants with both venous thrombosis and cancer were found, suggesting generalized effects of procoagulant pathways in patients with cancer and emphasizing the importance of coagulation in cancer-associated venous thrombosis. Results were most pronounced for factor VIII and von Willebrand factor. Levels of factor VII were increased in participants with cancer and were unaffected by the presence or absence of thrombosis. The finding of slightly increased levels of anticoagulant proteins, free protein S and TFPI in participants with cancer and venous thrombosis is suggestive of an additional role of anticoagulant pathways in cancer. These data give more insight into the relation between venous thrombosis and cancer.

Risk factors and predictors for recurrent venous thrombosis

In Chapter 6 the predictive value of coagulation factor VIII levels for recurrent venous thrombosis was studied. Recurrence rates steadily increased with higher factor VIII activity levels and patients in the highest category of FVIII (>200 IU/dL) had a three-fold higher recurrence rate than patients in the lowest category (<100 IU/dL). Results were robust in several sensitivity analyses and factor VIII was able to predict recurrence rates over a long time period. Adding factor VIII to an existing prediction model (DASH-score) improved its predictive value, and after replacing D-dimer by factor VIII, the model performed equally well if not better. Factor VIII will be able to refine recurrence risk estimation at an individual level and factor VIII should be considered in recurrence
Chapter 10

Such prognostic factors, however, do not yet provide enough distinctive power on their own to classify patients individually at high or low risk of recurrence. After identification of such prognostic factors the next step would be to create a prognostic model, the aim of which is to develop, validate and test the impact of statistical models that predict individual risks of a future outcome. For an individual with a given state of health, in our case patients with a first venous thrombotic event, a prognostic model converts the combination of predictor values to estimates of the risk of experiencing a specific endpoint within a specified time period. Therefore, after this thesis, the next step should be to focus on taking all factors together and use them as building blocks for a prognostic model, which will be able to predict recurrences at a much more refined and individual level.

Current Prediction models
Currently three prediction models have been published for recurrent venous thrombosis; 1) the Men continue and HERDOO2 rule; 2) the Vienna prediction model and 3) the DASH score.

Directions for future research
This thesis adds to the current knowledge on risk factors and predictors for recurrent venous thrombosis. This type of research is sometimes called prognostic factor research, in which prognostic factors are defined as factors able to distinguish between groups of people with a different average prognosis.[3] Such prognostic factors, however, do not yet provide enough distinctive power on their own to classify patients individually at high or low risk of recurrence. After identification of such prognostic factors the next step would be to create a prognostic model, the aim of which is to develop, validate and test the impact of statistical models that predict individual risks of a future outcome. For an individual with a given state of health, in our case patients with a first venous thrombotic event, a prognostic model converts the combination of predictor values to estimates of the risk of experiencing a specific endpoint within a specified time period. Therefore, after this thesis, the next step should be to focus on taking all factors together and use them as building blocks for a prognostic model, which will be able to predict recurrences at a much more refined and individual level.

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1. The 'Men continue and HERDOO2' rule (see Table 1) was published in 2008 by Rodger and colleagues.[5] In this multicentre prospective study, over 600 patients with a first unprovoked venous thrombosis were followed for a mean of 18 months. Clinical characteristics as well as blood samples were collected during anticoagulant treatment five to seven months after the start of treatment. The authors sought to determine the clinical predictors or combinations of predictors that identify patients with an annual recurrence risk of less than 3% after taking six months of anticoagulant treatment, which they considered sufficiently low to discontinue oral anticoagulants.

The authors found no combination of clinical predictors for identifying a low-risk subgroup of men, which is why men were advised to continue anticoagulant treatment long-term. Additionally, women with ≥2 of the following risk factors: postthrombotic signs (hyperpigmentation, edema or redness in either leg), D-dimer level ≥250 µg/L, BMI ≥30 kg/m² and age ≥65 years were advised to continue treatment. Authors concluded that women with a score of ≤1 (52% of women) could safely discontinue anticoagulant treatment after six months following a first unprovoked event.

The aim of Chapter 9 was to study whether individuals who receive antibiotic treatment (as a proxy for infectious disease), have an increased risk of first or recurrent venous thrombosis. By means of a self-controlled case series study design the risks of both a first deep vein thrombosis and a first pulmonary embolism were found to be increased at least three-fold during antibiotic use. The major advantage of a self-controlled case series design is that fixed confounders, like frailty, do not play a role. For recurrent venous thrombosis similar results were found, with a two-fold increased risk of recurrent venous thrombosis during periods of antibiotic use as compared with periods with no use. These results should increase awareness in clinicians of the risk of venous thrombosis in in- and out-patients who are ill and get antibiotics. Furthermore, acute infectious disease should be added to the list of provoking factors for venous thrombosis.
2. Two years after the ‘Men continue and HERDOO2’ rule, the Vienna prediction model (see Table 2) was published by Eichinger and colleagues.[6] In this multicentre prospective cohort study over 900 patients with a first unprovoked venous thrombosis were followed for recurrence with the aim to develop a simple risk assessment model. Median follow-up of the patients was 43 months after discontinuation of anticoagulant treatment. Blood was drawn shortly after discontinuation of treatment. Eichinger et al. found male sex, proximal deep vein thrombosis, pulmonary embolism and elevated D-dimer levels to be associated with recurrence. Using these variables a nomogram (see Figure) was developed that can be used to calculate risk scores and to estimate cumulative probabilities of recurrence. C-statistics for the models at 12 and 60 months were 0.67 and 0.65, respectively. Additionally, a web-based risk calculator was developed (http://cemsiis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/recurrent-vte/), to calculate risk scores and cumulative probabilities of recurrence in an individual patient. Based on these predicted risks the physician can decide whether to stop or continue anticoagulant treatment.

3. The DASH score (see Table 3) was developed in 2012 by Tosetto and colleagues by pooling individual patient data from seven prospective cohort studies.[8] Over 1800 patients with an unprovoked venous thrombosis, treated for at least three months, were included for analyses and followed for a median of 22 months. Blood was sampled several weeks after discontinuation of anticoagulant treatment. Abnormal D-dimer, Age <50 years, male Sex and venous thrombosis not associated with
Hormonal therapy (in women) were the main predictors of recurrence and were used to derive the DASH score. C-statistic for the model was 0.71. Patients with a score ≤1 had an annualized recurrence risk of 3%, while the risk was over 12% for patients with score ≥3. With 52% of patients falling into the first group, the authors concluded that in about half of the patients with unprovoked thrombosis life-long anticoagulation might be avoided.

### Table 3. DASH score

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated D-dimer levels one month after discontinuation of anticoagulant treatment</td>
<td>2</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td>1</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Women taking oral contraceptives</td>
<td>-2</td>
</tr>
</tbody>
</table>

Low risk of recurrence when the score ≤1

Before a prediction model can be adopted in practice it is necessary to show that predictions of the model are valid in another sample of patients than the specific context of the sample that was used for model development. This is important because the predictive performance of a model estimated on the development data is often optimistic, due to multiple testing with a limited sample size. Such external validation of abovementioned models was not performed until recently which is probably why the models are not currently used in the clinic. The only model externally validated so far is the Vienna prediction model.[9,10] Pooled individual data from five prospective studies were used to test the prognostic value of the model.[9] The authors concluded that the ability to distinguish risk of recurrent venous thrombosis was at least as good in the validation cohort as in the derivation cohort, with a calibration slope of 1.17 (95%CI; 0.71-1.64) and a C-statistic of 0.63 (vs 0.65 in the derivation cohort). Performance of the model was less in an external cohort of elderly patients.[10] Lastly, studies would have to be performed in which the impact of a prediction model on decision making and patient outcomes is investigated.

Some disadvantages and differences between the three models should be outlined. In the ‘Men continue and HERDOO2’ model no combination of clinical predictors for identifying a low-risk subgroup of men was found and all men were advised to continue anticoagulant treatment on the long-term. The authors did not have an explanation for this finding, although it seems unlikely that risk prediction is not possible at all in men. In this thesis the predictive value of levels of factor VIII for recurrent venous thrombosis was described (Chapter 6). Recurrence rates increased steadily with increasing factor VIII also in men. This suggests that not all men have a similar risk of recurrent venous thrombosis. Furthermore, in the HERDOO2 model levels of D-dimer were measured while patients were on anticoagulant treatment. Although in the clinic it would be a major advantage to assess recurrence risks while patients are still on anticoagulant treatment, several studies have shown that only 5-12% of patients have increased D-dimer levels during treatment with vitamin K antagonists.[11-13] One of abovementioned studies has actually suggested to omit the D-dimer measurement during anticoagulation.[13]

The Vienna prediction model has recently been updated for several time points after discontinuation of anticoagulant treatment and the model has both been internally and externally validated with reasonable outcomes. The model enables to predict recurrence rates both in men and women and D-dimer levels were measured after withdrawal of anticoagulant treatment. However, the Vienna model is considered complex for routine use. The model does not provide a simple scoring system and cut-off value for discontinuation or extension of anticoagulant treatment. This is probably the reason why this model is still not used much in the clinic.

The DASH-score provides a simple scoring system for both men and women and a cut-off value for when anticoagulant treatment may be safely discontinued. Interestingly, the DASH-model indicates age less than 50 as a risk factor for recurrence, while the Vienna model attributes a higher risk to age greater than 65. In the MEGA follow-up study age was not associated with recurrent venous thrombosis (Chapter 2). Additionally, hormone use at the first event (by women) is indicated to decrease the risk of recurrence, while in this thesis (Chapter 7) similar rates of recurrence for women who did or did not use hormones at time of the first event are reported.

### Development of a prediction model in the MEGA follow-up study

The MEGA follow-up study is favourable for development of a prognostic model for recurrent venous thrombosis. In total, nearly 5000 patients with a first venous thrombotic event were followed over a long period of time for recurrences.

Currently existing prognostic models (described above) all focus on patients with a first unprovoked event. This is because the recurrence risk is higher in these patients as compared with patients who had an event related to surgery or trauma for example. It is currently unknown for how long these patients should receive anticoagulant treatment. However, recurrent venous thrombosis in patients with a provoked first event is not uncommon.[15] In this thesis (Chapter 6) we have shown that although recurrence rates are low in patients with provoked first events, risk stratification is still possible in these patients. With a recurrence rate of 4% per year in patients with a provoked first event and factor VIII levels >200 IU/dL prolonged anticoagulation may still be warranted given the incidence rate of major bleeding of 1-2% per year.[16,17] Furthermore, the classification of an event as either unprovoked or provoked is artificial and controversial. In principle nearly all events are provoked by one or more factors. A prognostic model based on the MEGA follow-up study should take all patients into account, both patients with a provoked as well as patients with an unprovoked first event.
In the MEGA study blood was collected only in patients with their date of first thrombosis before June 1st 2002. This was for logistic reasons only. After multiple imputation of the factors measured in blood, all participants of the MEGA follow-up study can be included for the development of a prognostic model. Often recommendations are made for the maximum number of preselected predictors that should be estimated in a prognostic model. The reason for this is that including too many predictor variables would lead to the situation of ‘overfitting’ of a model, which causes optimism about a model’s performance in new subjects out of the data under study. A common opinion is that the ratio of events to predictors (events per variable; EPV) should not be less than 10:1.[18] In 4731 patients included in the MEGA follow-up study, 673 recurrent venous thrombotic events were identified, meaning that 67 predictor variables may be preselected for the development of the prognostic model. This is more than the currently available prediction models could include, 9 (91/10), 17 (176/10) and 23 (239/10) for the HERDOO2, Vienna and DASH models, respectively.[5,6,8]

Since patients with a cancer-associated first venous thrombosis are so distinct from patients with a non-cancer associated event with regard to clinical characteristics and mortality risk, a separate prognostic model could be useful for this group of patients. Louzada et al. have published a prediction score for recurrent venous thrombotic events in patients with a cancer-associated first event, including four independent predictors (sex, primary tumor site, stage and prior venous thrombosis).[19] The performance of the score in an external cohort was reasonable.[20]

A prognostic model for the prediction of recurrent events on the moment of discontinuation, or the moment of deciding on whether to discontinue or extend anticoagulant treatment, will be most useful for the clinic. This time-point is where follow-up should start in the MEGA follow-up study when developing a prognostic model. Ideally, the model includes factors that can be measured or collected during the anticoagulant treatment period, so that a decision can be made before anticoagulant treatment is unrightfully stopped (or continued). Factors that should in any event be preselected for the model, and are available in the MEGA follow-up study, are: age, sex, type of first event (provoked vs unprovoked), first PE vs DVT, proximal vs distal DVT, BMI and levels of factor VIII (given the results from Chapter 6). Of note, genetic factors might additionally play a role in a prognostic model for recurrent venous thrombosis, and should therefore be included in the list of preselected variables. The development of a prognostic model in the MEGA follow-up study should result in an easy to determine risk score and cut-off value for decisions on the duration of anticoagulant treatment.

To be able to predict the risk of recurrence at different moments in time, e.g., directly after the first event, at the moment of intended discontinuation of anticoagulant treatment or several years after a first event, a prediction model should be time-dependent. For this, clinical characteristics as well as factors measured in blood should be collected at several time-points in a prospective follow-up study. Unfortunately, in the MEGA follow-up study we have data on factors measured in blood from one time-point only.

**Conclusion**

Secondary prevention of recurrent venous can be achieved in two ways, either by elimination of modifiable risk factors or by extending the anticoagulant treatment period in patients at high risk of recurrence. The aim of this thesis was to identify modifiable risk factors for as well as factors that might be able to predict recurrent venous thrombotic events. This thesis reports on an increased risk of recurrences in women who continue or start using hormonal contraceptives after a first venous thrombotic event, suggesting that refraining from this modifiable risk factor decreases the risk of recurrence. Furthermore, this thesis describes several factors, male sex, unprovoked first event, levels of coagulation factor VIII and antibiotic use to be associated with recurrent venous thrombosis. These factors should eventually be taken together and used to build a prognostic model, which will be able to predict recurrences at a refined and individual level.
Reference List


