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**Title:** Risk factors and predictors for recurrent venous thrombosis: building blocks for a prognostic model

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Chapter 1

General introduction and Outline of this thesis
General introduction

Haemostasis, the highly regulated process of blood clotting after vascular damage, depends on a delicate interplay between bleeding and clotting. A shift of the haemostatic balance towards a prothrombotic state contributes to the development of obstructive clot formation in the venous system, and venous thrombosis.

The incidence of venous thrombosis is estimated to be around 1-2 per 1000 persons per year and increases exponentially with age up to about 5 per 1000 persons per year in the elderly.[1,2] Venous thrombosis commonly manifests as deep vein thrombosis of the leg, where it can cause symptoms of pain, redness and swelling. In about one third of the patients embolization occurs and parts of a clot lodges in the vasculature of the lung, termed pulmonary embolism. Pulmonary emboli present with symptoms of shortness of breath and chest pain on inspiration and are lethal in up to 20% of the cases.[3,4] Thrombosis rarely occurs, in about 10% of the total cases of venous thrombosis, in other veins of, e.g. the arms, retina, mesentery and portal vein or the cerebral sinus.[4]

It was in the 13th century that the first case of venous thrombosis that we know of was described.[5] Deep vein thrombosis was reported in the right leg of a young man in France. Several hypotheses were suggested through the centuries for understanding the mechanism underlying venous thrombosis. It was only in 1856 that Virchow proposed the modern pathogenesis of thrombosis, now known as Virchow’s triad. [6] This triad explains thrombosis as a result of changes in blood flow, damage of the vessel wall and changes in blood composition. Over the years a long list of risk factors for venous thrombosis has arisen, all of which can be fitted under at least one of the three components of the triad.[7]

Recurrent venous thrombosis

After a first event recurrent venous thrombosis is common, which is associated with considerable morbidity, mortality and health-care costs. Five-year cumulative incidence of recurrences is reported to be around 25%.[8-10] Case fatality rates of recurrent venous thrombosis are estimated at 11% during the first three months of anticoagulant treatment and the rate of fatal recurrent venous thrombosis is 0.3-0.5% per year after discontinuation of anticoagulant treatment.[11,12]

Secondary prevention of recurrent venous thrombosis could greatly reduce the number of events. Secondary prevention 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. For this we need knowledge of risk factors and/or predictors of recurrent venous thrombosis.

The difference between a risk factor and a predictor is that risk factors are causally related to the outcome of interest, in this case recurrent venous thrombosis, while predictors are associated with the outcome, but are not a causal factor for the outcome per se. For example, carrying a lighter in your pocket is not causally associated with an outcome such as lung cancer. However it will be able to predict an increased risk of lung cancer, since people carrying a lighter in their pockets are more often smokers than people who do not carry a lighter. Smoking is the risk factor for lung cancer.

To prevent recurrent venous thrombosis we need knowledge of both predictors and risk factors for recurrence. Ideally, we find information on modifiable risk factors. Modifiable risk factors are factors we can advise patients to refrain from or factors we can intervene on, and in that way decrease the patient’s risk of recurrence. This is in contrast to genetic factors that cannot be readily intervened on. The focus of this thesis will therefore not be on genetics. In this thesis the association between a modifiable risk factor and recurrence is described in both Chapters 7 and 8. The second option for prevention of recurrent venous thrombosis is by extending the anticoagulant treatment period. However, such life-long treatment is not feasible in all patients, considering the substantial risk of major haemorrhage (1-2% per year)[13,14], and should be targeted at high risk patients only. Estimating the risk of recurrent venous thrombosis has proven to be challenging while knowledge of good predictors is much needed.[15] These predictors can be either factors purely predictive of recurrences (Chapter 6) or risk factors for recurrence (Chapters 2, 4, 9).

Despite that risk factors for a first venous thrombotic event are well known, for recurrent venous thrombosis this is not the case. It appeared that the risk profile for a first event cannot be directly translated to recurrent events. For example, age is strongly associated with first events[3], while it is not, or at most very weakly, associated with recurrent venous thrombosis.[8,16,17] The same is true for the presence of genetic thrombophilia.[18]

Some risk factors for recurrent venous thrombosis have been described in the literature, of which the most important ones are the absence of a transient provoking risk factor at time of the first event and the presence of active cancer.[19] However, only a proportion of the patients can be classified as such. Additionally, male sex has proven to be a moderately strong risk factor for recurrent venous thrombosis.[20-22] Some other factors have been positively associated with recurrences as well (see Table for short overview).
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**Relation with recurrent venous thrombosis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relation with recurrent venous thrombosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked vs provoked 1st event</td>
<td>Strong[23]</td>
</tr>
<tr>
<td>Presence of active cancer</td>
<td>Strong[8,9,24]</td>
</tr>
<tr>
<td>Proximal vs distal deep vein thrombosis</td>
<td>Strong[25,26]</td>
</tr>
<tr>
<td>D-dimer levels (measured after discontinuation of anticoagulant treatment)</td>
<td>Strong[28-30]</td>
</tr>
<tr>
<td>Male sex</td>
<td>Moderately strong[20,22]</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Moderately strong[27]</td>
</tr>
<tr>
<td>Residual thrombosis in proximal veins</td>
<td>Moderately strong[31,32]</td>
</tr>
<tr>
<td>Hereditary thrombophilia</td>
<td>Weak, controversial[18,33-35]</td>
</tr>
<tr>
<td>Overweight/ obesity</td>
<td>Weak[36]</td>
</tr>
</tbody>
</table>

* Strong denotes: relative risk >2; Moderately strong: relative risk ~2; Weak: relative risk <1.5

The aim of this thesis is to identify additional modifiable risk factors for as well as factors that might be able to predict recurrent venous thrombotic events.

### Study populations

The MEGA study

The MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) study is a large case-control study into risk factors for venous thrombosis. [37] Between March 1999 and August 2004, 4956 consecutive patients with an objectively diagnosed first deep vein thrombosis of the leg or pulmonary embolism were included. Patients were aged 18-70 years and were enrolled from six anticoagulation clinics in the Netherlands. Anticoagulation clinics monitor all patients taking vitamin K antagonists in a well-defined geographical area. Control subjects, without a history of venous thrombosis, were partners of the patients (n=3297) or collected via random digit dialing (n=3000). All participants filled in a detailed questionnaire on their medical history and the presence of possible risk factors for venous thrombosis. Additionally, blood was collected from cases three months after discontinuation of anticoagulant treatment or one year after the event if cases continued anticoagulant treatment for more than one year. Controls who were partners of the cases provided blood at the same time as the case. Controls from the random digit dialing group provided blood within a few weeks after the questionnaire was sent.

The MEGA follow-up study

Of 4956 patients included in the MEGA study, 4731 gave written informed consent for future follow-up on recurrent venous thrombosis (MEGA follow-up study).[38] The aim of the MEGA follow-up study was to assess the incidence of recurrent events and to identify new risk factors and predictors of recurrences. The MEGA follow-up study is to date the largest non-register based study on recurrent venous thrombosis.

### General introduction

In diagnosing recurrent venous thrombosis it is sometimes challenging to distinguish between new thrombosis and extensions of a previous lesion (residual thrombosis). We aimed to make a clear distinction between the two and collected as many data as possible on recurrences during follow-up from different sources of information. Between June 2008 and July 2009 patients were asked whether they had developed a recurrent venous thrombotic event by means of a short answer form. Furthermore, between 2007 and 2009 the vital status of all MEGA follow-up patients was obtained from the Dutch population register and causes of death from the national registry of death certificates. Data from the answering forms, causes of death, anticoagulation clinics and discharge letters from treating physicians were combined to make a classification of certain and uncertain recurrences.

Data on the presence of risk factors or predictors for recurrent venous thrombosis were additionally obtained via different sources of information. First, all patients were asked to complete a questionnaire on potential risk factors after their first event. Second, our data were linked to the Dutch hospital data register which covers complete, nationwide data on hospital admissions since 1986. Third, all patient records were linked to the SFK register (the Dutch Foundation for Pharmaceutical Statistics).[39]

### Outline of this thesis

In Chapter 2 results from the MEGA follow-up study are reported and an accurately determined incidence rate of recurrent venous thrombosis using a strict definition of recurrence is presented. Additionally the influence of the previously described risk factors male sex and type of the first event (provoked or unprovoked) on risk of recurrence was studied.

Cancer has been shown to be one of the strongest risk factors for venous thrombosis. Of all first venous thrombotic events about 20-30% are cancer-related.[40-43] Furthermore, cancer increases the risk of a first venous thrombotic event four- to seven-fold.[9,37,44,45] To obtain a better insight in this relationship and to obtain an idea of current knowledge with regard to the risk of recurrent venous thrombosis in patients with cancer, Chapter 3 presents an extensive review of the literature on this topic.

Few studies have investigated the risk of recurrent venous thrombosis in patients with cancer. However, all of these studies report an increased recurrence risk. [8,9,24,46] The relation between cancer, diagnosed either before or after the first venous thrombotic event, and recurrent venous thrombosis in the MEGA follow-up study is presented in Chapter 4. Furthermore, recurrence risks were studied separately for different types of cancer and for different time periods after cancer diagnosis, which is helpful information in the clinic in case a decision on thromboprophylaxis has to be made.
Chapter 1

Despite a lot of research on the topic the pathophysiology underlying the relation between cancer and venous thrombosis is largely unknown. The relation between cancer and venous thrombosis is strong; however, not every patient with cancer develops thrombosis. To obtain a better insight in this relation plasma levels of coagulation factors, both procoagulant and anticoagulant, were studied in patients with and without cancer and patients with and without venous thrombosis [Chapter 5].

Levels of coagulation factor VIII have been shown to be strongly related to first venous thrombotic events. [47] Only a few studies, mostly with rather small sample sizes, studied the relation between factor VIII and recurrent venous thrombosis and showed contradictory results. [18,48,49] In Chapter 6 the predictive value of factor VIII levels for recurrent venous thrombosis in the MEGA follow-up study is described. Additionally, the effect of adding factor VIII to an existing prediction model for recurrent thrombosis was studied.

An important risk factor for a first venous thrombotic event is the use of oral contraceptives because of its high prevalence. [50-52] In Chapter 7 the aim was to study the risk of recurrent venous thrombosis in women who continue or start using hormonal contraceptives after a first venous thrombotic event and to see whether taking away this risk factor could reduce recurrence risk.

Another modifiable risk factor for venous thrombosis is seated immobility. It has been shown that for a first venous thrombotic event the risk is increased by immobility, such as during a long-haul flight, other types of travel or a sedentary lifestyle. [53-56] Chapter 8 discusses whether the risk of recurrent venous thrombosis is additionally increased after such periods of seated immobility and whether prophylactic measures could potentially decrease the recurrence risk.

Infections are currently not considered provoking risk factors for a first venous thrombotic event. However, a relation between infectious and inflammatory diseases and thrombosis has been shown before. [57-59] The risk of both first and recurrent venous thrombosis during periods of antibiotic use, as a proxy for infectious diseases, is presented in Chapter 9. Additionally the joint effect of both antibiotic use and genetic thrombophilia on the risk of venous thrombosis is discussed.

Chapter 9

Reference list

Chapter 1


Incidence and characteristics of recurrent venous thrombosis in a large cohort of patients with a first venous thrombosis

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