# Risk factors for a first and recurrent *venous thrombosis*

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# Contents

# 1

# General Introduction

## Venous thrombosis

When a blood vessel is damaged it is important that bleeding stops rapidly. In healthy individuals the coagulation system is triggered immediately. A clot is formed to stop the bleeding and to enable vessel repair. After the vessel wall integrity is re-established the clot is dissolved by the fibrinolytic system.

Venous thrombosis is a result of a disturbance of the balance of the pro- and anticoagulant system or the pro- and antifibrinolytic system towards the prothrombotic side. This disturbance can be caused by acquired and genetic risk factors. In the 19th century Virchow proposed a theory in which he considers three causes of thrombosis, i.e. alterations of the blood flow (stasis), vascular endothelial injury, or alterations in the constitution of the blood. These three conditions are known as Virchow's triad, which is still valid today[1].

Venous thrombosis is an occlusion by a blood clot of one or more of the veins; this occurs mostly in the leg but may affect every vein in the body. The occlusion of a vein in the leg may cause swelling, redness and pain of the affected limb. When part of a clot dislodges it can travel up through the lower caval vein through the heart to the lungs were occlusion of pulmonary vessels leads to symptoms of pulmonary embolism. Venous thrombosis occurs in 1-2 per 1000 persons per year[2]. The incidence increases with age from 1 per 10 000 in the young up to 1 per 100 in the elderly[3]. About one third of the thrombotic clots form emboli that cause pulmonary emboli[2,3]. Complications of venous thrombosis include pulmonary hypertension (incidence 3% per year)[4], the post thrombotic syndrome (cumulative incidence 25-50% after 1-2 years)[5], and bleeding due to treatment with anticoagulants (incidence of major bleeding 1.4-2.7% per year)[6].

Venous thrombosis is a potentially lethal disease due to pulmonary embolism. Pulmonary emboli are lethal in about 20% of the cases[3]. Mortality remains elevated for several years after the thrombotic event, mainly for patients with a first idiopathic venous thrombosis or patients with venous thrombosis due to malignancy[3]. Twelve percent of patients with venous thrombosis without malignancy die within one year after the thrombotic event. This implies that venous thrombosis has a major impact on mortality[3,7].

## Risk factors for a first venous thrombosis

Venous thrombosis is a multicausal disease. Many genetic and acquired risk factors have been described that increase the risk of venous thrombosis. Furthermore, many of these risk factors interact with each other, resulting in a higher risk of a thrombotic event than expected based on the separate effects of these factors[8,9]. Most genetic risk factors known are variations in genes that are involved in the coagulation system, i.e., mutations in protein C and S genes, factor V Leiden (FVL, rs6025) and the prothrombin G20210A mutation (rs1799963), FGG 10034 and Von Willebrand Factor (VWF)[10,11]. In a clinical setting screening for FVL[12] and PT20210A[13] after a venous thrombotic event is often performed,

although the clinical utility is disputed. The FVL mutation is prevalent with about 5% of the Caucasian population carrying this mutation. FVL increases the risk of venous thrombosis 5-fold and interacts synergistically with several acquired risk factors, e.g, oral contraceptive use and pregnancy. The factor V Leiden mutation reduces the ability of protein C to inactivate factor V. This reduced deactivation of factor V results in a prolonged activation of the coagulation system. The prothrombin mutation is less common than FVL, about 2% of the Caucasian population carries this mutation[13]. The PT20210A mutation is associated with elevated levels of prothrombin. PT20210A increases the risk of venous thrombosis about 3-fold[13]. Several other single nucleotide polymorphisms (SNPs) have been described to mildly increase the risk of venous thrombosis with relative risks varying from 1.2 to 4[14].

Known acquired risk factors are increasing age, oral contraceptive use, pregnancy, surgery, minor injuries, trauma, hormone replacement therapy, long haul flights, malignancies, and immobilization[7,15–18]. They are either associated with stasis or a prothrombotic state by affecting the coagulation system. Most of these factors are known to interact with genetic risk factors increasing the risk of venous thrombosis even further[19,20]. Despite this extensive knowledge on risk factors, the cause of venous thrombosis remains unknown in about one third of patients.

## Recurrent venous thrombosis

After a first venous thrombosis 15-40% of the patients will experience one or more recurrent events within 5 years[3,21–24]. Treatment with anticoagulation therapy after a venous thrombosis stops the clot from growing but does not dissolve it. The period in which the clot will be completely dissolved, if ever, depends on the size of the clot and differs per patient. Therefore, when a patient develops new symptoms after discontinuation of treatment for venous thrombosis it is often difficult to distinguish between old and new thrombi. In the literature, varying definitions of recurrence are used. Some studies perform regular ultrasounds to follow the dissolving of the clot, or growth of an old clot as proof of a recurrence[25,26]. Some studies define a recurrence as a thrombus found in patients who have new complaints after the first event, while others provide no definition at all[27,28]. However, most studies agree on defining as a recurrent event a thrombus in a new vein segment compared to the first event found on ultrasound[22,29–35]. This last definition might be incorrect when a first event was a thrombus of the leg and recurs as a pulmonary embolism. In theory the partly dissolved clot, which caused the first event, could be dislodged and causing the pulmonary embolism. While this would then need to be classified as the first event, it may easily be regarded as a recurrence. Due to these difficulties in diagnosis and differences in definition of recurrence the incidence of recurrent venous thrombosis varies widely in the literature.

Risk factors for a recurrent event seem to be different from those for a first event. Some of these differences can easily be explained because risk factors were of a transient nature or because prophylactic treatment is given whenever these factors reoccur (surgery, minor

injuries and pregnancy[22]). However, age, which is one of the major risk factors does not seem to increase the risk of recurrence, nor do genetic prothrombotic abnormalities[36–39]. The main risk factors for recurrence, which are currently known, are male sex and an idiopathic first event. Sex is not a major risk factor for first venous thrombosis. For a first venous thrombosis the risk is higher in women up to the age of 40 than in men, after the age of 40 the risk is higher in men than in women. Although it may seem that the difference in recurrence risk can easily be explained by discontinuation of oral contraceptives and prophylaxis during subsequent pregnancies, previous studies showed that this does not explain the difference in risk between men and women for a recurrent event[36,40].

## Venous thrombosis of the upper extremity

Venous thrombosis of the upper extremity is a rare form of venous thrombosis that is present in 4% of all patients with venous thrombosis[41]. Risk factors for this form of thrombosis are mainly similar to those for venous thrombosis of the leg. However, venous thrombosis of the upper extremity is most frequently caused by either a central venous catheter or the Paget-Schrötter syndrome[42–44], which factors are specific for the upper extremity.

## Study populations

### MEGA study

The Multiple Environmental and Genetic Assessment study of risk factors for venous thrombosis (MEGA study) is a large case-control study with over 5000 cases and over 5000 controls. Consecutive patients aged between 18-70 (n=5170) with a first venous thrombosis of the leg, arm, or pulmonary embolism were collected at six anticoagulation clinics in the Netherlands (Amersfoort, Amsterdam, Leiden, Rotterdam, The Hague, and Utrecht) between March 1999 and September 2004. Control subjects were either partners of the patients (n=3297) or were collected via random digit dialing (RDD) (n=3000), RDD controls came from the same area as the anticoagulation clinics and were frequency matched by age and sex to the cases. Patients and controls were asked to fill in an extensive questionnaire about their medical history and potential risk factors for venous thrombosis. Until June 2002, all participants were asked to provide a blood sample. From June 2002 onwards only DNA samples were taken with buccal swabs. Blood samples of patients were drawn at least 3 months after discontinuation of anticoagulation treatment or, when treatment was continued for more than one year, approximately one year after the thrombotic event. Partners of the patients provided blood samples at the same time as the case. Controls from the random digit dial group provided blood samples within a few weeks after the questionnaire was sent.

### MEGA follow-up study

The MEGA follow-up study is a follow-up of the participants of the MEGA study described above. Survival status of all participants was checked at the community registries in 2007.

Additionally, all cases and controls were followed in time with a median follow-up of five years. All patients and controls that indicated they were willing to participate in a follow-up study at the initial MEGA study were sent follow-up questionnaires between June 2008 and June 2009. These questionnaires comprised, for all participants, questions about the occurrence of arterial thrombosis and potential risk factors for both arterial and venous thrombosis. For the cases additional questions were added about the post-thrombotic syndrome and recurrent venous thrombosis. Recurrent events were adjudicated with information from discharge letters and anticoagulation clinics. The aim of the MEGA follow-up study was to assess the incidence of recurrent venous thrombosis, to identify new risk factors for a recurrent venous thrombosis, and to study the association between venous and arterial thrombosis and their common risk factors.

## Outline thesis

This thesis focuses on risk factors for a first and recurrent venous thrombosis of both the lower and upper extremity. Chapter 2, 3 and 4 concern the risk of thrombosis of the upper extremity and the risk factors for recurrence in these patients. In chapter 2 the current state of knowledge regarding risk factors for venous thrombosis of the upper extremity is reviewed. Blood type non-O and increased levels of FVIII, FXI and FIX are known to increase the risk of a first venous thrombosis of the leg. However, this had not been studied for venous thrombosis of the arm. In chapter 3 we investigate the influence of blood group and levels of coagulation factors on the risk of a first venous thrombosis of the upper extremity. In chapter 4 risk factors for a recurrent venous thrombosis after a first venous thrombosis of the upper extremity are studied. About 15% of the patients die shortly after a venous thrombosis event. However, the long-term effect on mortality in these patients was not well known.

Chapter 5, 6, 7 and 8 concern venous thrombosis of the leg. Both risk factors for a first and recurrent event, and the survival after a first venous thrombosis were studied. In chapter 5 we describe the long-term mortality after a first venous thrombosis. From chapter 5 we learned that patients with a first venous thrombosis had a 3.5-fold increased risk to die of chronic obstructive pulmonary disease (COPD). In chapter 6 we studied COPD as a risk factor for a first venous thrombosis. The incidence and definition of recurrent venous thrombosis varies widely in the literature. In chapter 7 we describe the incidence of a recurrent event in detail as well as the influence of sex, age and an idiopathic first venous thrombosis on recurrence. In chapter 8 we examine body height as a risk factor for both first and recurrent venous thrombosis for both men and women; until now this association was mainly studied in men for a first venous thrombosis.

# 2

# Current Perspective of venous thrombosis of the upper extremity

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## Summary

Venous thrombosis of the upper extremity is a rare disease. Therefore, not as much is known about risk factors, treatment and the risk of recurrence as for venous thrombosis of the leg. Only central venous catheters and strenuous exercise are commonly known risk factors for an upper extremity venous thrombosis. In this review an overview of the different risk factors, possible treatments and the complications for patients with a venous thrombosis of the upper extremity is given.

# Introduction

Venous thrombosis of the upper extremity (UEDVT), defined as a thrombus in the subclavian, axillary or brachial vein, accounts for 4-10% of all venous thromboses[45–50]. This figure may be an underestimation given that UEDVT is often asymptomatic[44,51,52]. The low incidence of UEDVT compared with the leg may be explained by the lower gravitational stress. Additionally, the veins of the upper extremities contain fewer valves than the legs which could be potential foci for thrombus formation. Furthermore, stasis contributing to the occurrence of thrombosis is very rare in the upper extremity. The most likely conditions for stasis to occur are surgery and plaster cast of the upper extremity[41,52].

# Primary venous thrombosis

UEDVT is usually divided into primary and secondary thrombosis[48,53]. Primary UEDVT includes idiopathic thrombosis and thrombosis associated with the thoracic outlet syndrome or effort (Paget-Schrötter syndrome)[42,43]. The incidence of primary UEDVT is 2 per 100 000 person-years[46,54] and accounts for approximately 30% of all UEDVT[48,54,55].

Thoracic outlet syndrome (TOS) relates to various forms of compression in the thoracic outlet. The thoracic outlet is located between the base of the neck and the axilla. Compression of the thoracic outlet can either be on the brachial plexus or on the blood vessels in the outlet. Compression of both nerves and vessels is rare. In approximately 3-10% of the cases, TOS will be vascular which can be divided into venous or arterial TOS[56]. UEDVT can be caused by venous TOS. In venous TOS the thoracic outlet veins are compressed by the clavicle and the first rib[57]. This will result in compression or sudden occlusion of the vein. Approximately 60% of patients with primary UEDVT have the thoracic outlet syndrome[47]. Treatment consists of either anticoagulation alone or in combination with resection of the first rib[57,58]. Paget-Schrötter syndrome, also called effort thrombosis, is a manifestation of TOS. The syndrome mostly occurs in young healthy persons, related to strenuous activity of the arm during sports[59–65]. The effort causes microtrauma of the vessel intima by repeated compression of the clavicle and first rib, which activates the coagulation[46]. The compression is mostly caused by trauma or by the enlarged muscles in the shoulder girdle[48,56,58,60,64,66].

# Secondary venous thrombosis

Secondary UEDVT is thrombosis with a known risk factor. These risk factors can be genetic or acquired[53,67,68].

### Central venous catheters

The main risk factor for UEDVT is a central venous catheter(CVC)[49,67]. The catheters are used to provide chemotherapy, medication and parenteral nutrition and for administration of fluids, blood products and hemodialysis[44]. Several studies investigated

the incidence and risk factors for UEDVT in patients with a CVC, as well as prophylaxis to prevent thrombosis[69–77].



CVCs can be divided into peripherally inserted catheters, chest catheters and pacemakers. Peripherally inserted catheters have an incidence of thrombosis from 10% to 38%[69,70,77]. The incidence of UEDVT for chest catheters ranges from 2% to 41%[71,72,75,77]. The risk of thrombosis is dependent of the diameter of the catheter; a larger diameter gives a higher risk of thrombosis[70]. The risk of UEDVT is lower for polyurethane and silicone catheters compared with polyethylene or Teflon-coated catheters[78,79].

Pacemakers give thrombosis in 10%. This risk increases with the number of leads from the pacemaker[80,81]. Most occlusions occur within the first 2 months after insertion of the catheter[70,82,83].

**Malignancy**

Malignancy is an important risk factor for UEDVT. However, the increased risk in patients with malignancy is mainly induced by CVCs Dhami & Bona, 1993; Girolami, Prandoni, Zanon, Bagatella, & Girolami, 1999)[86]. In the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a population-based case-control study, 179 patients with UEDVT were compared to 2399 control subjects. In patients without a CVC with an active form of malignancy an 18-fold increased risk of UEDVT compared with patients without active malignancy was found. Active malignancy was defined as malignancy diagnosed 5 years or less before first venous thrombosis[86]. A 7.7-fold increased risk of UEDVT was found when all, active and inactive, malignancies were included.

**Coagulation abnormalities and genetic risk factors**

In the literature the prevalence of coagulation abnormalities in patients with UEDVT ranges from 8% to 61%[45,68,87,88]. The differences can be explained by the size of these studies, including only between 18 and 51 patients. Additionally, the studies had different time points of blood collection: at diagnosis of thrombosis, 3 weeks after the event or after discontinuation of anticoagulation therapy. This can influence the assessment of coagulation abnormalities. Only antiphospolipid antibodies seem consistently more frequently present compared to the healthy population[87–89].

Factor (F) V Leiden[12] and the prothrombin 20210AP[13] mutation are common genetic risk factors in venous thrombosis of the leg, and may be a risk factor for UEDVT. Some studies reported an increased risk for either factor V Leiden or the prothrombin 20210A mutation or both. An Italian study included 115 patients with an UEDVT and 797 control subjects. A 5- to 6-fold increased risk of UEDVT was found for patients with one of the mutations[90]. In a Spanish study of 79 cases and 165 controls an increased risk was found for patients with the prothrombin 20210A mutation, no effect was found for the FV Leiden mutation[53]. A follow-up study including 257 patients with a CVC found a 3-fold increased risk of a UEDVT in patients with a mutation compared with patients without a mutation[74]. Although the majority of the other studies showed an increased risk for patients with the

FV Leiden or prothrombin 20210A mutation, the number of patients in these studies was small. Therefore, no solid conclusions can be drawn.

**Oral contraceptive use, surgery and plaster cast**

Oral contraceptive use did not increase the risk of UEDVT in most studies[48,87,90,91]. However, in a Spanish study a 5.7-fold (CI: 2.1-15.7) increased risk was found, and the MEGA study found a 2-fold (CI: 1.1-3.8) increased risk[53,86]. So, there is no consensus about oral contraceptive use as risk factor for UEDVT. Differences may be explained by the type of patients included in the studies. A study including patients with a primary UEDVT showed an increased risk while studies including patients with secondary UEDVT did not show an effect of oral contraceptives.

Surgery and plaster cast of the upper extremity result in stasis in the upper extremity. Only one study investigated surgery and plaster cast as a risk factor of UEDVT. This study found surgery of the upper extremity as a risk factor with an odds ratio of 13.1 (95% CI 2.1-80.6)[86]. Plaster cast of the arm increased the risk with an odds ratio of 7.0 (95% CI 1.7-29.5)[86].

**Other risk factors**

Other possible risk factors for UEDVT are obesity, hormone replacement therapy (HRT) and pregnancy. Few studies have investigated these risk factors. Obesity and HRT were no risk factors[86,92]. A case series reported pregnancy, especially in combination with ovary hyperstimulation syndrome, as a risk factor in women for UEDVT[93]. However no large studies were performed to assess the thrombotic risk for pregnancy.

## Treatment

Unfortunately, no randomised controlled trials have been performed on the optimal treatment for patients with UEDVT. Therefore, there is still debate about what the best therapy is and how side effects can be minimized. Anticoagulation is the most common treatment with a similar strategy as for deep vein thrombosis of the leg consisting of low molecular weight heparin and vitamin K antagonists. Removal of the main risk factor, for instance a CVC, probably reduces the risk of a recurrent event. However, in most cases removal of the CVC is not possible and therefore is inserted in the other arm or on the opposite site of the chest. Thrombolysis, surgery, thrombectomy and balloon dilatation with and without stent placing are used far less[94–98]. In these cases removal of a rib or correction of malformations of the ribs or clavicle may be part of the treatment. However, these aggressive forms of treatment may have serious side effects. Thrombolysis gives a higher risk of bleeding and surgery can cause pneumothorax, nerve damage and rethrombosis[98,99]. Balloon thrombectomy and venous stents can cause thrombosis by inducing intima damage[97]. In several pilot studies thrombolysis was compared with standard anticoagulation therapy in patients with a UEDVT. Most patients reacted well to thrombolysis and there were only a few more bleedings compared to the standard treatment[100–102]. A clear advantage of thrombolytic therapy has not been shown. Recently, the outcomes of the RIETE registry of patients with

venous thrombosis showed no difference in outcome after 3 months of therapy in patients with a deep vein thrombosis of the upper extremity or of the leg[103]. However, in this study treatment for UEDVT was different from that for thrombosis of the leg. Approximately 50% of the patients with UEDVT were only treated with low molecular weight heparins for 3 months and the other half with vitamin K antagonists. In venous thrombosis of the leg 70% of patients were treated with vitamin K antagonists. Therefore, the groups in this registry were not entirely comparable. These results show that patients with UEDVT with their current treatment have the same prognosis after three months as patients with venous thrombosis of the leg. Whether this is the most optimal treatment remains unclear.

## Complications

The main complications of UEDVT are pulmonary emboli (30%), post-thrombotic syndrome (PTS) and death[55,87,104–106]. PTS occurs in 7-44% of patients[55,107,108] (table 1). These percentages are based on small studies with different definitions of PTS. Mortality ranges from 15 to 50%, and is high because of major co-morbidity (e.g., malignancy, infection and multi-organ failure)[48,106,108].

In a few small studies the annual recurrence rate after a first UEDVT was 2% to 8%. However, groups were small and only one study found thrombophilia as possible risk factor for a recurrence; the other studies were too small to identify risk factors[90,106,108].

**Table 1.** Overview of different studies regarding complications in patients with venous thrombosis of the upper extremity

| Author | N of cases | %men | Mean age (range) | Primary vs Secondary | PTS | Recurrence (annual) | Mortality |
|---|---|---|---|---|---|---|---|
| Hingorani 1997[55] | 170 | 39 | 68 (9-101) | Both | 7% | - | 34% |
| Prandoni 1997[87] | 27 | 70 | 53 (19-79) | Both | 15% | 7% | 15% |
| Martinelli 2004[90] | 96 | 36 | 32 (14-61) | Primary | - | 2% | - |
| Baarslag 2004[106] | 50 | 42 | 52 (23-86) | Both | 18% | 8% | 50% |
| Prandoni 2004[108] | 53 | 31 | 44 -- | Both | 20% | 2% | 20% |
| Hingorani 2005 | 546 | 40 | 68 (1-101) | Both | - | - | 29% |
| Kahn 2005[109] | 34 | 46 | 51 (22-86) | Both | 44% | - | - |
| Hingorani 2006104 | 598 | 38 | 69 (9-101) | Both | - | - | 29% |

## Conclusion

UEDVT is a rare disease that mainly occurs in patients with a CVC. Most other risk factors are the same as for patients with a venous thrombosis of the leg. Mortality, pulmonary embolism and PTS are the most important complications of UEDVT but the incidences of these complications vary between studies. The optimal treatment of UEDVT remains unclear.

# 3

# Venous thrombosis of the upper extremity: effect of blood group and coagulation factor levels on risk

*British Journal of Haematology;149:118-123*

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## Summary

Venous thrombosis of the upper extremity is a rare form of thrombosis, accounting for around 4 percent of all venous thromboses, of which only a few risk factors are known. The aim of this case-control study was to investigate the effect of coagulation factors on risk of venous thrombosis of the upper extremity. Patients with venous thrombosis of the arm and partner controls were selected from the MEGA study, a large population-based case-control study. Participants with a malignancy were excluded. Odds ratios were estimated for elevated levels of factor II, VII, VIII, IX, X, XI, von Willebrand Factor (vWF), and fibrinogen, low levels of protein C, protein S, and antithrombin, and for blood group non-O. Substantially increased risks of venous thrombosis of the upper extremity were found for patients with high levels (above 90$^{th}$ percentile vs below) of factor VIII (Odds ratio (OR): 4.2, 95% confidence interval (CI): 2.2-7.9), vWF (OR: 4.0, 95% CI: 2.1-7.8), fibrinogen (OR: 2.9, 95% CI, 1.5-5.7), and for blood group non-O compared to O (OR: 2.1, 95% CI, 1.3-3.6). The other factors were not associated with an increased risk. Elevated levels of several procoagulant factors are associated with a strongly increased risk of venous thrombosis of the upper extremity.

# Introduction

Only 4 % of all cases of venous thrombosis are located in the upper extremity[41,51</sup>]. Therefore, most studies on risk factors for venous thrombosis focused on venous thrombosis of the leg or pulmonary embolism and only a few studies investigated the risk of venous thrombosis of the upper extremity, often restricted to a small number of risk factors. Malignancy, a central venous catheter, oral contraceptive use, surgery of the upper extremity, physical activity of the arm and the factor V Leiden[12] and prothrombin 20210A[13] mutation are known to increase the risk of venous thrombosis of the upper extremity in several studies, including the MEGA study44,53,63,72,77,85,86,90.

Individuals with elevated levels of procoagulant factors II, VIII, IX, and XI have an increased risk of venous thrombosis of the leg, with two- to threefold increased risks for those in the highest 10 percent of the population distribution[13,110–112]. Furthermore, blood group non-O is associated with a two-fold increased risk of venous thrombosis of the leg[113]. Only a few studies investigated the effect of procoagulant factors in patients with venous thrombosis of the upper extremity. Two studies examined the effect of factor VIII and fibrinogen. High levels of factor VIII were found to be present in the same number of patients with venous thrombosis of the upper extremity as in patients with venous thrombosis of the leg[114]. Similarly a high prevalence of high levels of fibrinogen was found[115]. However, in both studies no comparisons with the general population were made and hence no risk estimates were reported.

Deficiencies of anticoagulants protein C, protein S, and antithrombin substantially increase the risk of venous thrombosis of the leg[116]. Studies on the association of these defects with upper extremity thrombosis are scarce and have yielded conflicting results[45,88,91,94].

The aim of this study was to investigate the levels of pro- and anticoagulant factors and blood group as risk factors for venous thrombosis of the upper extremity.

# Methods

### Study population

Analyses were performed as part of a large population-based case-control study. Patients and control subjects were selected from the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis. Details of this study have been described elsewhere[7]. In the overall study over 5000 consecutive patients with deep venous thrombosis of the leg, a pulmonary embolism, or a venous thrombosis of the upper extremity between the age of 18 and 70, and their partners (>3000) were included. Patients were treated in 6 anticoagulation clinics in the Netherlands.

From March 1999 until September 2004, 329 consecutive patients with a venous thrombosis of the upper extremity were invited. Of these 329 patients, 224 participated (68%). There

were no differences in sex and age between those who did and did not participate. Blood was obtained from patients and control subjects included up to July 2002. Since the risk factors in the current study involve plasma factor levels, a blood sample is necessary. Consequently, 107 patients and 1825 controls were eligible for this study. Venous thrombosis was objectively confirmed with either ultrasonography, duplex sonography or computed tomography. Partners of patients with venous thrombosis in the overall study were included as control subjects. These were therefore partners of patients with different types of venous thrombosis, including deep-vein thrombosis of the leg and pulmonary embolism. Control subjects did not have a history of venous thrombosis and were between 18 and 70 years. Individuals with a malignancy (31 cases and 57 controls) and individuals without a blood sample (7 cases and 329 controls) were excluded from the present study. In total 69 patients with a venous thrombosis of the upper extremity and 1439 control subjects were included.

**Data collection**

All participants were asked to fill in a questionnaire on acquired risk factors for venous thrombosis within a few weeks after the index date. For patients the index date was date of the thrombotic event. For control subjects the index date was the date of diagnosis of thrombosis of their partner. Oral contraceptive use was considered to be present when used within 3 months before the index date. Idiopathic venous thrombosis was defined as present when occurring in the absence of factor V Leiden, prothrombin 20210A mutation, oral contraceptive use, surgery, plaster cast and, injury within 3 months before thrombosis, central venous catheter within a month before thrombosis and pregnancy or puerperium (< 5 weeks after delivery) at time of thrombosis. Both patients and control subjects were invited for a blood draw and interview at least 3 months after discontinuation of vitamin K antagonist treatment of the patient. Infection was present when patients reported a febrile disorder at time of blood draw. When duration of treatment was more than one year patients were invited for a blood draw at least 12 months after the thrombotic event. The mean time between index date and blood draw was 10 months for cases (range 4-24 months) and 7 months for controls (range 1-34 months).

All participants filled in an informed consent form and gave permission to obtain information about their medical history. This study was approved by the Ethics Committee of the Leiden University Medical Center, the Netherlands.

**Laboratory measurements**

Blood samples were drawn into vacuum tubes containing 0.1-volume 0.106-mol/L trisodium citrate as anticoagulant. Activity of factor II, VII, VIII, X, and XI was measured with a mechanical clot detection method on a STA-R coagulation analyzer. All measurements were performed following the instructions of the manufacturer (Diagnostica Stago, Asnières, France). Levels of factor IX antigen were determined by enzyme-linked immunosorbent essay (ELISA). Von Willebrand factor antigen was measured with the immuno-turbidimetric method, using the

STA liatest kit (rabbit anti human VWF antibodies). Fibrinogen activity was measured on the STA-R analyzer according to the method of Clauss. The 20146G/- (rs8176719), 21463C/G (rs7853989), 21867A/G (rs8176749), and 21996C/- (rs8176750) blood group polymorphisms were determined by a 5'nuclease assay (Taqman; Applied Biosystems, Foster City, California) using a standard PCR reaction mix (Eurogentec, Seraing, Belgium) and an allele specific fluorescent probe equipped with a minor groove binding moiety (Applied Biosystems).



Definitions of low levels of antithrombin, protein S, and protein C have been described elsewhere[117]. In brief, protein C, protein S, or antithrombin deficiency was defined as value below the mean minus two standard deviations in the control subjects. Due to unreliable test results, individuals with a blood sample at time of pregnancy were excluded from the analysis of protein C and protein S. The same applied to individuals using oral contraceptives at time of the blood sample in the determination of protein S. Sixty-six out of 69 patients and 1430 out of 1439 controls are left for the analysis of protein C and 57 patients vs. 1322 controls for protein S. The risk of vitamin K dependent factors was determined for 57 patients with a blood draw after discontinuation of vitamin K antagonist treatment. There were no missing data for the pro- and anticoagulant factors.

**Statistical analysis**

Odds Ratios (OR) and 95% confidence intervals were calculated as an estimate of the risk of venous thrombosis associated with coagulation factor levels and blood group non-O. Odds Ratios were adjusted for age and sex with a logistic regression model. The 90$^{th}$ percentile in the control subjects was used as cut off point for factors II, VII, VIII, IX, X, and XI, von Willebrand factor (VWF), and fibrinogen. For those factors with an increased risk for patients above the 90$^{th}$ percentile, tertiles were defined on the basis of the distribution among control subjects to investigate a dose response relation using the lowest tertile as a reference. Individuals with blood group non-O were compared with individuals with blood group O. The thrombotic risks associated with elevated factor VIII and VWF levels, and blood group were mutually adjusted. Since previous research found a joint effect of factor VIII and oral contraceptive use in patients with a venous thrombosis of the leg, the joint effect of factor VIII above the 90$^{th}$ percentile with oral contraceptive use among women was assessed[118–120]. Participants with low factor VIII and without oral contraceptive use at the time of index date were used as a reference group. The joint effect was adjusted for age. All analyses were performed using SPSS 14 (SPSS Inc, Chicago, Ill).

# Results

There were slightly more men in the control group than in the patient group: 49 versus 44 percent. Median age of the 69 patients was 39 (5$^{th}$-95$^{th}$ percentile 21-65 years) compared with 51 (5$^{th}$-95$^{th}$ percentile 29-66 years) in the 1439 controls (table 1). The prevalence of infection was similar between cases and control subject. White blood cell count was 5.6 versus 5.7 respectively.

Mean levels of procoagulant factors in patients with venous thrombosis of the upper extremity and control subjects are shown in table 2. Mean levels of factor VIII, VWF and fibrinogen were higher among the cases. All other procoagulant factors were similar in cases and controls or even higher in the control than the case group. The distribution of blood group differed for cases and controls. After dichotomization by the 90$^{th}$ percentile, elevated levels of factors II, VII, IX, and X were not associated with an increased risk of an upper extremity venous thrombosis (table 3). Mean levels of factor VIII, VWF, and fibrinogen were higher in patients than in controls (mean difference: factor VIII (21.7IU/ml, 95%CI,

**Table 1.** Baseline characteristics of the study population, including 69 patients with a venous thrombosis of the upper extremity and 1439 control subjects.

| | Patients N (%) | Controls N (%) |
|---|---|---|
| Sex (% men) | 30 (44) | 706 (49) |
| Median age (years) | 39 | 51 |
| CVC* | 4 (6) | 0 (0) |
| Infection[%] | 19 (27) | 321 (23) |
| WBC* (mean, SD) | 5.6 (1.4) | 5.7 (1.7) |
| Idiopathic thrombosis | 22 (32) | - |
| Oral contraceptive use[#] | 24 (62) | 131 (18) |

*CVC=Central venous catheter, WBC=White blood cell count
[#] In women (24 out of 39 cases, 131 out of 733 control subjects) at time of the index date
[%] At time of blood sample

**Table 2.** Mean levels of procoagulant factors and the prevalence of blood group in 69 patients and 1439 control subjects

| | Patients | Controls |
|---|---|---|
| **Mean level coagulation factor** | **Mean (SD)*** | **Mean (SD)*** |
| FII[†] | 98 (35) | 111 (18) |
| FVII[†] | 91 (35) | 112 (25) |
| FVIII | 131 (44) | 109 (37) |
| VWF | 138 (68) | 113 (49) |
| FIX[†] | 102 (20) | 106 (19) |
| FX[†] | 100 (42) | 117 (20) |
| FXI | 100 (19) | 101 (20) |
| Fibrinogen | 4.0(0.8) | 3.0(0.6) |
| Blood group | (%) | (%) |
| O | 32 | 47 |
| Non-O | 68 | 53 |

Factor II, VII, VIII, X, and XI were expressed in IU/ml; VWF and fibrinogen in g/l; factor IX in U/dl.
*SD= standard deviation
[†]Vitamin K dependent factors, figures were calculated after exclusion of patients using vitamin K antagonist treatment at time of blood draw leaving 57 patients compared with 69 patients in the analysis of the vitamin K independent factors

12.7-30.7), VWF (24.8 g/l, 95%CI, 12.7-36.9), and fibrinogen (0.1 g/l, 95%CI, 0.01-0.3)). Elevated levels of fibrinogen were found in 19% of patients i.e. over 4.15 g/l. An elevated level of fibrinogen (i.e. above the 90$^{th}$ percentile) was associated with a 2.9-fold (95% CI: 1.5-5.7) increased risk of thrombosis compared with low levels (below 90$^{th}$ percentile), after adjustment for age and sex.

Twenty-two percent of the patients had an elevated level of factor VIII, i.e. over 155 IU/ml (table 3). Individuals with an elevated level of factor VIII had a 4.2-fold (95% CI: 2.2-7.9) increased risk compared with those with low levels after adjustment for age and sex.

Twenty percent of patients had an elevated level of VWF, i.e. over 170 g/l. Individuals with elevated levels of VWF had a 4.0-fold (95% CI: 2.1-7.8) increased risk of venous thrombosis compared to those with low levels after adjustment for age and sex.

Of all patients, 68% had blood group non-O compared with 53% of all controls. Blood group non-O was associated with a 2.1-fold (95% CI: 1.3-3.6) increased risk of venous thrombosis compared with blood group O, after adjustment for age and sex. Associations between factor VIII, VWF and blood group non-O have been described previously[110]. In control subjects, levels of factor VIII and VWF differed between blood group O and non-O. The mean difference for individuals with blood group O compared with non-O for factor VIII was 34 IU/ml (95% CI: 30-39), for VWF the mean difference was 37 g/l (95% CI: 32-41). In a model with blood group, von Willebrand factor and factor VIII levels, all effects were attenuated, particularly those of factor VIII (OR 1.7, 95%CI (0.7-3.6) and

**Table 3.** The risk of venous thrombosis of the upper extremity for procoagulant factors

| Procoagulant factor | 90$^{th}$ percentile cutt-off point | N of patients >90th percentile (%) | OR (95% CI) | Adjusted OR (95% CI)* |
|---|---|---|---|---|
| FII† | 129.0 IU/ml | 5(9) | 1.0 (0.4-2.5) | 0.9 (0.4-2.3) |
| FVII† | 145.0 IU/ml | 2(4) | 0.3 (0.1-1.4) | 0.5 (0.1-1.9) |
| FVIII | 155.0 IU/ml | 15(22) | 2.5 (1.4-4.6) | 4.2 (2.2-7.9) |
| VWF | 170.0 g/l | 14(20) | 2.5 (1.4-4.6) | 4.0 (2.1-7.8) |
| FIX† | 131.1U/dl | 5(9) | 0.9 (0.3-2.2) | 1.1 (0.4-2.7) |
| FX† | 141.0 IU/ml | 5(9) | 0.9 (0.4-2.3) | 0.9 (0.3-2.3) |
| FXI | 126.0 IU/ml | 8(12) | 1.3 (0.6-2.7) | 1.5 (0.7-3.2) |
| Fibrinogen | 4.15 g/l | 13(19) | 2.2 (1.2-4.2) | 2.9 (1.5-5.7) |
| **Blood group** | | **N of patients blood group non-O** | **OR (95% CI)** | **Adjusted OR (95% CI)*** |
| Non O vs. O | - | 47(68) | 1.9 (1.1-3.2) | 2.1 (1.3-3.6) |

*Adjusted for age and sex
†Vitamin K dependent factors, figures were calculated after exclusion of patients using vitamin K antagonist treatment at time of blood draw leaving 57 patients compared with 69 patients in the analysis of the vitamin K independent factors

VWF (OR 1.9, 95%CI (0.8-4.7)), while blood group non-O remained associated with an 1.7-fold risk (95% CI: 1.0-2.8). None of the patients had a protein S deficiency. Only one patient had low protein C levels and only one patient low antithrombin levels. Therefore, the thrombotic risk for these anticoagulant factors could not be estimated.



Increased risks of venous thrombosis were seen for elevated levels of factor VIII, VWF, and fibrinogen. To explore a dose response relation between the levels of these factors and the risk of venous thrombosis, factor levels were divided in tertiles. Cut-off values for tertiles (in the controls) and risk estimates are shown in table 4. With the lowest tertile as a reference category, there was a clear dose response relation for both VWF and factor VIII levels. For fibrinogen levels both the second and third tertile showed similarly increased risks.

Since many female patients were using oral contraceptives at time of the thrombotic event and previous studies showed a high joint effect of oral contraceptive use and elevated factor VIII levels in patients with a venous thrombosis of the leg, we considered the possibility of a synergistic effect between elevated levels of factor VIII and oral contraceptive use. Results are shown in table 5. An elevated level factor VIII alone as well as use of oral contraceptive use only, were associated with an increased risk of venous thrombosis of the upper extremity (OR 5.3, 95%CI (1.3-20.5) and 7.5, 95%CI (2.2-25.5) respectively). The thrombotic risk was highest for women with both elevated levels of factor VIII and oral contraceptive use (OR 30.5, 95%CI (8.8-105.7)).

**Table 4.** Factor VIII, VWF, and fibrinogen and the risk of venous thrombosis of the upper extremity

| **Coagulation factor (cut-off points for tertiles)** | **1st Tertile** | **2nd Tertile*** | **3rd Tertile*** |
|---|---|---|---|
| Factor VIII (89, 120) | 1# | 2.2 (1.3-3.9) | 8.8 (3.9-19.8) |
| VWF (87, 122) | 1# | 2.0 (1.1-3.5) | 5.9 (2.8-12.2) |
| Fibrinogen (3.0, 3.5) | 1# | 2.5 (1.3-4.9) | 2.3 (1.2-4.1) |

* Adjusted for age and sex
# Reference category

**Table 5.** Joint effect of factor VIII and oral contraceptive use and the risk of thrombosis in the upper extremity.

| **Oral contraceptive use** | **High factor VIII** | **Patients N** | **Controls N** | **OR (95% CI)*** |
|---|---|---|---|---|
| - | - | 9 | 523 | 1# |
| + | - | 18 | 122 | 5.3 (1.3-20.5) |
| - | + | 6 | 79 | 7.5 (2.2-25.5) |
| + | + | 6 | 9 | 30.5 (8.8-105.7) |

*Adjusted for age
#Reference category

## Discussion

In this study we assessed the association between levels of pro- and anticoagulant factors and blood group and the risk of venous thrombosis of the upper extremity. Elevated levels of factor VIII, VWF, fibrinogen, and blood group non-O increased the risk of a venous thrombosis of the upper extremity. Elevated levels of factor II, factor VII, factor IX, factor X, and factor XI were not associated with an increased risk. We were not able to assess the risk of venous thrombosis of the upper extremity associated with protein C, protein S, or antithrombin deficiency.

The overall prevalence of deficiencies of anticoagulant factors protein C, protein S, and antithrombin among patients in several studies varies between 2% up to 12%[88,89,92]. In the current study no patients with protein S deficiency were identified; only one patient had a protein C deficiency, and only one patient was antithrombin deficient (both 3%). Given that the population prevalence of these abnormalities varies between 0.2% (protein C deficiency) and 0.02% (antithrombin deficiency), our findings are compatible with highly increased risks.

After dichotomization at the 90$^{th}$ percentile as measured in the control subjects, elevated levels of factor VIII, VWF, and fibrinogen were found to increase the risk of a first venous thrombosis of the upper extremity. There was also a clear dose response relation for factor VIII and VWF after stratification of the levels in tertiles. For fibrinogen no gradual increase in risk over the tertiles was observed.

Factor VIII, VWF, and fibrinogen are acute phase proteins. Therefore the question rises whether the elevated levels are a cause or consequence of venous thrombosis of the upper extremity. Blood was drawn at least 4 months after venous thrombosis. When comparing patients with a blood draw within one year with those with a blood draw more than one year after the thrombotic event, levels of factor VIII, VWF, and fibrinogen were similar (mean differences: factor VIII (2.4 U/dl, 95%CI, -21.8-26.6), VWF (0.9 U/dl, 95%CI, -36.4-38.2), and fibrinogen (-0.2 g/l, 95%CI, -0.6-0.3)). Furthermore, the prevalence of reported febrile disorders at time of blood draw and mean white blood cell count were similar between patients and controls. Finally, the effect of blood group is likely to be mediated via von Willebrand factor and factor VIII levels, and of course invariant. These results indicate that it is unlikely that the elevated levels of factor VIII, VWF, and fibrinogen are due to an acute phase reaction, which corroborates what has been proposed before for patients with venous thrombosis of the leg[121]. Thus, elevated levels of factor VIII, VWF, and fibrinogen are likely to be a cause of venous thrombosis of the upper extremity rather then a consequence of the disease.

Blood group non-O was associated with a two-fold increased risk of venous thrombosis of the upper extremity. After adjustment for factor VIII and VWF the risk of venous thrombosis of the upper extremity for blood group non-O compared with O was similar to the crude risk estimate, indicating that blood group non-O increases the risk of venous thrombosis via a

different pathway than factor VIII and VWF levels. After additional adjustment for blood-group and VWF or factor VIII, the risk of venous thrombosis associated with elevated factor VIII levels decreased from a 4.2 to a 1.7-fold increased risk, whereas the risk associated with elevated VWF levels decreased from a 4.0 to a 1.9-fold increased risk. This shows that the effect of factor VIII and VWF is partly due to the effects of blood group non-O.

There was a synergistic effect seen for high levels of factor VIII and oral contraceptive use, which was supra-additive.

This is the first study that assessed the risk of venous thrombosis of the upper extremity associated with elevated procoagulant factors. Although the number of patients was low due to the exclusion of individuals with a malignancy, we found an increased risk of upper extremity thrombosis for patients with an elevated level of factor VIII, VWF, and fibrinogen. The results for VIII, VWF, fibrinogen, and blood group non-O were similar to results found for venous thrombosis of the leg. Due to the small number of patients with anticoagulant protein C, protein S, and antithrombin deficiency, we were unable to estimate the risk of venous thrombosis of the upper extremity associated with low levels of anticoagulant factors, although the finding of two patients among 69 with such a defect is highly suggestive of an increased risk.

This study showed that elevated levels of several of the procoagulant factors are risk factors for both deep venous thrombosis of the leg as well as venous thrombosis of the upper extremity. However, there are also differences with regard to coagulation factors as risk factor for a venous thrombosis of the leg or of the upper extremity. Factors II, IX and XI have been described as risk factors for venous thrombosis of the leg but do not appear to increase the risk of venous thrombosis of the upper extremity in our study. This might be explained by the number of patients in our study. Although our study is the largest study investigating the effect of coagulation factors on venous thrombosis in the upper extremity among individuals without a malignancy, we only included 69 patients. A hypothetical explanation for the different coagulation factors that give an increased risk for deep venous thrombosis of the leg and or the upper extremity could be that venous thrombosis of the leg is likely to be more often induced by stasis (plaster cast, travel, hospital admission) and venous thrombosis of the upper extremity more often by injury of the vessel wall (CVCs, physical effort). In the presence of an injury of the vessel wall it might be important that factors related to the acute phase are elevated compared to other factors. If venous thrombosis is due to stasis, it might be less important which procoagulant abnormality is present. However, this hypothesis should be tested in a different study.

In conclusion, we found an increased risk of venous thrombosis of the upper extremity in patients with an elevated level of fibrinogen, factor VIII, VWF, and in patients with blood group non-O. However, due to the low number of patients the confidence intervals are wide.

# 4

# Recurrent thrombosis and survival after a first venous thrombosis of the upper extremity

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## Summary

Little is known about the consequences of a first venous thrombosis in the upper extremity. We studied the incidence of, survival, and risk factors for recurrence in a follow-up study. We followed up 224 patients 18 to 70 years of age after a first venous thrombosis of the arm. Information was collected through anticoagulation clinics, the national death registry, discharge letters, and questionnaires. The median follow-up was 3 years, during which time 30 patients experienced a recurrent event, yielding an incidence rate of 43.2 per 1000 person-years. Survival was reduced: 55 out of 224 patients died, which was 5.4-fold higher than age- and sex-adjusted population rates (standardized mortality ratio 5.4; 95% CI 4.2-7.0). The risk of recurrence was 2-fold higher in women than in men (hazard ratio 1.8; CI 95% 0.9-3.9). A central venous catheter at the time of first thrombosis was associated with a reduced risk of recurrence. A body mass index >= 25 kg/m$^2$ and a first non-subclavian thrombosis appeared to increase the risk of a recurrent event. Prothrombotic mutation carriers did not appear to have an increased recurrence risk. The risk of recurrence was high, with women, patients with body mass index>= 25 kg/m$^2$, and patients with a first non-subclavian vein thrombosis having a higher risk of recurrence. Patients with a first venous thrombosis of the arm have a poor vital prognosis.

# Introduction

The incidence of venous thrombosis varies between 1 per 10 000 in young adults and 1 per 100 persons per year in the very old, with a population average of 1 to 3 per 1000 persons per year[2,3]. About 4% of all cases of venous thrombosis are located in the upper extremities[41,51]. Because of its rarity, thrombosis of the arm has not been investigated as extensively as deep venous thrombosis of the leg or pulmonary embolism. However, the incidence of upper extremity venous thrombosis increases over time[90,122,123]. This is mainly due to the increasing use of central venous catheters (CVCs) which, combined with malignancy, is the strongest determinant of upper extremity venous thrombosis, with >1000-fold increased risk compared with patients without a CVC and malignancy[44,86]. Besides foreign objects such as CVCs and pacemaker leads, the main known causes of arm thrombosis are a hypercoagulable state, as induced by malignancy or coagulation abnormalities, and stasis in veins. The latter can be caused by a variety of related syndromes, ie, trauma of the arm, effort-related compression of the deep veins of the upper extremity (Paget-Schrötter syndrome), and compression caused by the thoracic outlet syndrome[41,46,68,86,90,91,124]. A few of the major coagulation abnormalities appear to enhance the risk of arm thrombosis as they do for venous thrombosis of the lower extremities[41,68]. Factor V Leiden, Protein C and S deficiency, anticardiolipin antibodies and lupus anticoagulants are frequent among patients with a venous thrombosis of the upper extremity[87–89,91].

Because of the low incidence, few studies have investigated recurrent venous thrombosis of the arm and its risk factors[90,103,106,108]. In these studies, the cumulative incidence of recurrence after 1 year was 2% to 5%[90,106,108]. Inclusion criteria and end points differed between studies. One study included patients with an idiopathic venous thrombosis of the arm and reported only venous thrombosis of the arm as a recurrent event[90]. Two studies assessed risk factors for a recurrence among patients with primary or secondary venous thrombosis of the arm and included all types of venous thrombosis as recurrent events[106,108]. Prothrombotic mutations appeared to be associated with a recurrent event in 1 study of 90 patients with a first primary venous thrombosis of the arm[90]. However, another study did not confirm these results[106].

In the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study (MEGA-study), 224 consecutive patients with a first venous thrombosis of the arm were included in the present follow-up study. The aim was to investigate survival and the incidence of recurrent venous thrombosis in any location in relation to risk factors such as the presence of a CVC, malignancy, prothrombotic mutations, and other putative risk factors.

# Materials and Methods

### Patient Selection

Two hundred twenty-four consecutive patients 18 to 70 years of age with a first venous thrombosis of the upper extremity were included between March 1999 and August 2004.

The MEGA study is a large population-based case-control study to assess risk factors for a first venous thrombosis. Details of this study have been given elsewhere[7,86]. Patients were included from the files of six anticoagulation clinics, which monitor virtually all patients who receive treatment with vitamin K antagonists in the Netherlands, each in a well-defined geographical region. A venous thrombosis of the internal jugular vein, subclavian, axillary, brachial or the superficial basilic and cephalic veins was considered to be an upper extremity venous thrombosis. Fifteen patients were also diagnosed with a pulmonary embolism or a venous thrombosis of the lower extremity. Venous thrombosis of the upper extremity was confirmed with either ultrasound, contrast venography or computed tomography[86].



**Data collection**

In 2006, municipal registries were contacted to retrieve the most recent addresses of patients and to assess vital status. Causes of death were obtained from the Central Bureau of Statistics Netherlands (CBS), which stores all Dutch death certificates. An inquiry form was sent to patients who were still alive and who had initially agreed to participate in a follow-up study. The inquiry form asked about subsequent visits to anticoagulation clinics and the occurrence of a recurrent event in any location. Patients were sent a follow-up questionnaire about putative risk factors for a recurrent venous thrombosis, either by mail or via the Internet. Patients who did not reply were contacted by phone. Information about recurrences and duration of initial vitamin K antagonist treatment for all 224 patients also was obtained from anticoagulation clinics. Recurrences were included when confirmed by ultrasound, contrast venography or computed tomography according to the discharge letters. Information regarding putative risk factors at time of first venous thrombosis was obtained from the baseline questionnaire and from the discharge letters of the first thrombosis[7]. An event was defined as idiopathic in the absence of surgery, oral contraceptive use, injury and plaster cast in the previous 3 months, malignancy, absence of CVC in the previous month, and absence of puerperium, factor V Leiden mutation or prothrombin 20210A mutation. All participants gave informed consent. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

**Blood collection and laboratory analysis**

Blood samples were taken at least 3 months after discontinuation of vitamin K antagonist treatment for the first thrombotic event. Blood draws were collected from 67 patients. Blood samples were drawn into vacuum tubes containing 0.1 volume 0.106 mol $L^{-1}$ trisodium citrate as anticoagulant. Blood samples were separated into plasma and cells through centrifugation. Prothrombin activity, Factor VII activity, Factor VIII activity, Factor X activity, and Factor XI activity were measured with a mechanical clot detection method on a STA-R coagulation analyzer. All measurements were performed following the manufacturer's instructions (Diagnostica Stago, Asnieres, France). Levels of factor IX antigen were determined by ELISA. Fibrinogen activity was measured on the STA-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time

of a diluted plasma sample was measured. Von Willebrand factor antigen was measured with the immunoturbidimetric method, using the STA liatest kit (rabbit anti-human von Willebrand factor antibodies), following the instructions of the manufacturer (Diagnostica Stago). DNA was collected with buccal swabs from patients who were unable to give a blood sample and from all patients who were included beginning in June 2002. In total, DNA samples were collected from 178 patients. High molecular weight DNA was collected by using a salting-out method and stored at -20 °C until amplification. DNA-analysis of the factor V Leiden and prothrombin 20210A mutation was performed with a combined polymerase chain reaction method. Assessment of these mutations in DNA retrieved from buccal swabs was performed identically to the method for DNA obtained from whole blood. A detailed description of these methods was described previously[7].

**Statistical Analysis**

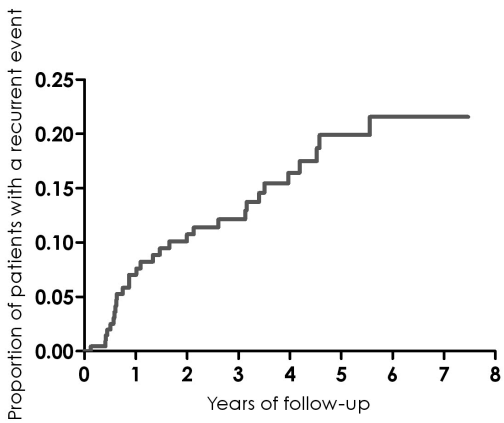
Cumulative incidence was estimated by the Kaplan-Meier technique. Incidence rates were the number of new events over the total number of person-years. Person-years were calculated from date of first event and from discontinuation of the initial vitamin K antagonist treatment until recurrent event, death or end of study, whichever came first. Participants who died during follow-up of a cause other than venous thrombosis were censored at date of death. Patients who were not able to complete the inquiry form were censored at their last contact within the MEGA study and considered study withdrawals. The end of study date was October 1, 2006. Hazard ratios (HRs) were estimated with a Cox proportional-hazards model. Adjustments were made for age and sex. We did not adjust for race because our follow-up study included >95% whites. Cox analysis was performed in the overall cohort of 224 patients and in 163 patients after they had discontinued vitamin K antagonist treatment. Median duration of vitamin K antagonist treatment was 6 months (5th percentile, 2 months; 95th percentile, 57months). High levels of prothrombin, factor VII activity, factor VIII activity, factor IX antigen, factor X activity, factor XI activity, von Willebrand factor, and fibrinogen were defined as a level above the 90th percentile in the group of patients without a recurrent event. Standardized mortality ratios (SMRs) were estimated for the overall patient group with the general Dutch population as a reference[125] and in men and women separately with the sex-specific population rates as reference. These SMRs estimate the rate of death relative to age- and sex-adjusted rates from the general population or, in other words, give the ratio of the observed and expected number of deaths when population rates are applied to the cohort. Data from 2003 were used to represent the average general population of the period from 1999 till 2006. Confidence intervals were based on a Poisson distribution. All analyses were performed with SPSS version 14 (SPSS Inc, Chicago, Ill). The authors had full access to and take responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

# Results

## Patients

Of the 224 patients, 47% were men, and the median age at time of first thrombosis was 46 years (5th percentile, 21 years; 95th percentile, 67 years). The median follow-up period was 3 years (range 0 to 7.5 years). Of the 30 recurrences, 9 were during vitamin K antagonist treatment. Four of these 9 events were within the first 6 months of treatment. The overall 2-year cumulative incidence of a recurrent venous thrombosis was 8% (95% CI 4 to12). The incidence rate was 43.2 per 1000 person-years (95% CI 27.8 to 58.7 per 1000 person-years), ie, >4% recurrence risk per year (The Table and Figure 1). The time between first and second events varied from 45 days to 5.5 years. Of the 30 recurrences, 18 were located only in the upper extremity, 1 in the arm in combination with a pulmonary embolism, 6 in the leg, 1 was a Budd-Chiari syndrome, and 4 were pulmonary emboli without a known origin. Of the 19 patients with a recurrent thrombosis in the arm, 14 thromboses were located in the same arm as the first occurrence, but 5 were on the opposite side. Of these 19 patients 8 had a malignancy, compared with 70 out of all 224 patients. Four of these 8 patients developed a recurrent thrombosis (50%) in the same arm as the first event. Of the 22 patients with a recurrent event without malignancy, 10 (45%) developed the event in the same arm as the first event.

Of the 224 patients, 31 patients were censored (because of recurrence, death resulting from causes other than venous thrombosis or withdrawal from the study) during the initial 6 months of treatment. Of the remaining 193 patients, 163 discontinued treatment during our study (115 within 6 months, 48 after >6 months), and 30 patients were still receiving anticoagulant treatment at the end of follow-up. Apart from the overall group of 224 patients,




| Period in months | 0-6 | 7-12 | 13-18 | 19-24 | 25-30 | 31-36 | 37-42 | 43-48 | 49-54 | 55-60 | 61-86 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N at risk | 224 | 184 | 155 | 144 | 138 | 128 | 110 | 102 | 85 | 69 | 59 |
| N events | 4 | 6 | 4 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 1 |

**Figure 1.** Kaplan Meier for risk of recurrent event in the overall group of 224 patients

**Table 1.** Risk factors at baseline and the risk of a recurrent event in the overall group of 224 patients with a first upper extremity venous thrombosis and the subgroup of 163 patients after discontinuation of vitamin K antagonist treatment

| | Overall group of patients | | | | | Subgroup of patients after treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | N Recurrences (%) | Incidence rate* | Hazard ratio | Adjusted Hazard Ratio§ | N | N Recurrences (%) | Incidence rate* | Hazard ratio | Adjusted Hazard ratio§ |
| Overall | 224 | 30(13) | 43.2 | | | 163 | 21 (13) | 40.1 | | |
| Men | 106 | 10(9) | 29.9 | 1 | 1 | 81 | 6(7) | 22.2 | 1 | 1 |
| Women | 118 | 20(17) | 55.6 | 1.8 (0.9-3.9) | 1.8 (0.9-3.9) | 82 | 15(18) | 59.2 | 2.6 (1.0-6.7) | 2.6 (1.0-6.7) |
| Age < 50 years | 123 | 20(16) | 51.2 | 1 | 1 | 88 | 13(15) | 44.5 | 1 | 1 |
| Age > 50 years | 101 | 10(10) | 32.9 | 0.6 (0.3-1.3) | 0.6 (0.3-1.3) | 75 | 8(11) | 34.6 | 0.8 (0.3-1.9) | 0.8 (0.3-1.9) |
| No malignancy | 154 | 22(14) | 42.8 | 1 | 1 | 116 | 14(12) | 34.6 | 1 | 1 |
| Malignancy | 70 | 8(11) | 44.4 | 1.0 (0.5-2.3) | 1.1 (0.5-2.4) | 47 | 7(25) | 58.7 | 1.6 (0.6-4.0) | 1.9 (0.7-5.3) |
| No CVC | 168 | 28(17) | 53.3 | 1 | 1 | 123 | 19(15) | 45.8 | 1 | 1 |
| CVC | 56 | 2(4) | 11.9 | 0.2 (0.1-0.9) | 0.2 (0.1-1.0) | 40 | 2(5) | 18.3 | 0.4 (0.1-1.7) | 0.4 (0.1-1.6) |
| No Surgery | 194 | 26(13) | 48.1 | 1 | 1 | 135 | 17(13) | 37.8 | 1 | 1 |
| Surgery | 30 | 4(13) | 43.8 | 0.9 (0.3-2.7) | 1.1 (0.4-3.2) | 28 | 4(14) | 53.7 | 1.4 (0.5-4.1) | 1.5 (0.5-4.6) |
| Provoked | 156 | 21(13) | 43.8 | 1 | 1 | 110 | 16(15) | 47 | 1 | 1 |
| Idiopathic | 68 | 9(13) | 41.7 | 1.0 (0.4-2.1) | 1.2 (05-2.7) | 53 | 5(9) | 27.3 | 0.6 (0.2-1.6) | 0.8 (0.3-2.3) |
| Patients with location | 162 | | | | | 124 | | | | |
| Subclavian vein | 114 | 11(10) | 28.1 | 1 | 1 | 88 | 9(10) | 29.8 | 1 | 1 |
| Non subclavian vein | 48 | 10(21) | 62.4 | 2.2 (0.9-5.2) | 2.0 (0.8-2.7) | 36 | 7(19) | 60 | 2.0 (0.8-5.4) | 1.9 (0.7-5.0) |
| Only subclavian vein | 53 | 4(8) | 21.7 | 1 | 1 | 40 | 3(8) | 22 | 1 | 1 |
| Other single vein | 44 | 9(20) | 62.0 | 2.8 (0.9-9.1) | 2.7 (0.8-8.7) | 32 | 6(19) | 58.2 | 2.6 (0.6-10.3) | 2.7(0.7-10.8) |
| Single veins | 97 | 13(13) | 39.5 | 1 | 1 | 72 | 9(13) | 37.5 | 1 | 1 |
| Multiple veins | 65 | 8(12) | 35.9 | 0.9 (0.4-2.1) | 0.9 (0.4-2.2) | 52 | 7(13) | 39 | 1.0 (0.4-2.7) | 1.0 (0.4-2.7) |
| Patients with known BMI | 203 | | | | | 149 | | | | |
| BMI (kg/m2) <25 | 122 | 13(11) | 34.1 | 1 | 1 | 90 | 9(10) | 31 | 1 | 1 |

**Table 1.** *Continued*

| | Overall group of patients | | | | | Subgroup of patients after treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | N Recurrences (%) | Incidence rate* | Hazard ratio | Adjusted Hazard Ratio§ | N | N Recurrences (%) | Incidence rate* | Hazard ratio | Adjusted Hazard ratio§ |
| 25-29 | 56 | 9(16) | 46.9 | 1.3 (0.6-3.1) | 1.6 (0.7-3.8) | 44 | 7(16) | 46.3 | 1.4 (0.5-3.8) | 1.7 (0.6-4.8) |
| ≥ 30 | 25 | 6(24) | 90.2 | 2.5 (0.9-6.5) | 2.7 (1.0-7.3) | 15 | 3(20) | 62.8 | 1.9 (0.5-7.0) | 2.1 (0.5-8.1) |
| Women aged 18-50 | 64 | | | | | 43 | | | | |
| No oral contraceptives | 28 | 7(25) | 89.8 | 1 | 1 | 17 | 5(18) | 103.9 | 1 | 1 |
| Oral contraceptives | 36 | 8(22) | 68.5 | 0.8 (0.3-2.1) | 0.8 (0.3-2.1) | 26 | 5(14) | 56.1 | 0.5 (0.2-1.9) | 0.5 (0.2-1.9) |
| Patients with DNA sample | 178 | | | | | 135 | | | | |
| Without FVL or G20210A | 149 | 20(13) | 41.3 | 1 | 1 | 112 | 13(12) | 34.3 | 1 | 1 |
| With FVL or G20210A | 29 | 3(10) | 27.3 | 0.7 (0.2-2.2) | 0.7 (0.2-2.2) | 23 | 3(13) | 37.2 | 0.9 (0.3-3.5) | 0.8 (0.3-3.0) |

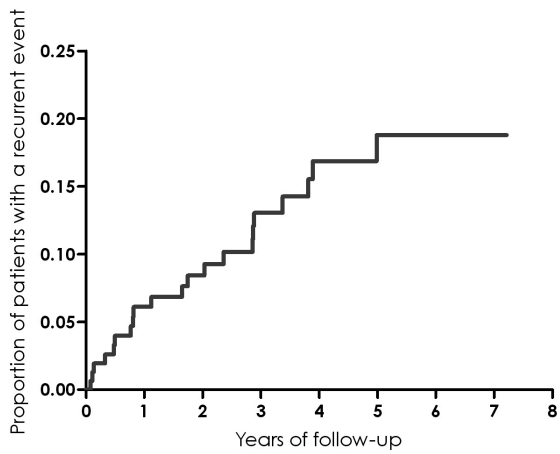
*per 1000 person-years; § All analyses were adjusted for age and sex, except when the analysis was restricted to one sex or age group

we also report the results of these 163 patients after their discontinuation of treatment. Of the 163 patients who discontinuated vitamin K antagonist treatment, 21 subsequently had a recurrent event. The median follow-up after discontinuation of vitamin K antagonist treatment in these patients was 2 years (range 0 to 7.2 years) (Figure 2). The 2-year cumulative incidence was 7% (95% CI 2 to12). The incidence rate after discontinuation was 40.1 per 1000 person-years (95% CI 23.0 to 57.3). The incidence of recurrence for the 61 patients who did not discontinue treatment at any time during follow- up (224-163=61, of whom 9 had a recurrence) was 122.5 per 1000 person-years 95% CI 42.4 to 202.4. Some of these (4 out of 9) were early recurrences, during the first 6 months of treatment; median duration of follow-up was 6 months (5th percentile, 1 month; 95th percentile, 75 months).

**Risk factors at baseline**

The table shows the effects of putative risk factors present at the time of first venous thrombosis on the incidence of a recurrent event for the overall group of 224 patients and for 163 patients after discontinuation of vitamin K antagonist treatment.

In the overall group female sex (adjusted HR [HRadj] 1.8; 95% CI 0.9 to 3.9), a first nonsubclavian vein thrombosis (HRadj, 2.0; 95% CI 0.8 to 2.7) and body mass index (BMI) >=25 kg/m$^2$ (BMI 25-29 kg/m$^2$ : HRadj, 1.6; 95% CI 0.7 to 3.8; BMI >=30 kg/m$^2$ : HRadj, 2.7; 95% CI 1.0 to 7.3) were associated with a higher risk of a recurrent event. A CVC at time of first venous thrombosis was associated with a decreased risk of recurrence (HRadj, 0.2; 95% CI 0.1 to 1.0). The other factors did not show an effect on recurrence risk (the Table).




| Period in months | 0-6 | 7-12 | 13-18 | 19-24 | 25-30 | 31-36 | 37-42 | 43-48 | 49-54 | 55-60 | 61-70 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N patients at risk | 163 | 138 | 128 | 120 | 107 | 98 | 86 | 69 | 54 | 50 | 41 |
| N events | 6 | 3 | 1 | 2 | 2 | 3 | 1 | 2 | 0 | 1 | 0 |

**Figure 2.** Kaplan Meier for risk of recurrent event in the subgroup of 163 patients after discontinuation of vitamin K antagonist treatment

The results in 163 patients after discontinuation of vitamin K antagonist treatment did not differ from the overall results for most putative risk factors. Only the effect of malignancy and oral contraceptive use seemed to be different. Malignancy at time of first thrombosis was associated with a weakly elevated risk of a recurrence (HRadj, 1.9; 95% CI 0.7 to 5.3), whereas women who used oral contraceptives at time of their first event had a decreased risk of a recurrent event (HRadj, 0.5; 95% CI 0.2 to 1.9). Most of these women (32 out of 36 for whom information about oral contraceptive use after the initial event was available) had discontinued oral contraceptives after the initial event.



Among all 224 patients, 70 were diagnosed with malignancy at or shortly after the time of the initial event; 44 of these patients died during follow-up. The overall relative risk of recurrence in patients with malignancy was 1.1 (95% CI 0.5-2.4). Of the 47 patients with malignancy who discontinued vitamin K antagonist treatment 7 had a recurrent event after discontinuation (58.7 per 1000 person-years; 95% CI 15.2 to 102.3). Fourteen recurrences occurred in the 116 patients without malignancy (34.6 per 1000 person-years; 95% CI 16.5 to 52.8). Of the 61 patients who were treated with anticoagulants throughout follow-up, 23 had a malignancy. Of these 23 patients, 1 developed a recurrent venous thrombosis during vitamin K antagonist treatment (30.6 per 1000 person-years; 95% CI 0 to 122).

**Coagulation Factors**

A blood sample was drawn from 67 patients after they had stopped using vitamin K antagonists. Of these 67 patients, 10 experienced a recurrent event. HRs were calculated for elevated levels of factor IX and factor XI. Of 6 patients with elevated factor IX levels, 1 patient had a recurrent event, compared with 9 out of 61 patients with normal factor IX, which suggests a 2-fold increased risk (HRadj, 2.1; 95% CI 0.2 to 23.0). Of 6 patients with elevated factor XI levels, 1 patient had a recurrent event, compared with 9 out of 61 patients with normal FXI activity, again suggesting an elevated risk (HRadj, 3.3: 95% CI 0.4 to 30.5), although in both instances with a wide CI. None of the patients with high levels of factor II, factor VII, factor VIII, factor X, von Willebrand factor, and fibrinogen experienced a recurrent event.

**Mortality**

Fifty-five out of 224 patients (25%) died during follow-up, 34 of whom were women. Twenty five of these 55 patients died during the first year. Median age at death was 58 years (5th percentile 37 years, 95th percentile 69 years). Malignancy was the main cause of death. Forty-four out of 55 patients died of malignancy, of whom 26 were women, ie, of the 70 patients with a malignancy, 63% (44/70) had died at the end of follow-up. In comparison, among the 154 patients without malignancy, 11 patients (7%) had died. Other causes of death were the recurrent event itself (n=2), or death related to autoimmune diseases (n=2), pulmonary diseases (n=4) and heart failure (n=3).

The risk of death compared to the general population, expressed as an SMR was 5.4-fold (95% CI, 4.2 to 7.0) increased. The SMR was 7.7 (95% CI, 5.1 to 11.9) for men compared to the

male population and 15.5 (95% CI 11.1-21.6) for women compared to the female population. When patients with malignancy were excluded, the overall SMR was 1.1 (95% CI, 0.6 to 2.2); SMR was 0.5 (95% CI, 0.1 to 3.4) for men and 4.7 (95% CI, 2.3 to 9.9) for women.

**Risk Factors Shortly Before a Recurrent Venous Thrombosis**

Of the initial 224 patients, 72 were not able to fill in the questionnaire, 55 died, 2 emigrated, and 15 refused to participate in further follow-up. Of the remaining 152 patients, 126 patients returned the inquiry form, and 104 patients answered additional questions by mail, Internet or phone. Of these 104 patients, 13 were still using vitamin K antagonist treatment and were therefore excluded. Of 91 patients, 12 had a recurrent event. Four had a malignancy, 2 had surgery and 3 patients either carried the Factor V Leiden or the Prothrombin 20210A mutation, 1 event was related to pregnancy and 2 were idiopathic.

## Discussion

We studied the risk of recurrent thrombosis and death in a large cohort of 224 patients with a first venous thrombosis of the upper extremity. The cumulative incidence of recurrence after 2 years was 8% (95% CI, 4 to 12%), and the incidence rate of recurrence was 43.2 per 1000 person-years (95% CI, 27.8 to 58.7). Women had a 2-fold higher recurrence risk than men and appeared to have, contrary to men, a decreased survival in the absence of malignancy. There appeared to be an increased risk of recurrence for patients with a first nonsubclavian vein thrombosis and for patients with a BMI >= 25kg/m$^2$. Patients with a first thrombosis resulting from a CVC had a decreased risk of a recurrent event.

After discontinuation of treatment (n=163) the 2 year cumulative incidence was similar at 7% (95% CI, 2 to 12%), which was also similar to incidences found in 2 previous smaller studies (4.2% and 7%) that included only patients after discontinuation of treatment[90,108]. The incidence of recurrence in patients who did not discontinue treatment during our study was high (122.5 per 1000 person-years; 95% CI, 42.4 to 202.4). This result is difficult to interpret, for, firstly, this figure includes patients with early recurrences (during the first 6 months of treatment) and patients with end stage disease or a malignancy.

In one respect, our results are strikingly different from results of previous studies focusing on recurrence after a venous thrombosis of the leg. Men with a venous thrombosis of the leg clearly have a higher risk of recurrence than women[24,30,36,126,127]. In contrast, in venous thrombosis of the arm we found an increased risk of recurrence for women. There is no clear explanation for the gender difference in patients with a venous thrombosis of the upper extremity. We found a reduced recurrence risk for women who used oral contraceptives at the time of their first thrombosis. However, most women discontinued oral contraceptive use after the initial event. Therefore, oral contraceptive use does not explain the difference in risk between men and women.

The incidence rate of recurrence appeared to increase with BMI, whereas BMI was not a clear risk factor for a first thrombotic event in the arm[86,92,128]. First events in the subclavian vein tended to recur less often than thromboses in other veins of the arm. The reason may be the removal of the CVC in these patients because most CVCs are located in the subclavian vein. However, we do not have data about removal of CVCs and therefore we are not able to corroborate this explanation. Patients with malignancy appeared to have an increased risk of a recurrent event after treatment and prolonged treatment in these patients may be beneficial.



Only 14 of the 30 recurrences were in the same arm as the initial thrombosis. When we exclude the 4 pulmonary emboli with unidentified origin, we find that at least 12 recurrences, roughly half, occurred in another location. There were no differences in malignancy and prothrombotic defects between the patients with a recurrence in the same location and patients with a recurrent event in another location.



Nine of the 30 recurrence occurred during treatment. Four of these events were within 6 months after the first event; therefore, it is uncertain if they are true recurrence or extensions of the original clot. Only 1 of these 4 recurrences was in a different extremity. It should be noted that the results of the overall group did not differ from the results of the subgroup of 163 patients after discontinuation of treatment.

A thrombosis of the arm is associated with a poor prognosis: 25 % (55 of 224) patients died, and 25 of these deaths were in the first year after thrombosis. These were mainly patients with cancer.

The factor V Leiden and prothrombin 20210A mutation, present in 17% of patients, did not affect recurrence risk. This finding is in line with previous studies on recurrence risk after a first venous thrombosis of the leg[22,23,36]. An analysis regarding levels of coagulation factors could be performed in 67 patients. Only a few patients had abnormal levels, and most of them did not have a recurrent event. Although our follow-up study on patients with a first venous thrombosis of the upper extremity is one of the largest studies performed so far, the number of patients with prothrombotic defects was small, and thus CIs were wide. Therefore, no firm conclusions can be drawn from these results and clinical strategies of testing for prothrombotic abnormalities cannot be recommended.

We were able to trace all 224 patients indirectly via anticoagulation clinics. One hundred and twenty six patients were contacted directly by the inquiry form. We did not have information about the exact location of the first venous thrombosis in all patients. Because the inability to contact patients and the absence of exact information in discharge letters are not likely to be related to location of the thrombus, we do not believe they biased our results. Information on risk factors preceding the second event was available for 91 patients who discontinued vitamin K antagonist treatment through a follow-up questionnaire. Only 2 of the 12 recurrent events in this group were idiopathic, indicating that patients with risk factors may need more attention. Four of these recurrences were in patients with malignancy.

## Conclusions

Patients with a first venous thrombosis of the arm have an increased risk of death compared to the general population that is mainly due to malignancy. Eight percent of the patients experienced a recurrence within 2 years. Being female, having a BMI >25 kg/m$^2$, and having a first nonsubclavian vein thrombosis seem to be the most important risk factors for a recurrent venous event in patients with a venous thrombosis of the upper extremity.

# 5

# Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors.

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## Summary

Venous thrombosis is a common disease with a high mortality rate shortly after the event. However, details on long term mortality in these patients are lacking. The aim of this study was to determine long term mortality in a large cohort of patients with venous thrombosis. 4947 patients from the Multiple Environmental and Genetic Assessment study of risk factors for venous thrombosis (MEGA study) with a first non-fatal venous thrombosis or pulmonary embolism and 6154 control subjects without venous thrombosis, aged 18 to 70 years, were followed up for eight years. Death and causes of death were retrieved from the Dutch death registration. Standardized mortality ratios (SMRs) were calculated for patients compared with control subjects. Several subgroups were studied as well. 736 participants (601 patients and 135 controls) died over a follow-up of 56999 person-years. The overall mortality rate was 22.0 per 1000 person-years (95%CI: 20.3-23.9) for patients and 4.5 per 1000 person-years (95%CI: 3.8-5.4) for controls. Patients with venous thrombosis had a 4.1-fold (95%CI: 3.8-4.4) increased risk of death compared with controls. The risk remained increased up to eight years after the thrombotic event, even when no additional comorbidities were present. The highest risk of death was found for patients with additional malignancies (SMR 5.8, 95%CI: 5.2-6.4). Main causes of death were diseases of the circulatory system, venous thrombosis and malignancies. Main limitation was a maximum age of 70 at time of inclusion for the first event. Therefore results cannot be generalized to those in the highest age categories. Patients who experienced a first venous thrombosis had an increased risk of death, which lasted up to eight years after the event, even when no comorbidities were present at time of thrombosis. Future long-term clinical follow-up could be beneficial in these patients.

# Introduction

Venous thrombosis is a multicausal disease that occurs in 1-3 per 1000 persons per year[2,3,116]. Venous thrombosis is associated with considerable morbidity and mortality. About 10-20% of patients develop a recurrence within five years[22,24,30] and up to 50% develop post-thrombotic syndrome within several months after the thrombotic event[129]. The mortality rate after venous thrombosis is about 20% within one year[3,130]. Mortality is 2 to 4-fold higher for patients with pulmonary embolism, of whom 10-20% die within three months after the event, than for patients with a deep vein thrombosis of the leg[3,50,131,132]. Malignancy is the main cause of death, however, when only patients without malignancy are followed, 12% die within a year after the thrombosis[3,7]. Another predictor is the underlying cause of the first thrombosis, where those with thrombotic events provoked by surgery or trauma have a lower three-year mortality risk than those with idiopathic thrombosis[3]. These figures imply that venous thrombosis has a major impact on survival. It is currently unknown whether this poor prognosis is limited to the period shortly after the thrombotic event, or persists for extended periods.

In the present study we determined long term survival in a large cohort of consecutive patients with a first venous thrombosis compared with age- and sex matched subjects without venous thrombosis, who were all followed for up to eight years.

# Methods

### Study population and data collection

We used a cohort consisting of all patients and control subjects from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis-study (MEGA study). Details of the study are described elsewhere[7,14]. In short, the MEGA study was set up as a case-control study including 4965 consecutive patients aged 18 to 70 years with a first objectively verified venous thrombosis of the leg or pulmonary embolism and 6297 control subjects recruited between March 1999 and September 2004.

Patients were recruited from six anticoagulation clinics in the Netherlands, which exclusively monitor out-patient treatment with vitamin K antagonists in well-defined geographical regions. Patients were included in the study after a median period of one month (range 13-64 days) after the diagnosis of thrombosis.

The control group consisted of partners of patients (n=3297) and a random control group matched on age and sex (n=3000), recruited between January 2002 and December 2004 using random digit dialing. All patients and controls filled in a detailed questionnaire on risk factors for venous thrombosis and several comorbidities present at time of venous thrombosis (patients) or at time of inclusion in the study (controls).

Vital status was ascertained through community registries, where all inhabitants are registered. Causes of death were obtained from the Central Bureau of Statistics Netherlands, the national repository for death certificates. Both primary and secondary causes of deaths were retrieved. Causes of death were coded according to the ICD-10 classification[125,133].

In the current study an additional control group was used. We compared cause-specific death rates of the patients to those of the general Dutch population, which due to its size of the reference group allowed analyses of cause-specific death rates, for which the control group of the MEGA study was too small.



**Follow-up and Statistical analysis**

The observation time was from 30 days after the venous thrombosis, or a similar date in the thrombosis-free cohort, to either death, end-of-follow-up (between February 2007 and May 2009), emigration (n=164, 1.5%), or loss-to-follow-up (n=173, 1.5%), whichever occurred first.

For 152 individuals (1.4%, 9 patients) follow-up was less than 30 days, and they were excluded. Censoring due to emigration concerned 164 individuals (1.5%) and to loss-to follow-up 173 individuals (1.5%). This implies that follow-up was complete for 97 percent of the cohort. Vital status was obtained from the community registries and date of retrieving vital status was used as end date of follow-up, if patients were still alive. It was not possible to retrieve all vital statuses at the same date. Therefore, the end-date of follow-up lies between February 2007 and May 2009.

The cohort of thrombosis-free individuals has a mortality that was exactly equal to the general population (SMR 1.0, CI95 0.9-1.2), and there were no differences in mortality within the thrombosis-free cohort, between those who were recruited as partners of thrombosis patients or by random digit dialing.

Cumulative incidences and mortality rates were calculated at 1, 5, and 8 years of follow-up. Survival was estimated and visualized by Kaplan Meier life-tables and survival curves.

Standardized mortality ratios (SMRs) were calculated to estimate relative rates of all cause mortality, e.g. by type of initial thrombosis. The SMR is the ratio of the observed number of deaths over the number of deaths expected when the mortality rate in the cohort of patients, with its specific age and sex distribution, was the same as that in the reference group. SMRs were calculated for the complete cohort of patients and for several subgroups of venous thrombosis patients: 1) for patients with active malignancy at time of inclusion or diagnosed within six months after thrombosis, 2) for patients with a provoked first thrombosis without malignancy, 3) for patients with an idiopathic first thrombosis, and 4) according to type of first venous thrombosis (PE or DVT). An idiopathic thrombosis was defined as a thrombosis not related to surgery, hospital admission, injury, plaster cast, active malignancy, oral contraceptive use, or pregnancy, all in the year previous to the thrombotic event or during

puerperium. SMRs for these categories of patients were calculated with the mortality rates of the complete control group as a reference; and also using only the rates of the controls belonging to the same category (e.g., patients with a provoked event were compare to controls who also had had surgery or plaster cast, etc). This latter analysis was performed to estimate the effect of venous thrombosis on survival conditional on other risk factors for thrombosis.

Hazard ratios of death from all causes per year of follow-up were calculated to estimate the decrease of mortality over time for the different sub-groups. To calculate the hazard ratios per year the hazard of dying in year X was calculated with all persons that survived up to year X. If they survived the whole of year X they were censored at the end of that year.

To calculate the reduction in median life expectancy we used the average life table of the birth cohorts of 1935-1965 of the Dutch population to create a population comparable in life expectancy to the MEGA study. To estimate the median life expectancy for the non-malignant patients we multiplied the death rate per year for the Dutch cohort from the mean age at time of thrombosis by sex. The median life expectancy is the age at which half of a birth cohort of newborns had died. For this calculation we assumed an equal distribution of relative mortality after thrombosis in our population.

The influence of the presence of concurrent disease at the time of thrombosis on mortality was assessed by contrasting the patient cohort with the thrombosis-free cohort by Cox regression in strata of participants with or without concurrent diseases present. In addition, the annual hazard ratios were adjusted for the number of concurrent diseases present at time of thrombosis in the Cox model Concurrent diseases were diabetes, lever disease, kidney disease, heart failure, rheumatoid arthritis, chronic bronchitis, emphysema, myocardial infarction, stroke or hemorrhage of the brain, surgery 3 months prior to thrombosis and multiple sclerosis.

Hazard ratios were adjusted for sex and age. The assumption of proportionality was tested both visually from the Kaplan Meier curve, and statistically, with the proportional hazard test provided by the software package used.

For the analysis of cause-specific mortality SMRs were calculated with the rates from the general population as reference. Analyses were performed using STATA 10.1. (Stata Corporation, College Station, Texas). This study was approved by the Ethics Committee of the Leiden University Medical Center and written informed consent was obtained from all participants.

# Results

### Baseline characteristics

4947 patients with a first venous thrombosis and 6154 controls were followed during a total period of 27 270 and 29729 person-years, respectively. The baseline characteristics of patients and controls are described in table 1. Median duration of follow-up was 5.5 years (range 1

month-9.9 years) for patients and 4.4 years (range 1 month-9.1 years) for controls. 601 (12%) patients died and 135 (2%) controls. Median time between inclusion and death was 1.7 years (range 36 days-9.2 years) for patients and 2.9 years (range 57 days–8.1 years) for controls.

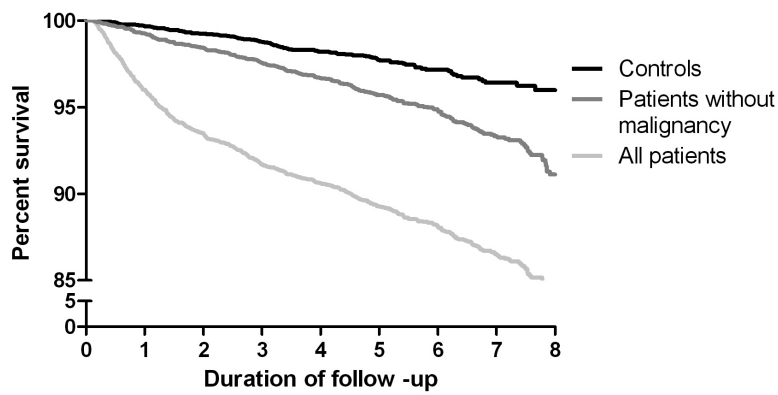
### Overall mortality

The overall mortality rate after thrombosis was 22.0 per 1000 person-years (CI95: 20.3-23.9), and the overall mortality rate for the control subjects was 4.5 per 1000 person-years (CI95 3.8-5.4). The figure shows an increased risk of mortality for all patients compared with controls and for patients without malignancy compared with control subjects up to eight years after the thrombotic event.



### Mortality of patients with malignancy

Patients with venous thrombosis and malignancy had, as expected, the highest risk of mortality. Overall, 55% of the patients' with malignancy and thrombosis died during follow-up, half of whom during the first year after thrombosis (table 2). Patients with malignancy had a 17-fold increased risk of death (SMR 17.5; CI95: 15.8-19.4) compared to the control group. Remarkably, when patients with malignancy and thrombosis were compared with individuals with malignancy without thrombosis they still had a five times higher rate of death (SMR5.8; CI95: 5.2-6.4) (table 3).




| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| N Controls | 6154 | 5954 | 5830 | 5159 | 3553 | 2420 | 1447 | 828 |
| N Controls died | 19 | 27 | 26 | 26 | 14 | 11 | 9 | 3 |
| N Patients | 4947 | 4669 | 4484 | 4296 | 3700 | 2915 | 2136 | 1351 |
| N Patients died | 197 | 121 | 86 | 47 | 49 | 33 | 33 | 35 |
| N Patients without malignancy | 4297 | 4194 | 4098 | 3963 | 3421 | 2704 | 1997 | 1270 |
| N Patients without malignancy died | 32 | 35 | 36 | 33 | 32 | 21 | 27 | 27 |

Figure 1. Kaplan Meier survival curves for patients and controls

**Table 1.** Baseline characteristics of the study population

| | Patients n=4947 % (N) | Controls n=6154 % (N) |
|---|---|---|
| Sex (% men) | 46 % (2271) | 46 % (2854) |
| Mean age at index† (range) | 49 (18-70) | 47 (18-70) |
| Median age at index† (range) | 50 (18-70) | 48 (18-70) |
| Malignancy* | 13 % (619) | 4 % (233) |
| Diabetes | 3.7% (183) | 3.2% (195) |
| Liver disease | 0.5% (27) | 0.3% (20) |
| Kidney disease | 1.2% (59) | 0.4% (23) |
| Myocardial infarction | 2.8% (137) | 1.8% (113) |
| Heart failure | 1.2% (76) | 1.0% (60) |
| Stroke or hemorrhage of the brain | 3.0% (154 ) | 1.8% (115) |
| Chronic bronchitis | 5.1% (253) | 2.7% (165) |
| Emphysema | 1.3% (66) | 0.6% (35) |
| Multiple Sclerosis | 0.5% (30) | 0.3% (17) |
| Rheumatoid arthritis | 3.0% (144) | 2.1% (132) |

*Malignancy at time of or within 6 months after the index date types of cancer have been previously reported (12).
†Index date was date of thrombosis for patients and date of participation in the study for control subjects.

**Table 2** Cumulative incidences of mortality for different subgroups and controls overall, during the 1st year and during the first 5 years of follow-up.

| | | 1 year | | 5 years | | Overall (8 years) | |
|---|---|---|---|---|---|---|---|
| | *N at risk | N§ | Cum Inc (95%CI) † | N§ | Cum Inc (95%CI) † | N§ | Cum Inc (95%CI) † |
| Patients | 4947 | 197 | 4.0% (3.4-4.5) | 500 | 10.1% (9.3-10.9) | 601 | 12.1% (11.6-13.4) |
| Malignancy + | 650 | 165 | 25.4% (22.0-28.7) | 332 | 51.1% (47.2-54.9) | 358 | 55.1% (51.3-58.9) |
| Malignancy - | 4297 | 32 | 0.7% (0.5-1.0) | 168 | 3.9% (3.3-4.5) | 243 | 5.7% (5.0-6.3) |
| Provoked | 2949 | 21 | 0.7% (0.4-1.0) | 94 | 3.2% (2.6-3.8) | 122 | 4.1% (3.4-4.9) |
| Idiopathic | 1348 | 11 | 0.8% (0.3-1.3) | 74 | 5.5% (4.3-6.7) | 121 | 9.0% (7.5-10.5) |
| Controls | 6154 | 19 | 0.3% (0.2-0.4) | 112 | 1.8% (1.5-2.2) | 135 | 2.2% (1.8-2.6) |

*N=number, †Cumulative incidence with 95% confidence interval, § Number of deaths, ו Individuals with malignancy excluded $Idiopathic venous thrombosis were those without malignancy, surgery, hospital admission, injuries, plaster, oral contraceptive use and pregnancy or puerperium.

### Mortality rates for patients without malignancy

Patients with venous thrombosis without malignancy had an overall 2-fold increased risk of mortality compared to the control group (table 3). The risk was comparable for patients with different forms of thrombosis (DVT vs PE) and for patients with a provoked or an idiopathic thrombosis.

**Table 3.** Standardized mortality ratios (SMR)

| | N patients (events) | SMR overall (95% CI)* | SMR specific (95% CI)† |
|---|---|---|---|
| Overall | 4947 (601) | 4.1 (3.8-4.4) | 4.1 (3.8-4.4) |
| Malignancy + | 650 (358) | 17.5 (15.8-19.4) | 5.8 (5.2-6.4) |
| Malignancy - | 4297 (243) | 1.9 (1.7-2.2) | 2.2 (2.0-2.5) |
| DVT# | 2505 (144) | 2.0 (1.7-2.3) | 2.3 (2.0-2.7) |
| PE# | 1257 (72) | 2.0 (1.6-2.5) | 2.3 (1.8-2.8) |
| DVT + PE# | 535 (27) | 1.4 (0.9-2.1) | 1.6 (1.0-2.5) |
| Provoked‡ | 2949 (122) | 2.0 (1.6-2.3) | 2.4 (2.0-2.9) |
| Idiopathic$ | 1348 (121) | 1.9 (1.6-2.3) | 2.1 (1.8-2.5) |

*SMRs are calculated with the non-thrombosis cohort as a reference, †SMRs are calculated with the controls with the same selection criteria as the patients as a reference, ‡ Individuals with malignancy excluded # DVT are patients with a first venous thrombosis of the leg without malignancies, PE are patients with a first pulmonary embolism without a diagnosis of a DVT without malignancies, DVT+PE are patients diagnosed with both PE and DVT without malignancies. $Idiopathic venous thrombosis were those without malignancy, surgery, hospital admission, injuries, plaster, oral contraceptive use and pregnancy or puerperium.



Table 4 shows the hazard ratios year by year during follow-up. The relative risk of death was highest during the first three years, in all groups. Overall, patients with thrombosis had a persistent elevation in the risk of death, except for those with transient provoking factors; in this group the risk became, over time, similar to that of subjects who had provoking factors at baseline but did not suffer thrombosis. In contrast, for those who suffered idiopathic thrombosis, the risk of death remained over two-fold increased up to eight years after the thrombosis.

The reduction of median life expectancy for those without malignancy was five years for men and women. The estimated median life expectancy was 76 for men and 79 for women compared to 81 and 84 years respectively for the Dutch population.

### Comorbidity

Patients with thrombosis and without malignancy have an increased risk of death which could be explained by concurrent other major disorders (table 4). When we stratified our study population for those with and without concurrent disorders we found no difference in risk of death in the stratum of participants with comorbidities (HR 1.4 (1.0-2.0) for patients with venous thrombosis compared to controls). However, for patients without concurrent major disorders at time of thrombosis overall a HR of 2.5 (95CI: 1.9-3.4) was found compared to controls without concurrent disorders and thrombosis. The increased risk of death among patients with venous thrombosis can therefore not fully be explained by the presence of these concurrent disorders.

### Causes of death

The main primary cause of death was malignancy (n=392, 65%) followed by diseases of the circulatory (n=80, 13%) and respiratory (n=34, 6%) system (table 6). Twenty-four patients died of pulmonary embolism (which is classified under circulatory) either as primary cause (n=7) or as a complication (n=17).

**Table 4.** Hazard Ratios per year with the control group as a reference

| | **Year of FU[§]** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **Overall** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Controls** | **HR[‡¶] (CI95)** | **HR (CI95)** | **HR (CI95)** | **HR (CI95)** | **HR (CI95)** | **HR (CI95)** | **HR (CI95)** | **HR (CI95)** | |
| Overall | All[*] | 15.9 (7.8-32.2) | 8.9 (4.5-17.6) | 4.5 (2.5-8.1) | 1.7 (1.0-3.1) | 2.7 (1.4-5.0) | 2.0 (1.0-4.9) | 2.3 (1.1-4.9) | 4.2 (0.5-33.9) | 4.8 (3.8-6.0) |
| Malignancy | All | 105.7 (51.4-217.4) | 51.9 (25.6-105.0) | 26.7 (14.2-50.5) | 3.1 (1.4-6.4) | 11.6 (5.3-25.4) | 6.4 (2.7-15.2) | 4.1 (1.4-12.1) | 3.0 (0.2-51.8) | 25.3 (19.6-32.5) |
| Malignancy | malignancy[†] | 17.6 (4.4-71.0) | 11.6 (2.8-47.1) | 5.3 (1.7-17.2) | 1.8 (0.4-7.9) | 2.3 (0.5-10.2) | - | 0.6 (0.1-2.3) | - | 6.6 (3.9-11.2) |
| Provoked# | All | 4.0 (1.8-9.0) | 3.4 (1.6-7.4) | 1.8 (0.9-3.7) | 1.2 (0.6-2.6) | 2.7 (1.4-5.5) | 1.0 (0.4-2.6) | 1.7 (0.7-4.1) | 3.4 (0.3-36.1) | 2.2 (1.8-2.9) |
| Provoked# | Risk factors | 6.7 (1.6-28.5) | 3.8 (1.1-12.8) | 1.6 (0.6-4.5) | 1.5 (0.5-4.8) | 1.7 (0.7-4.7) | 1.2 (0.3-4.5) | - | 1.8 (0.1-21.4) | 2.6 (1.7-4.1) |
| Idiopathic[$] | All | 2.3 (0.8-6.5) | 2.2 (0.9-5.5) | 2.6 (1.2-5.6) | 1.9 (0.9-4.2) | 1.3 (0.5-3.1) | 1.8 (0.8-4.0) | 2.6 (1.1-6.0) | 4.3 (0.5-37.8) | 2.1 (1.6-2.8) |
| Idiopathic[$] | No risk factors | 2.5 (0.7-8.3) | 2.8 (0.9-8.7) | 4.1 (1.5-11.2) | 1.5 (0.7-3.2) | 1.9 (0.6-5.8) | 1.6 (0.7-4.0) | 2.7 (1.0-6.9) | - | 2.4 (1.7-3.5) |

*All=all controls were taken into account, [†]Selected=controls with the same characteristics as the patient subgroup were taken into account, e.g. selected malignancy are only controls with malignant disease, ‡HR=Hazard Ratio, [§]FU=Follow-up, ‡- Hazard ratio could not be calculated, because there were no events, ¶All Hazard ratios were adjusted for age and sex and number of comorbidities.. #individuals with malignancy excluded, $Idiopathic venous thrombosis were those without malignancy, surgery, hospital admission, injuries, plaster, oral contraceptive use and pregnancy and were not during puerperium.

Cause-specific mortality was compared with data from the general population. Patients had two times higher rates of deaths from diseases of the circulatory system (n=80, SMR 2.2, CI95: 1.8-2.7) and three-times higher death rates of diseases from the respiratory system (n=34, SMR 3.3, CI95: 2.4-4.7) than the general population. Venous thrombosis and malignancy were the causes of death with the highest SMR compared to the general population (table 5). Patients who died of diseases of the respiratory system mainly died of chronic obstructive pulmonary diseases or pneumonia as primary cause of death. Five patients died of either a subarachnoid or intracerebral hemorrhage of whom three were on anticoagulation treatment at time of death.

For patients without malignancy the main causes of death were diseases of the respiratory system and diseases of the circulatory system (SMR 3.4, CI95: 2.3-4.9 and 2.3, CI95: 1.8-2.9, respectively). Compared with the general population they did not have an increased risk of death due to malignancies (table 5).



## Discussion

We studied long term mortality after a first venous thrombosis in 4947 patients followed for a median period of 5.5 years, compared with a thrombosis-free cohort of 6154 individuals. The overall mortality rates were 22.0 per 1000 person-years for all patients. Overall, the death rate in patients was 4.0-fold increased and in those without a malignancy over two-fold increased. In all patients except those with a transient provoking risk factor underlying the initial event, death rates remained elevated up to eight years after the thrombotic event.

Not many studies have studied the long term risk of mortality after venous thrombosis. In a previous study from Norway, the cumulative incidences at one year were much higher than

**Table 5.** Increased mortality per cause of death compared with the Dutch population

| Cause of death (primary) | *N (%) overall | †SMR overall (CI95) | N (%) patients without malignancy | SMR patients without malignancy (95% CI) |
|---|---|---|---|---|
| I00-I99 Diseases of the circulatory system | 80 (13) | 2.2 (1.8-2.7) | 72 (30) | 2.3 (1.8-2.9) |
| I21 Acute myocardial infarction | 26 (4) | 2.6 (1.8-3.8) | 23 (10) | 2.7 (1.8-4.0) |
| I61 Cerebral Hemorrhage | 4 (0.6) | 1.9 (0.7-5.0) | 2 (1) | 1.1 (0.3-4.4) |
| I63 Cerebral infarction | 1 (0.1) | 0.7 (0.1-5.1) | 1 (0.5) | 0.8 (0.1-6.0) |
| I64 Stroke | 2 (0.3) | 0.9 (0.2-3.6) | 2 (1) | 1.1 (0.3-4.3) |
| I26 & I80 Venous thromboembolism | 7 (1) | 3.9 (1.9-8.3) | 7 (3) | 4.2 (2.0-8.8) |
| C00-C99 Neoplasms | 392 (65) | 5.1 (4.7-5.7) | 69 (29) | 1.1 (0.8-1.3) |
| J00-J99 Diseases of the respiratory system | 34 (6) | 3.3 (2.4-4.7) | 29 (12) | 3.4 (2.3-4.9) |
| J44 Chronic obstructive pulmonary disease | 19 (3) | 3.6 (2.3-5.7) | 16 (7) | 3.6 (2.2-5.9) |
| J18 Pneumonia | 5 (0.8) | 2.0 (0.8-4.7) | 5 (2) | 2.3 (1.0-5.6) |

*N=number
†SMR=Standardized mortality Ratio

those we found. In the Norwegian study a cumulative incidence at one year of 14.5% was found for cases with an idiopathic venous thrombosis, of 9.7% for provoked cases, and of 63.4% for cancer patients, while we found cumulative incidences of 0.8%, 0.7% and 25.4% respectively[3]. These differences result from the inclusion of inpatients in the Norwegian study, thereby also counting early deaths, and the inclusion of patients of all ages, while our study was restricted to patients younger than 70 at the time of the first event. This implies that overall mortality in patients with venous thrombosis is even higher than we report. Because of our extended follow-up for up to eight years after the thrombotic event, our most important observation is that increased mortality for thrombosis patients persists for a prolonged time. Furthermore, we showed that, when only the long term survival is taken into account, there is no longer a difference in survival for patients with a DVT and PE. This indicates that the highly increased risk of death for those with pulmonary embolism is mainly present during the first month after venous thrombosis. Recently, an Austrian study did not find an increased risk of long-term mortality for patients with venous thrombosis[134]. However, they included patients at a median time of 14 months after thrombosis up to 6 years after the thrombotic event. Due to this delayed inclusion only long-term survivors of thrombosis were included in the Austrian study and therefore no increase in mortality was found.

We confirmed previous observations that patients with malignancy and venous thrombosis have a very poor prognosis, substantially worse than patients with cancer without thrombosis, with a 5.8-fold difference in our study[135,136]. Although death from recurrent thrombosis was clearly elevated after a first thrombotic event, most patients died of other causes, mainly of the circulatory system. While one is tempted to explain this by pre-existing comorbid conditions, death rates were also persistently elevated after idiopathic thrombosis and in those without any major illnesses.

Main causes of death, apart from malignancies, were diseases of the circulatory and respiratory system. These results are in line with previous studies which described associations between risk factors for venous and arterial thrombosis as well as an increased risk of arterial thrombosis for those who experienced venous thrombosis[137–139]. Alternatively, misclassification of cause of death may explain (part of) the results, especially when no further research into the cause of death was performed, although one would expect this to affect the results in the opposite direction (patients with previous pulmonary embolism may be more readily misclassified as having died of pulmonary embolism than of other lung diseases than those without a history of pulmonary embolism).

Our study may have suffered from some limitations: as discussed above causes of death were not objectively verified. However misclassification by the physician determining the cause of death is most likely to have been equal in this population and in the general population, which would have led to an underestimation of the risks we have found. Furthermore, we only recruited patients after discharge from hospital, and therefore overall mortality is

underestimated. Moreover, our results cannot be extrapolated to patients older than 70 years at the time of thrombosis, or to children.

Among the major strengths of this study are the large size of the cohort, and the long follow-up period. Mortality data was retrieved from the national registry where 98.5% of participants were found. Therefore, loss to follow-up was minimal and dates of death were accurate. This was the first study that calculated mortality rates compared with the general population and compared to specific control groups. Therefore, we were able to define overall risks of death up to eight years after thrombosis as well as the risk for several subgroups. Our results underline the major consequences of venous thrombosis, not only with regard to morbidity but also to mortality.

# 6

# Chronic obstructive pulmonary disease and pulmonary embolism

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## Summary

Previous studies have suggested an increased risk of pulmonary embolism in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) but not of deep venous thrombosis. The aim of this study was to assess the risk of deep venous thrombosis and pulmonary embolism conferred by COPD in a large case-control study on risk factors for venous thrombosis (MEGA study). 3897 patients with venous thrombosis and 5752 controls were included. The presence of COPD before the thrombotic event or index date was assessed by questionnaires. Participants were classified as having COPD when they reported to have chronic bronchitis or emphysema and were using medication for these disorders. COPD was reported by 186 patients (4.8%) and 132 controls (2.2%). COPD was associated with a 3.2-fold (CI95 2.4-4.2) and a 1.6-fold (CI95 1.2-2.1) increase in risk of pulmonary embolism and deep venous thrombosis respectively. For pulmonary embolism relative risks increased with severity of COPD to an odds ratio of 4.6 (CI95 4.1-5.1) but for deep venous thrombosis they increased only minimally. We postulate 5 possible explanations for the differentially increased risk found for pulmonary embolism and deep venous thrombosis. In conclusion, COPD is a moderately strong risk factor for pulmonary embolism while the risk of deep venous thrombosis is only slightly increased.

# Introduction

In the 1960s, the first reports on an association between chronic obstructive pulmonary disease (COPD) and pulmonary embolism were published[1,2]. Since then, two case series reported a prevalence of around 20% for a history of pulmonary embolism (PE) among patients with COPD, which is much higher than the prevalence of a history of pulmonary embolism in the general population (incidence 0.4 per 1000 per year)[3,4]. More recently, Schneider et al. reported from the UK General Practitioners Research Database (GPRD) a 2.5-fold increased risk of pulmonary embolism in patients with mild COPD and a 7.5-fold increased risk for patients with severe COPD compared with patients without COPD[5]. Results for venous thrombosis of the leg were inconclusive with relative risks of 1.37 for mild COPD and 0.79 for severe COPD. These results concerned a relatively small nested case-control study in a cohort of COPD and non-COPD patients with 136 patients with PE and 210 with DVT. Schneider et al argued that the difference in relative risks for DVT and PE was possibly due to misclassification of PE in COPD patients in the absence of a true association.

In the MEGA study we previously reported increased mortality (3.7-fold) due to COPD in patients with venous thrombosis compared with the general population[6]. In another report from the same study investigating risk factors for venous thrombosis, an 8-fold increase in risk of pulmonary embolism was found for individuals with recent pneumonia while the risk of DVT was only 3-fold increased compared with individuals without pneumonia[7,8]. These data indicate an association between inflammatory lung diseases and venous thrombosis, and, moreover, an association that is mainly if not exclusively present for PE and not for DVT.

We studied the association between COPD and venous thrombosis of the leg and pulmonary embolism separately in a large case-control study. Furthermore we postulate and critically examine several non-causal explanations for the higher risk of pulmonary embolism than of deep venous thrombosis of the leg associated with COPD, such as misclassification, confounding, bias, or differences in baseline risks of pulmonary embolism and deep venous thrombosis of the leg.

# Methods

### Ethics statement

This study was approved by the Ethics Committee of the Leiden University Medical Center and written informed consent was obtained from all the participants. The investigation has been conducted according to the principles expressed in the Declaration of Helsinki.

### Study population

The MEGA study is a large population based case-control study into risk factors for venous thrombosis, which included 4956 patients with a first venous thrombosis of the leg, pulmonary embolism or both, from six anticoagulation clinics in the Netherlands

between March 1999 and September 2004. These clinics exclusively monitor outpatient treatment with vitamin K antagonists in a well-defined geographical region. In total 6297 controls were included, of whom 3000 via random digit dialing and 3297 partners of the cases. All patients and controls filled in a detailed questionnaire on risk factors for venous thrombosis[9,10]. The questions also concerned comorbidities, among which emphysema and chronic bronchitis; and a list of current medications. For this study, COPD was defined as self-reported emphysema or chronic bronchitis in combination with medication use for COPD, which was defined as all medication registered for the indication COPD in the Netherlands[11]. Only patients with either a diagnosis of deep venous thrombosis of the leg without pulmonary embolism or pulmonary embolism without concurrent DVT, confirmed with discharge letters were included for all analysis, patients with both PE and DVT were only included in the analysis of COPD as risk factor for DVT and or PE. Participants were excluded if the questions about COPD were not filled in. In total 447 patients were excluded because they had a combined diagnosis of DVT and PE, and 630 patients and 548 controls were excluded because of missing data on either medication use or the presence of chronic bronchitis or emphysema. Therefore 4281 patients and 5752 controls were included in the analysis (figure 1). While chronic bronchitis and emphysema are both classified as COPD, emphysema is generally considered as the more severe condition. The risk of chronic bronchitis and emphysema was therefore also analyzed separately. Odds ratios and 95% confidence intervals were calculated for cases with DVT versus controls and for cases with PE versus controls.



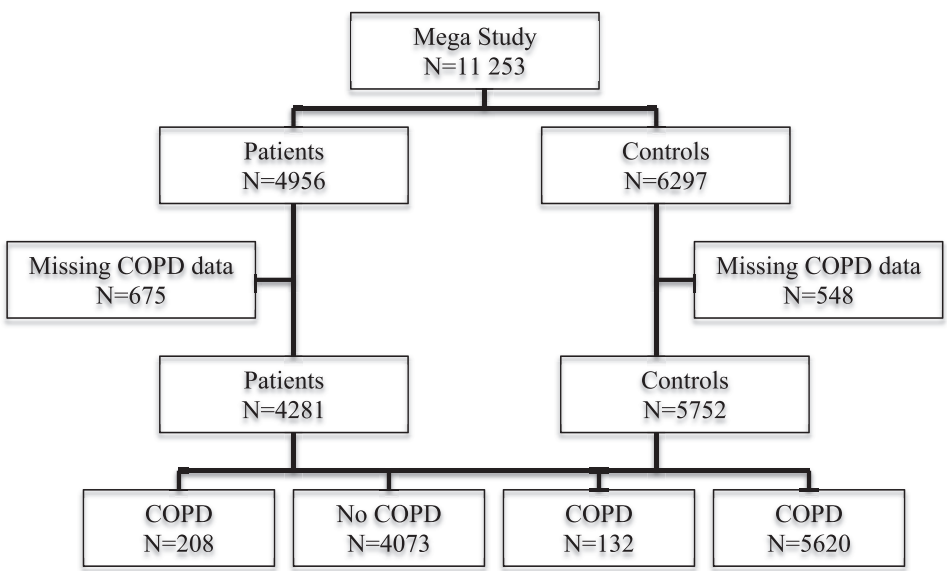


**Figure 1.** Flowchart of the study population

As sensitivity analysis we double-checked the self reported cases of COPD with the Dutch hospital admission database. In this database all diagnoses of hospital admissions are registered. We linked our patients in two ways; we linked those found by the questionnaires to those in the registry and checked how many patients from the MEGA study have been admitted for the diagnosis COPD independent of self-reported COPD. For both ways we calculated the OR overall and for DVT and PE separately.

**Explanations**

We postulate five different explanations for a differential effect on risk of deep venous thrombosis of the leg and pulmonary embolism by COPD. These explanations include differences due to the scale used to measure the effect, misclassification of either the outcome or exposure, confounding and a further exploration of the causal pathway, which could be through the use of corticosteroids. All explanations were tested using available information from questionnaires and discharge letters.

Putative explanations considered for a differential effect of COPD on PE and DVT:

1. A difference in relative risk is not necessarily a difference in absolute risk
2. Misclassification of diagnosis of COPD as PE
3. Diagnostic suspicion bias
4. Confounding by smoking
5. Medication use (i.e., corticosteroids)

Explanation 1 is related to the difference in the overall risk for pulmonary embolism and deep venous thrombosis of the leg. Previous studies showed that the incidence of PE is about half that of DVT[12,13]. The absolute risk (incidence) of venous thrombosis in the presence of a risk factor is a function of the incidence in the population without the risk factor and the extra risk caused by the risk factor we are interested in (incidence rate difference). The incidence for patients without the risk factor is similar to the reported overall incidence when the prevalence of the risk factor studied is low, which is the case for COPD.

One may argue that there is truly a different effect of a risk factor on two diseases, when it causes more cases of one disease than the other, i.e., if the incidence rate difference in the absence and presence of the risk factor for one disease is greater than for the other. This is graphically displayed in figure 2.

To determine whether the differences found were not due to differences in baseline risk for PE and DVT, the absolute increase in risk in the presence of COPD should be estimated. This was not directly possible in our own study due to the case-control design. Therefore, we used population incidence rates reported by Naess et al[13]. The characteristics of this study population from Norway are similar to those of the participants of the MEGA study and therefore we expect these baseline incidences to be similar to the baseline incidences in our study population in The Netherlands.

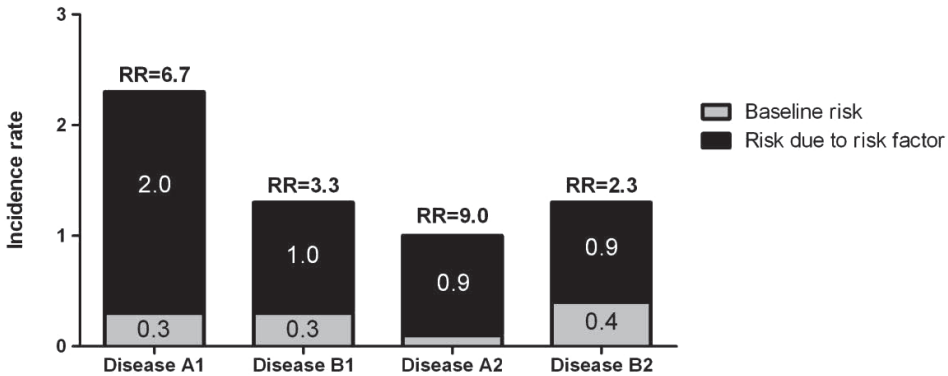


**Figure 2.** Explanation 1: Differences in baseline and additional risks. Difference in RR for two different diseases can be explained by a different effect of a risk factor on the two different diseases (diseases A1 and B1) or by a difference in baseline risk (diseases A2 and B2). Due to the low baseline risk of disease A2, the relative risk is much higher for A2 than the relative risk for disease B2, although the additional risk due to the risk factor of interest is the same for both diseases.



Explanation 2 is about misclassification of the diagnoses of COPD and PE. In this scenario COPD exacerbations are misclassified as PE. This kind of misclassification will not be present for patients with COPD and DVT as the clinical symptoms are obviously different. Whether the diagnoses of COPD and PE can be confused depends mainly on the diagnostic technique used. Diagnosis by CT-scan will not confuse COPD and PE, while diagnosis by VQ-scanning or perfusion-scan may do so[14,15]. We tried to estimate in two ways to what extent COPD exacerbations could have been misclassified as pulmonary embolism. First, we checked the methods of diagnoses for PE and stratified the analysis for method of diagnosis. Secondly, we used an indirect method. From patients who were initially included in the MEGA study with a pulmonary embolism but were later excluded because pulmonary embolism was not objectively proven, discharge letters and questionnaires were checked for the prevalence of COPD in these patients. If diagnoses were done correctly, one would expect a higher prevalence of COPD and other pulmonary diseases among patients who were initially suspected of PE in whom PE was subsequently ruled out than in those with PE. If the incidence of other pulmonary diseases was lower in the excluded patients, this might indicate that misclassification had been present.

Explanation 3 concerns overlap of the diagnoses due to diagnostic suspicion bias. PE patients may also have an asymptomatic DVT and vice versa. When patients are diagnosed with a pulmonary embolism, an ultrasound to exclude the presence of a DVT is usually not made; vice versa, in cases with DVT without symptoms of PE, the presence of PE is generally not examined. This could lead to bias when patients with COPD and DVT are more often checked for PE than patients with COPD and PE for DVT. While we excluded patients who were diagnosed with both PE and DVT, we checked discharge letters to find out how

often additional diagnostics were performed in patients with a diagnoses of only DVT or PE and whether this differed among patients with deep venous thrombosis of the leg and pulmonary embolism and among patients with and without COPD. Discharge letters from all patients with venous thrombosis and COPD were checked for additional diagnostics for either PE or DVT as well as discharge letters from a random sample of one hundred patients without COPD with pulmonary embolism and one hundred patients without COPD with deep venous thrombosis of the leg.

Explanation 4 concerns possible confounding by smoking. Smoking status could be a confounder of the relation between COPD and the occurrence of PE or DVT, as smoking is a risk factor for both COPD and venous thrombosis[16,17]. To test whether the effect found could be explained by smoking we included smoking with COPD in two logistic models, one with DVT and one with PE as endpoint. Smoking was categorized in three groups, never, current and previous smokers. Previous smokers were defined as ever smokers who stopped smoking one year before they filled in the questionnaire. This to avoid too include participants that stopped smoking between their thrombotic event and filling in the questionnaire. Furthermore, to examine whether the presence of both COPD and smoking could lead to synergy we also stratified patients and controls in 6 groups: current, previous, and non-smokers, with or without COPD, and studied the relative risk of DVT or PE in these groups.

Explanation 5 involves the usage of corticosteroids and in contrast to the explanations above is an explanatory mechanism for a causal association. Corticosteroids are used as treatment for COPD and are associated with an increased risk of venous thrombosis[18]. Therefore, a higher risk of pulmonary embolism than DVT may be explained by the use of such medication, if this would specifically affect risk of PE. Therefore, odds ratios were calculated stratified on corticosteroid usage. Information on corticosteroid use was also obtained from the medication list in the questionnaire.

# Results

### Effect of COPD on the risk of DVT and PE

In total, 543 participants reported suffering from chronic bronchitis or emphysema before the thrombosis. Of these 543 participants, 340 were using medication for their disease. In total, 208 cases and 132 controls reported having COPD before thrombosis or inclusion and used medication for it. Thirty-eight percent of COPD patients used fluticasone, 30% used salbutamol, 19% salmeterol, and 13% used several other medications. Of the subjects with COPD, 156 patients and 104 controls reported chronic bronchitis and 52 patients and 28 controls emphysema. Patients with COPD had a 1.6-fold increased risk of DVT compared with patients without COPD (odds ratio (OR): 1.6; 95%CI, 1.2-2.1), while they had a 3.2-fold increased risk of PE compared with patients without COPD (OR: 3.2; 95%CI, 2.4-4.2). This risk increased with severity of COPD, i.e. patients with emphysema had a higher risk of

PE (OR: 4.6, CI95 4.1-4.5) than patients with chronic bronchitis (OR: 2.6, CI95 2.3-2.9). This effect was not seen in patients with DVT (chronic bronchitis OR: 1.5, CI95 1.2-1.8, emphysema OR: 1.4 CI95 0.8-2.0) (table 2). Patients with COPD had a variable risk of PE and DVT. There was no consistent trend seen overall and for chronic bronchitis and emphysema separately compared to those with only DVT or PE (table 2). When we linked these patients to the Dutch hospital admission database we found 32 cases and 14 controls that were admitted for COPD. With those cases we found an OR of 2.7 (CI95 1.5-5.1) for venous thrombosis. When we stratified the results for cases of DVT and PE we found an OR of 1.7 (CI95 0.8-3.7) and 4.1 (CI95 2.0-8.6) respectively. When we double-checked and looked at all the cases of COPD found in the admission database those found and not found by means of our questionnaires we found 74 patients and 29 controls with COPD. With these cases an overall OR of 3.1 (CI95 2.0-4.7). For DVT and PE we found an OR of 1.7 (CI951.0-2.9) and an OR 5.1 (CI95 3.2-8.4) respectively.



**Explanation 1: Different baseline risk of PE and DVT**

Population rates are 0.3 per 1000 person-years for PE and 0.5 per 1000 person-years for deep venous thrombosis of the leg[13]. With the odds ratios we found this implies that the incidence of DVT among COPD patients is 0.8 per 1000 person-years and the incidence or PE among COPD patients 1.0 per 1000 (0.5*1.6=0.8 and 0.3*3.2=1.0). Therefore there is a larger increase in the incidence of PE than of DVT due to COPD (incidence rate difference 0.7 per 1000 person-years for PE (1.0-0.3) and 0.3 per 1000 person-years for DVT (0.8-0.5)). When COPD was stratified according to severity (chronic bronchitis versus emphysema) the incidence rate of pulmonary embolism (and accordingly, the incidence rate difference) clearly increased with severity (0.8 for chronic bronchitis versus 1.4 for emphysema per 1000 person-years) while the incidence rate of DVT did not (0.8 versus 0.7 per 1000 person-years, respectively) (table 2). Therefore, both on an absolute and a relative scale COPD increases the risk of PE more than that of DVT.

**Table 1.** Baseline characteristics of patients and controls

| Variable | Patients | Controls |
|---|---|---|
| N | 4281 | 5752 |
| Sex (% men) | 45.9% | 46.3% |
| Age (mean) | 48.9 | 47.2 |
| BMI (kg/m2) (mean) | 27.8 | 26.7 |
| Smoking | 59.6% | 56.1% |
| Malignancies | 13.3% | 4.7% |
| Factor V Leiden | 13.7% | 4.0% |
| DVT (N) | 2467 | - |
| PE (N) | 1412 | - |
| PE+DVT (N) | 402 | - |

**Table 2.** Odds ratios, incidence rates and incidence rate differences for risk of DVT and PE in patients with COPD

| Diagnosis | COPD yes/no | N cases | N controls | OR (CI95) | Incidence rate* | Incidence rate difference |
|---|---|---|---|---|---|---|
| DVT | Yes | 88 | 132 | 1.6 (1.2-2.1) | 0.8 per 1000 | |
| | No | 2379 | 5620 | 1 (ref) | 0.5 per 1000 | 0.3 per 1000 |
| PE | Yes | 98 | 132 | 3.2 (2.4-4.2) | 1.0 per 1000 | |
| | No | 1314 | 5620 | 1 (ref) | 0.3 per 1000 | 0.7 per 1000 |
| PE+DVT | Yes | 22 | 132 | 2.5 (1.6-3.9) | 1.3 per 1000 | |
| | No | 380 | 5620 | 1 (ref) | 0.5 per 1000 | 0.8 per 1000 |
| | **Chronic bronchitis yes/no** | | | | | |
| DVT | Yes | 70 | 104 | 1.5 (1.2-1.8) | 0.8 per 1000 | |
| | No | 2379 | 6168 | 1 (ref) | 0.5 per 1000 | 0.3 per 1000 |
| PE | Yes | 66 | 104 | 2.6 (2.3-2.9) | 0.8 per 1000 | |
| | No | 1524 | 6168 | 1 (ref) | 0.3 per 1000 | 0.5 per 1000 |
| PE+DVT | Yes | 20 | 104 | 3.1 (1.9-5.1) | 1.5 per 1000 | |
| | No | 380 | 6168 | 1 (ref) | 0,5 per 1000 | 1.0 per 1000 |
| | **Emphysema yes/no** | | | | | |
| DVT | Yes | 18 | 28 | 1.4 (0.8-2.0) | 0.7 per 1000 | |
| | No | 2379 | 6168 | 1 (ref) | 0.5 per 1000 | 0.2 per 1000 |
| PE | Yes | 32 | 28 | 4.6 (4.1-5.1) | 1.4 per 1000 | |
| | No | 1524 | 6168 | 1 (ref) | 0.3 per 1000 | 1.1 per 1000 |
| PE+DVT | Yes | 2 | 28 | 1.2 (0.3-4.9) | 0.6 per 1000 | |
| | No | 380 | 6168 | 1 (ref) | 0.5 per 1000 | 0.3 per 1000 |

*incidence rates are per 1000 person-years
OR=Odds Ratio, ref=reference, CI95=95% confidence interval, DVT=Deep vein thrombosis, PE=pulmonary embolism, COPD=chronic obstructive pulmonary disease.



### Explanation 2: Misclassification

One third of all patients with COPD and PE had been diagnosed by CT-scan (33 of 98), a method that cannot lead to confusion of PE and COPD diagnoses. When including only patients with PE who were diagnosed by CT scan, the risk of PE in individuals with COPD was 3-fold increased compared with individuals without COPD (OR: 3.0; 95%CI 2.0-4.4). Similarly, when including only patients with PE who were diagnosed by VQ-scan, the risk of PE in individuals with COPD was 3.3-fold increased compared with individuals without COPD (OR: 3.3; 95%CI 2.4-4.4). Furthermore, a total of 39 patients were initially included in the MEGA study but subsequently excluded because PE was not objectively confirmed. Of these patients 13% had COPD compared with 6% among the patients with pulmonary embolism in our study. These figures demonstrate that misclassification due to diagnosing COPD exacerbations, as PE does not explain the increased risk of PE in COPD patients.

### Explanation 3: Diagnostic suspicion bias

Table 3 shows the proportions of subjects in whom diagnostic procedures for both DVT and PE were performed for those with and without COPD and pulmonary embolism and venous thrombosis of the leg separately. These proportions are about the same in all groups. This shows that there is not an excess of PE diagnosed in COPD patients due to more intense diagnostic work-up. In addition, for most patients with pulmonary embolism discharge letters reported that no symptoms were observed of the leg and vice versa.

### Explanation 4: Confounding by smoking

When we adjusted for smoking the ORs for both DVT and PE did not change, indicating that the relation found was not confounded by smoking (table 3). When we looked into synergistic effects between COPD and smoking we did not observe any for patients with DVT but the effects of smoking and COPD seemed to add up for PE (table 4).



### Explanation 5: Medication

Table 5 shows the stratified analysis for corticosteroids. In both strata the effect of COPD is more pronounced for PE than DVT. In COPD patients who did not use steroid drugs the risk of PE was 2.9-fold increased (95% CI, 2.1-3.9) compared with those without COPD, which is similar to the overall effect. This implies that the differential effect of COPD on PE cannot be explained by steroid use.

**Table 3.** Explanation 3: Additional diagnostics performed in the several groups

| Diagnosis | Additional diagnostics PE/DVT |
|---|---|
| DVT – COPD | 14% (n=388) |
| DVT + COPD | 11% (n=10) |
| PE – COPD | 17% (n=238) |
| PE + COPD | 13% (n=12) |

DVT=deep vein thrombosis, PE=pulmonary embolism, COPD=Chronic obstructive pulmonary disease

**Table 4.** Explanation 4: confounding by smoking

| Risk factors | DVT (OR (CI95)) | DVT (ORadj* (CI95)) | PE (OR (CI95)) | PE (ORadj* (CI95)) |
|---|---|---|---|---|
| COPD | 1.6 (1.2-2.10 | 1.5 (1.2-2.0) | 3.2 (2.4-4.1) | 3.2 (2.4-4.2) |
| Smoking | | | | |
| Current smoker | 1.1 (1.0-1.3) | 1.1 (1.0-1.3) | 0.8 (0.7-0.9) | 0.8 (0.7-0.9) |
| Previous smoker | 1.4 (1.2-1.5) | 1.4 (1.2-1.5) | 1.8 (1.6-2.0) | 1.8 (1.6-2.0) |

*Adjusted for smoking or COPD respectively.
OR=Odds Ratio, CI95=95% confidence interval, ORadj=Adjusted Odds ratio, DVT=deep vein thrombosis, PE=pulmonary embolism, COPD=chronic obstructive pulmonary disease.

**Table 5.** Odds ratios for DVT and PE for different combinations of COPD and smoking

| COPD | Smoking | DVT (OR (CI95)) | PE (OR (CI95) |
|---|---|---|---|
| No | No | 1 (ref) | 1 (ref) |
| Yes | No | 2.0 (1.3-3.2) | 2.8 (1.6-4.8) |
| No | Current | 1.1 (1.0-1.3) | 0.8 (0.7-0.9) |
| Yes | Current | 1.5 (0.9-2.4) | 3.3 (2.1-5.2) |
| No | Previous | 1.4 (1.2-1.6) | 1.8 (1.6-2.1) |
| Yes | Previous | 1.9 (1.2-3.0) | 5.0 (3.3-7.5) |

OR=Odds ratio, CI95=95% confidence interval, ref=reference category, DVT=deep vein thrombosis, PE pulmonary embolism, COPD=chronic obstructive pulmonary disease

**Table 6.** Explanation 5: Stratification corticosteroids

| | Overall (OR(CI95)) | Corticosteroids + (OR(CI95)) | Corticosteroids – (OR(CI95)) |
|---|---|---|---|
| DVT | 1.6 (1.2-2.1) | 1.5 (0.9-2.6) | 1.6 (1.2-2.2) |
| PE | 3.2 (2.4-4.2) | 4.2 (2.6-6.7) | 2.9 (2.1-3.9) |

OR=Odds ratio, CI95=95% confidence interval, DVT=deep vein thrombosis, PE=pulmonary embolism



# Discussion

In this large study we found a threefold increased risk of PE in patients with COPD, which was clearly higher than the effect on DVT. Patients with COPD had a 3.2-fold (95% CI, 2.4-4.2) increased risk of pulmonary embolism compared with those without COPD while the risk of deep venous thrombosis of the leg was only 1.6-fold (95% CI, 1.2-2.1) increased. The differential effect was stronger when severity of the COPD was taken into account. None of five possible explanations for the difference we proposed were likely to account for the difference. The difference was present both on an absolute and relative scale. The absolute risk of PE increased with severity of COPD while the incidence of DVT did not (explanation 1). Neither could it be explained by misclassification of either the exposure or outcome as there were no differences in risks found for those diagnosed with VQ-scanning and CT (explanation 2) or to differences in additional diagnostics between those with and without COPD (explanation 3). The difference was not caused by smoking habits (explanation 4). Lastly, a causal explanation through differences in medication use could be rejected because there were no differences in the risks found for those using and not using corticosteroids (explanation 5).

The results that we describe are similar to the results of Schneider et al[5], although more pronounced. Schneider et al. found a 2.2-fold increased risk of pulmonary embolism and a 1.4-fold increased risk of deep venous thrombosis of the leg in individuals with COPD compared with individuals without COPD. Schneider et al. split their results for mild, moderate and severe COPD. They also saw an increase in the risk of PE with severity of COPD, up to a 7-fold increase in risk of PE in severe COPD patients compared with individuals without COPD.

Some limitations should be mentioned. Firstly, all our data have been collected by questionnaires and discharge letters. Therefore, we may have missed some diagnoses of COPD or included cases of chronic asthma that were diagnosed as COPD. However, it is likely that this misclassification would be the same in patients with DVT and PE. Therefore we performed a sensitivity analysis with the Dutch hospital admission database. Although most patients with COPD are not admitted for this indication and those found are therefore the most serious cases of COPD we still found comparable ORs overall and DVT and PE separately compared to our self-reported data. Furthermore, we did not have data on long function. Therefore, the diagnosis emphysema may not have been more severe than chronic bronchitis in all patients. Thirdly, explanations 2 and 3 cannot be fully excluded in this study due to lack of information, as not all information is always mentioned in the discharge letters. However, also in this case it is unlikely that this is different for patients with DVT or PE. When we studied the risk of DVT and PE in patients with COPD there was no clear trend toward either those with only DVT or PE, which could indicate a possible mechanism between COPD and venous thrombosis. However there were only 22 cases with COPD and both PE and DVT. It is therefore difficult to draw conclusions from this group.

When we dismiss the alternative explanations for our findings, we may speculate on other, more causal explanations. Possibly, COPD plays a role in a local development of pulmonary thrombi rather than that they invariably arise from embolization from the leg. A similar differential risk between pulmonary embolism and DVT has been shown in patients with other pulmonary inflammatory diseases such as pneumonia and chronic asthma[7,8,19] These consistent results of associations between pulmonary inflammatory diseases and pulmonary thrombi make a local development of these thrombi a possibility worth considering. In asthma patients, due to the chronic inflammation in the lungs, the production of fibrin in the lungs is up-regulated and levels of protein C are downregulated[8,20]. This may lead to a local prothrombotic state. These shifts in fibrin production and protein C levels initiated by local inflammation in the lungs due to asthma could also play a role in patients with chronic bronchitis, emphysema and pneumonia. The role of smoking should also be considered in the causal mechanism, as smoking has been described as a mild risk factor for venous thrombosis as well[16,17]. However, the effect estimated for both COPD and smoking did not change in the multivariate model. This indicates that smoking is not a confounder in the relation between COPD and DVT or PE. It also indicates that COPD is not on the causal pathway between smoking and DVT or PE, i.e. that the presence of this condition does not explain the relation that has been described between smoking and risk of VT.

In conclusion, we found a threefold increased risk of pulmonary embolism for patients with COPD, which was substantially higher than that of deep venous thrombosis of the leg. This was strongest for those with severe COPD who had a 4.6-fold increased risk. This finding may be a result of locally arising pulmonary thrombi due to damage and inflammation in the lungs.

# 7

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

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## Summary

The reported incidence of recurrent venous thrombosis (VT) varies widely between 12-30% within 5 years after the first event. The risk profile for recurrence is different from that for a first event, for example with respect to the influence of age and sex. The aim of this study was to estimate the incidence of a recurrent event, its location as well as the effect of age and sex in a large cohort of patients with a first VT. We followed 4731 patients who were diagnosed with a first VT between 1999 and 2004 (MEGA study) until 2008-2009. Recurrences were adjudicated from self-reported information in questionnaires, from anticoagulation clinics and discharge letters. We designed a decision rule to define for each patient if they had a recurrence according to the available information. We calculated incidence rates of recurrence and hazard ratios (HR) to estimate the effect of various factors on a recurrent event. 673 out of 4731 patients had a recurrent event. 219 additional patients in whom the diagnosis was uncertain were censored at the time of possible recurrence. 4731 patients were followed during a period of 24 124 person-years (py) (mean 5 years). The overall incidence of recurrence was 27.9 per 1000py (95%CI 25.8-30.0). The cumulative incidence at 5 years was 11.3%. Men had a 2.2-fold (95% CI 1.9-2.6) higher risk of a recurrent event than women. Age was not associated with an increased risk of recurrence (HR 1.0, 95%CI 1.0-1.0 per year increase in age). Patients with anticoagulation treatment for less than 3 months were at higher risk of recurrence than patients with treatment for more than 3 months. Patients with pulmonary embolism (PE) were more likely to have a PE as recurrent event than patients with DVT (HR 1.9 95%CI 1.4-2.8) and patients with thrombosis of the leg (DVT) were more likely to have a DVT as recurrent event (HR 1.5 95%CI 1.1-1.9) than patients with PE. In conclusion, this large study provides precise estimates of recurrence risk, which is substantial at about 3% per year, but less than found in some other studies. Men are more likely to have a recurrent event and age has no effect. The manifestation (PE or DVT) of recurrence is often the same as that of the first event.

# Introduction

Venous thrombosis is a multicausal disease that occurs in 1-3 per 1000 persons per year[2,3]. It is associated with substantial mortality and morbidity including recurrence. The cumulative incidence of recurrent venous thrombosis is much higher than that of a first event and varies between studies from 4-11% within the first year to 12-30% in the five years after the first event[21,33,36,38,155]. Incidence rates of recurrence also vary between studies, from 25 to 46 per 1000 person-years[36,38]. Sources of this variation include definition of recurrence, setting and size of the study (clinical setting versus research setting) and starting point of follow-up.

In contrast to a first event, only a few risk factors are known to be associated with risk of recurrent thrombosis, such as male sex, the presence of a malignancy, and an idiopathic first venous event[21,36,38,156–162]. Age, which is the strongest risk factor for a first venous thrombosis does not, or only slightly, increase the risk of a recurrent event[36,157–161]. However, the separate effects of age, male sex and an idiopathic first venous thrombosis are not well established, mainly as a result of small sample sizes of the studies reported so far, different cut off points for age and different definitions for idiopathic venous thrombosis.

The best way to prevent recurrence is by anticoagulant treatment. However, this has the obvious drawback of a major bleeding risk, which is not outweighed by the prevention of thrombosis. Therefore, duration of anticoagulant treatment is limited, and the optimal duration is not well known, despite several trials into this issue[22,26,30,127].

A recent study showed that recurrent events do not occur at random sites[163]. To be able to predict the location of recurrence may influence the duration of treatment especially when a recurrent pulmonary embolism is more likely than a deep venous thrombosis of the leg.

To address all the issues mentioned above, we performed a large follow-up study of almost 5000 patients with a first venous thrombosis. In this study we estimated the risk of recurrence, the separate associations of age, sex and an idiopathic first thrombosis with the risk of a recurrent event, the effect of different durations of anticoagulation and the relation between site of first and recurrent events.

# Methods

### Study population

Patients were included from the MEGA study[7,14], a large population based case-control study into risk factors for a first venous thrombosis, which included consecutive patients at six anticoagulation clinics in the Netherlands between March 1999 and September 2004. In total 5182 cases and 6297 controls were included in the MEGA case-control study. From these cases, patients with a deep venous thrombosis of the leg, pulmonary embolism or both were included and patients with a venous thrombosis of the upper extremity were

excluded from follow-up. A total of 4956 cases were eligible for the follow-up study. Of these cases 225 indicated that they did not want to participate in a follow-up study and were therefore excluded (figure 1) leaving 4731 patients for the follow-up study. This study was approved by the Medial Ethics Committee of the Leiden University Medical Center and all participants gave written informed consent.

Information about recurrences was retrieved in two ways, i.e., from the patients themselves via a short questionnaire and from the anticoagulation clinics, which monitor all outpatients' anticoagulant treatment with vitamin K antagonists. The short questionnaire consisted of two main questions: 1) "Did you have a recurrent event?" and 2) "In which hospital or by which doctor was it diagnosed?". Questionnaires were sent by mail between June 2008 and July 2009. When questionnaires were not returned, the questions were asked by telephone interview. During the same period information on possible recurrences of all patients was obtained from the anticoagulation clinic where they were initially included for their first event and, in case they moved house, at the clinic near their new address. Information on the duration of anticoagulant treatment was also obtained from the anticoagulation clinics.

For all potential recurrences found by the questionnaire, anticoagulation clinic or both, discharge letters were requested from the clinician who diagnosed the recurrence according to the patient and/or the clinic.

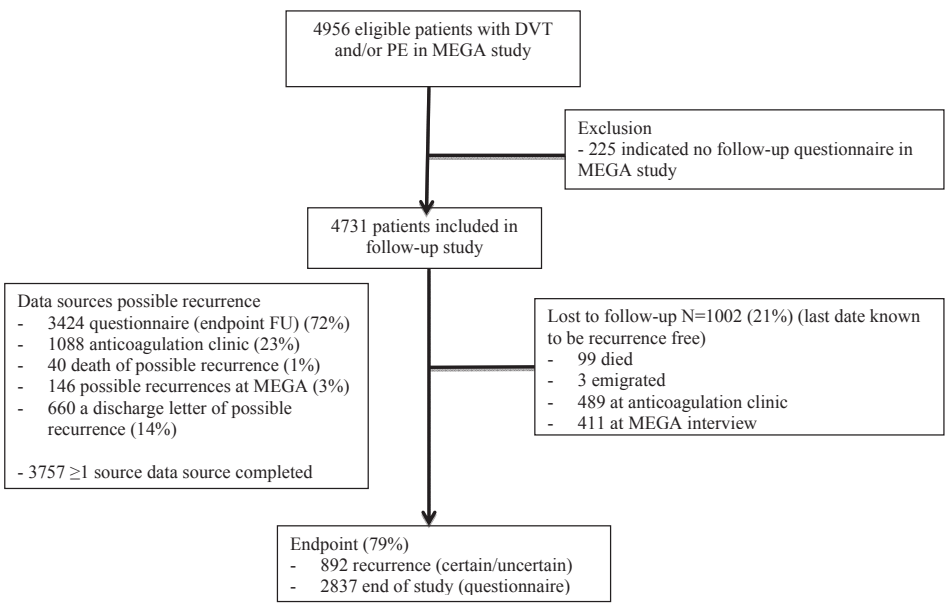


**Figure 1.** Flowchart of follow-up.

**Definition of recurrence**

A decision rule regarding certainty of the diagnosis was made according to the information collected per patient. The reported recurrences were classified into certain recurrences and uncertain recurrences. In this study only certain recurrences were used as endpoint and patients with an uncertain recurrence were censored at time of their uncertain recurrence, since they were definitely recurrence-free until that time.

To be classified as a certain recurrence, a reported recurrence should fulfil one of the following three criteria.

1. A discharge letter was present concluding a diagnosis of recurrence, based on the available clinical and radiological data. This recurrence should be in a different vein or in a different part of the body than the first event. The discharge letter had to contain information about instrumental diagnostic procedures. If the location of either the first or second thrombosis was unclear, an event was still classified as a certain recurrence if at least three months had passed since the first thrombosis.
2. A discharge letter was not available (for example when the treating physician was unknown) but information from both the anticoagulation clinic and the patient reported a recurrence at a clearly different location than the first event (contralateral leg, or DVT after PE or vice versa) or a time period of more than a year had passed between the two events (figure 2).
3. A registered cause of death from pulmonary embolism or venous thrombosis at least six months after the first event.

Uncertain recurrences were defined by four criteria, one of which had to apply:

1. A diagnosis of a possible recurrence in the discharge letter, where clinical and radiological data could not distinguish between an extension of the first and a new thrombotic event.
2. A discharge letter was not available (for example when the treating physician was unknown) but both the patient and the anticoagulation clinic reported a recurrence within a year after the first event.
3. Information was only available from either the patient or the anticoagulation clinic (figure 2).
4. A registered cause of death from pulmonary embolism or venous thrombosis within six months after the first event.

**Statistical analysis**

The end of follow-up was defined as the date of a recurrent event and in the absence of a recurrence, the date of filling in the short questionnaire. If a patient did not fill in a questionnaire they were censored at the last date we knew them to be recurrence free. This could be either the last date we knew patients to be recurrence-free, or the last visit to the anticoagulant clinic, date of death or emigration, or the last moment the patient was known to be recurrence-free from information of the MEGA case-control study (figure 1).

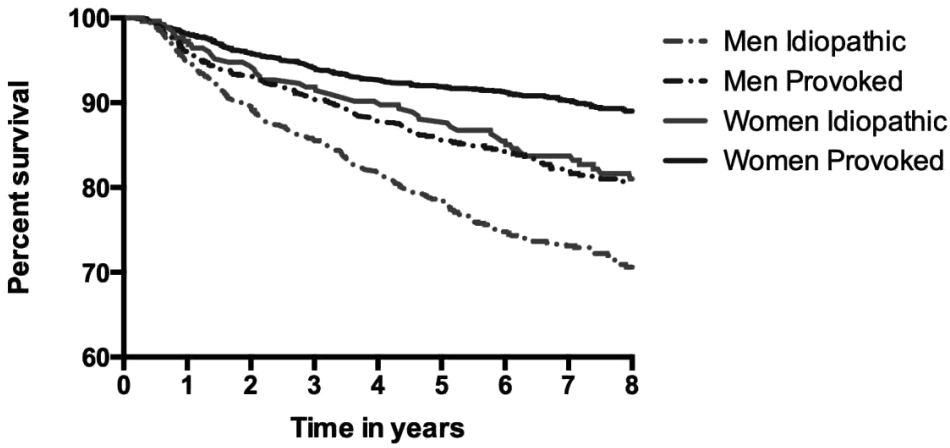


**Figure 2.** Risk of recurrence for idiopathic versus provoked first venous thrombosis stratified for sex. Duration of follow-up in years
- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium.
- Provoked venous thrombosis was defined as thrombosis due to surgery, plaster of minor injuries, oral contraceptive use, hormone replacement therapy use, pregnancy and puerperium.



Duration of follow-up was calculated in two ways, i.e, 1) by starting follow-up at the date of the first event or 2) by starting follow-up at the date of discontinuation of anticoagulant therapy. Both incident rates and cumulative incidences (at one, two and five years) of recurrence were calculated from these two starting points.

In order to find a range of the incidence of recurrence which includes the true incidence of recurrence, we calculated, as a sensitivity analysis, incidences of recurrence for all possible recurrences combined (certain and uncertain) and separately for certain recurrences with both starting points of follow-up (starting from baseline and discontinuation of treatment). Additionally we refined our estimation of the incidence of recurrence by a multiple imputation analysis in patients with an uncertain recurrence. With the multiple imputation analysis the recurrence status of the uncertain recurrences was estimated using information on all comorbidities and risk factors present at time of first venous thrombosis[162,163].

Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster cast, hormone use (oral contraceptives and hormone replacement therapy), pregnancy all within three months before the event, puerperium, and active malignancies at the time of the event. Kaplan Meier estimates adjusted for competing risks were estimated for men and women and for patients with an idiopathic and provoked first venous thrombosis separately. Incidence rates were calculated for men and women and idiopathic and provoked cases separately in different age categories to study risk patterns for these three factors (age, sex and idiopathic thrombosis).

For the analysis on risk factors and optimal duration of anticoagulation, only the certain recurrences were used and the uncertain recurrences were censored at time of the reported recurrence. Hazard ratios were calculated for all potential risk factors, and all hazard ratios were adjusted for age and sex when applicable. All hazard ratios were calculated with follow-up time starting at time of first venous thrombosis. The effect of male sex was also studied in a restricted analysis excluding women who used oral contraceptives or hormone replacement therapy at time of the first thrombotic event as well as women who were or had recently been pregnant at that time. Age was studied both as a continuous and a categorical variable with age categories of 10 years. These effects were studied in the overall group of patients and in patients without cancer and life-long anticoagulation treatment. The latter restriction was done to see the effect of these risk factors in those without another very strong risk factor of thrombosis (cancer) and in those who cannot be treated more than they already were (lifelong treatment).

First and recurrent events were compared for location (lungs or leg). Left versus right-sided first and recurrent thrombosis of the leg were analysed. Observed numbers versus expected numbers when locations and sides would be random were calculated as well as hazard ratios for site of recurrence per site of first thrombosis.

For the analysis on effect of duration of anticoagulation therapy, patients with malignancies at time of thrombosis were excluded. Duration of anticoagulation therapy was calculated in months. Survival curves were made for patients who used anticoagulation therapy for 1-3 months, 4-6 months, 7-12 months, and more than 12 months. To compare the different durations of anticoagulation therapy in groups with a similar indication we made separate survival curves for those with an idiopathic first venous thrombosis and for those with a provoked venous thrombosis due to surgery, plaster cast or minor injuries. All survival curves were adjusted for competing risks due to death.

Analyses were performed with SPSS v21.0 (Chicago, Ill) and STATA SE 12 (Stata Corporation, College Station, Tx) for Windows.

# Results

### Population

Mean age of the patients at time of first venous thrombosis was 48 years and 54% of the patients were women. Mean duration of follow-up was 5.1 years when follow-up started at time of venous thrombosis and 5.0 years when follow-up started after discontinuation of anticoagulation treatment. Total volumes of follow-up were 24 124 and 20031 patient-years respectively. In total 79% of patients (n=3729) had a complete follow-up of whom 2 837 filled in the questionnaire and 892 were followed until (possible) recurrence. In total 1002 (21%) patients did not complete follow-up either due to death (n=99) or emigration (n=3) without recurrence, or did not reply to further queries after a last visit at the anticoagulation clinic (n=489) or at a point later during the follow-up period (n=411) (figure 1).

**Recurrences**

From different sources we obtained information about recurrence status from 3 757 patients. A total of 972 possible recurrences were found that needed to be confirmed. From the information obtained from clinicians, we concluded that 80 of these were not recurrences but were diagnoses of either post-thrombotic syndrome or suspected recurrences that were excluded by ultrasound or CT-scan to be a recurrent event. Therefore, 892 recurrent events could be further classified. Of these, a total of 673 patients were classified to have a certain recurrence. 593 patients fulfilled criterion one for certain recurrence. Fifty-eight patients were identified as a certain recurrence with criterion 2 and 22 patients with criterion three. 219 patients had an uncertain recurrence of which 32 fulfilled criterion 1, 19 criterion 2, 159 recurrences fulfilled criterion 3, and 9 fulfilled criterion 4.

**Incidence of recurrence**

When we let follow-up start at time of the first venous thrombosis, we found an incidence of 27.9 per 1000 person-years (CI95: 25.8-30.0) when only certain recurrences were taken into account. When both certain and uncertain recurrences were counted as recurrent events, as a sensitivity analysis, we found an incidence of 37.0 per 1000 person-years (CI95: 34.6-39.4) (table 1). These incidence rates corresponded to a 5 years cumulative incidence range of 11% and 15% respectively.

Of the 673 certain recurrences, 61 (9%) occurred during anticoagulation therapy prescribed after the first thrombotic event, whereas 53 of the 219 uncertain recurrences (24%) occurred during treatment. When follow-up was started after discontinuation of anticoagulation treatment, the incidence of recurrence was 30.6 per 1000 person-years (CI 95: 28.1-33.0) when only certain recurrences were taken into account. When both certain and uncertain recurrences were taken into account an incidence of 38.8 (CI95: 36.1-41.6) per 1000 person-years was found. The corresponding 5 years cumulative incidences were 13% and 19%. When recurrence status was imputed in the group who had uncertain recurrences the incidence of recurrence became 29.4 (CI95 27.4-31.7) per 1000 person-years when follow-up started at time of first venous thrombosis and 32.0 (CI95: 29.6-34.6) when follow-up started after discontinuation of treatment (table 1).

The recurrence rate was high during the first 1.5 years, i.e. 54 per 1000 (CI95: 45-65) person-years at 1 year and 42 per 1000 (CI95: 33-52) person-years at 1.5 years, but gradually decreased to 25 per 1000 (CI95: 18-34) person-years after 4 years. After this time the incidence of recurrence remained stable at 25 per 1000 person-years.

**Risk factors**

Table 2 shows the incidences of recurrence stratified by age, sex, and whether the first venous thrombosis was idiopathic or not. Incidences were in all instances higher for men than for women. No clear effect of age was seen in any of the categories.

**Table 1.** Recurrence rates

| Type of recurrence | N | Person- years | Incidence (CI95) | 5 years cum incidence | N men | Incidence men (CI95) | N women | Incidence women (CI95) |
|---|---|---|---|---|---|---|---|---|
| **Start follow-up after 1st thrombosis** | | | | | | | | |
| Certain | 673 | 24124 | 27.9 (25.8-30.0) | 11.3% | 427 | 41.1 (37.2-45.0) | 246 | 17.9 (15.7-20.1) |
| Uncertain | 219 | 24124 | 9.1 (7.9-10.3) | 3.9% | 119 | 11.4 (9.4-13.5) | 100 | 7.3 (5.9-8.7) |
| Certain & Uncertain | 892 | 24124 | 37.0 (34.6-39.4) | 15.2% | 546 | 52.5 (48.1-56.9) | 346 | 25.2 (22.5-27.9) |
| Imputed recurrences | 711 | 24124 | 29.4 (27.4-31.7) | 12.0% | 454 | 43.7 (39.8-47.8) | 257 | 18.7 (16.5-21.1) |
| **Start follow-up start after discontinuation of treatment** | | | | | | | | |
| Certain | 612 | 20031 | 30.6 (28.1-33.0) | 15.5% | 395 | 46.5 (41.9-51.1) | 217 | 18.8 (16.3-21.3) |
| Uncertain | 166 | 20031 | 8.3 (7.0-9.5) | 4.2% | 89 | 10.5 (8.3-12.7) | 77 | 6.7 (5.2-8.2) |
| Certain & Uncertain | 778 | 20031 | 38.4 (35.6-41.1) | 19.7% | 484 | 57.0 (51.9-62.1) | 294 | 25.5 (22.6-28.4) |
| Imputed recurrences | 641 | 20031 | 32.0 (29.6-34.6) | 14.2% | 415 | 46.6 (42.3-51.3) | 226 | 19.6 (17.1-22.3) |

**Table 2.** Incidences of recurrence in several subgroups

| Age | Men all | | | Men, first Idiopathic VT | | | Women all | | | Women, first idiopathic VT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (years) | N, total | N, rec/FUy | IR (CI95) | N, total | N, rec/FUy | IR (CI95) | N, total | N, rec/FUy | IR (CI95) | N, total | N, rec/FUy | IR (CI95) |
| 18-30 | 93 | 17/415 | 41.0 (21.5-60.5) | 34 | 6/174 | 34.5 (6.9-62.1) | 402 | 41/2030 | 20.2 (14.0-26.4) | 12 | 1/69 | 14.5 (0.0-43.0) |
| 30-40 | 290 | 48/1459 | 32.9 (23.6-42.2) | 138 | 26/680 | 38.2 (23.5-52.9) | 530 | 46/2985 | 15.4 (10.9-19.9) | 18 | 3/118 | 25.4 (0.0-54.2) |
| 40-50 | 446 | 102/2158 | 47.3 (38.3-56.5) | 206 | 51/1011 | 50.4 (36.6-64.2) | 652 | 55/3612 | 15.2 (11.2-19.2) | 47 | 8/261 | 30.7 (9.5-51.9) |
| 50-60 | 656 | 128/3529 | 36.3 (30.0-42.6) | 330 | 82/1693 | 48.4 (37.9-58.9) | 551 | 49/2998 | 16.3 (11.7-20.9) | 80 | 10/565 | 17.7 (6.7-28.7) |
| 60-70 | 679 | 132/3103 | 42.5 (35.2-49.8) | 331 | 83/1646 | 50.4 (39.6-61.2) | 432 | 55/2103 | 26.2 (19.3-33.1) | 108 | 24/622 | 38.6 (23.2-54.0) |
| Total | 2164 | 427/10394 | 41.1 (37.2-45.0) | 1039 | 248/5205 | 47.6 (41.7-53.5) | 2567 | 246/13729 | 17.9 (15.7-20.1) | 265 | 46/1634 | 28.2 (20.1-36.3) |

- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium

Men had a 2.2-fold (95% CI; 1.9-2.6) increased risk of a recurrent event compared with women after adjustment for age (figure 3, table 3). After exclusion of women who used oral contraceptives, hormone replacement therapy, or were pregnant at time of first venous thrombosis the relative risk increased to a 2.8-fold (95% CI; 2.2-3.6) increased risk in men (table 3).

Age at time of first venous thrombosis was not associated with an increased risk of recurrence (table 3). When age was divided in 10-year categories the risk of recurrence was still similar in all groups (table 3).

Patients with a first idiopathic venous thrombosis had a 2.0-fold (95% CI; 1.7-2.3) increased risk of recurrence compared with patients with a provoked first venous thrombosis. However, after adjustment for sex this relative risk diminished to 1.4 (95% CI; 1.2-1.7). An increased risk of recurrent thrombosis after an idiopathic first event was mainly present in men (figure 2). Exclusion of patients with cancer and life-long treatment did not lead to more than trivial changes in the effects of age, sex, and idiopathic vs. provoked first thrombosis (table 3).



### Location of recurrent versus first thrombosis

Sixty-two percent of the recurrences were DVTs, 31% were PEs, 5% had DVT and PE, and 1% of recurrences were in a different location (upper extremity, portal vein, intestines or sinus) (table 4). Recurrences occurred more than expected at the same location as the first event (table 4). Patients

**Table 3.** Risk factors for recurrent venous thrombosis.
***adjusted for** age and sex when applicable.

| Risk factor | HR (CI95) | Adjusted HR (CI95)* | HR (CI95) excl cancer and lifelong treatment | Adjusted HR (CI95) excl cancer and lifelong treatment |
|---|---|---|---|---|
| Men vs women | 2.3 (1.9-2.7) | 2.2 (1.9-2.6) | 2.5 (2.1-3.0) | 2.4 (2.0-2.9) |
| Men vs women without hormones | 3.0 (2.4-3.7) | 2.8 (2.2-3.6) | 3.6 (2.7-4.6) | 3.5 (2.7-4.5) |
| Age (per year) | 1.01 (1.01-1.02) | 1.00 (1.00-1.01) | 1.00 (1.00-1.01) | 1.00 (1.00-1.01) |
| Age categories | | | | |
| Age 18-30 | 1 (ref) | 1 (ref) | 1 (ref) | 1(ref) |
| Age 30-40 | 0.9 (0.6-1.2) | 0.8 (0.6-1.1) | 0.9 (0.6-1.3) | 0.7 (0.5-1.1) |
| Age 40-50 | 1.1 (0.8-1.5) | 0.9 (0.7-1.3) | 1.1 (0.8-1.6) | 0.9 (0.6-1.2) |
| Age 50-60 | 1.2 (0.9-1.6) | 0.9 (0.6-1.2) | 1.3 (0.9-1.7) | 0.9 (0.6-1.2) |
| Age 60-70 | 1.5 (1.1-2.0) | 1.0 (0.8-1.4) | 1.5 (1.1-2.1) | 1.0 (0.7-1.4) |
| Idiopathic 1st VTE | 2.0 (1.7-2.3) | 1.4 (1.2-1.7) | 2.2 (1.9-2.6) | 1.6 (1.3-1.9) |

- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium.
- Women without hormones were those without pregnancy, puerperium, oral contraceptive use and use of hormone replacement therapy.
*Adjustments were made for age and sex whenever applicable

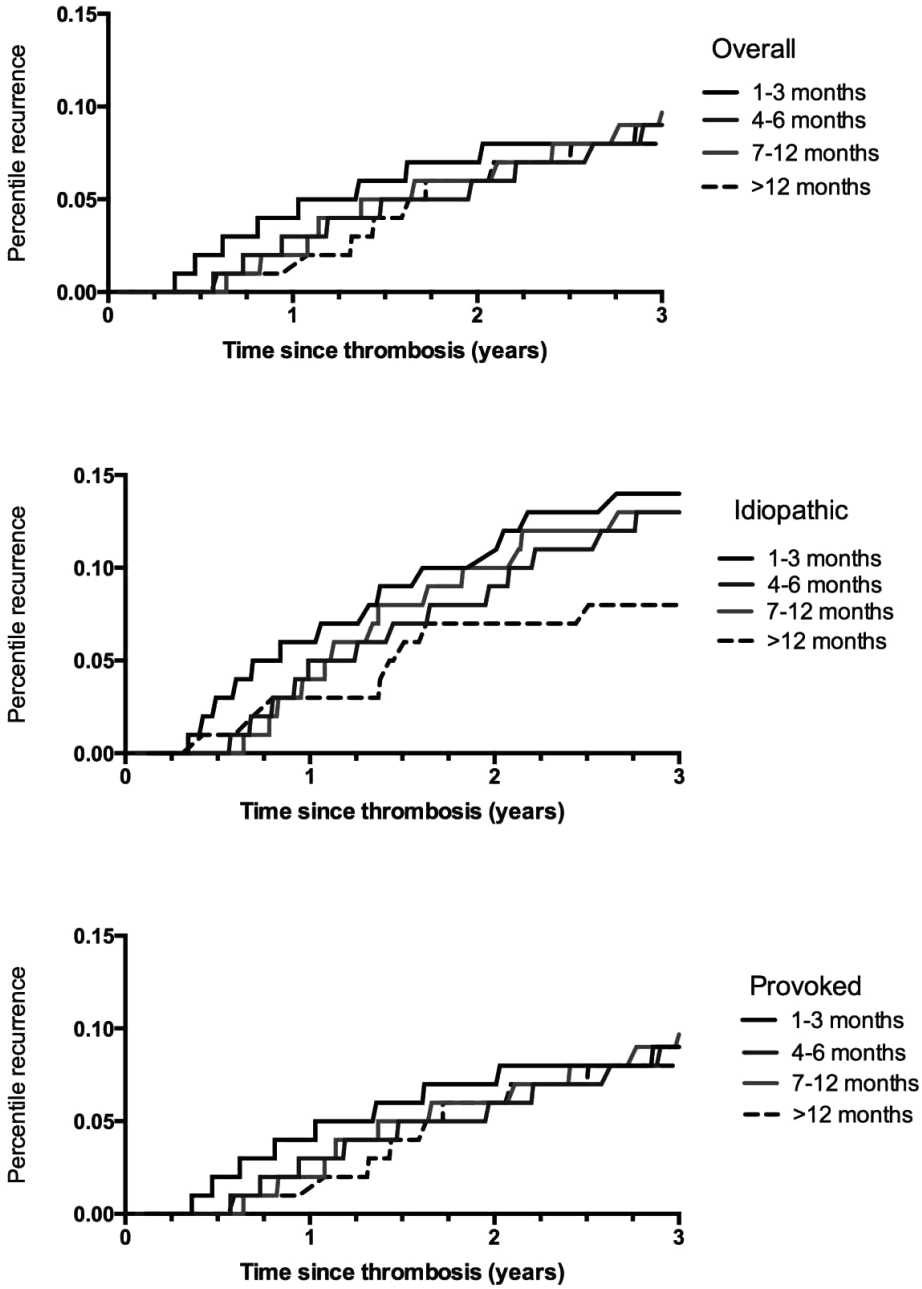


**Figure 3.** Cumulative risk of recurrence for different subgroups and different durations of treatment when follow-up started at time of first venous thrombosis.
- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium.
- Provoked venous thrombosis was defined as thrombosis due to surgery, plaster of minor injuries.

with DVT were 1.5-fold (95%CI 1.1-1.9) more likely to have a DVT as second event than patients with a pulmonary embolism. Patients with a first PE were 1.9 fold (95%CI 1.4-2.8) more likely to get a recurrent PE than those with a first DVT or with a DVT and PE.

In patients who had a first DVT in their left leg, the side of the recurrent DVT appeared to be equally distributed whereas in patients who had a first DVT in their right leg, the chance of a recurrent event in the right leg was slightly higher (60%) than a recurrent event in the left leg (table 5).

**Anticoagulation therapy for the initial event**

For this analysis, a total of 575 patients with a diagnosis of malignancy were excluded as these patients often have treatment for prolonged periods of time or for life. Of the 4156 patients without malignancy, duration of anticoagulation therapy for the initial event was obtained for 4053 (98%) patients. Numbers of patients for the different subgroups and durations of anticoagulation therapy are shown in table 6. Most patients (43%) received 4-6 months of anticoagulation treatment after the first venous thrombosis. Patients with an idiopathic first venous thrombosis were slightly more likely to have received more than 6 months of anticoagulant therapy than those with a provoked first venous thrombosis (33% vs. 28%) whereas patient with a clear provoking factor were slightly more likely to have received less than 4 months of treatment than those with a first idiopathic venous thrombosis (28% vs. 23%). Figure 3 shows the cumulative incidence of recurrence over time of all patients without malignancies for four different duration periods of anticoagulation therapy. This figure shows that most recurrences occurred during the first 2.5 years after the first event



**Table 4.** Location first versus recurrent thrombosis, observed versus expected.

| | Recurrence | | | | |
|---|---|---|---|---|---|
| 1st event | **DVT** | **PE** | **DVT+PE** | **Other** | **Total** |
| DVT | 319 (267) | 71 (99) | 23 (58) | 4 (0) | 424 |
| PE | 44 (99) | 105 (37) | 4 (21) | 1 (0) | 157 |
| DVT + PE | 51 (58) | 29 (21) | 9 (13) | 3 (0) | 92 |
| Total | 414 (424) | 205 (157) | 36 (92) | 8 (0) | 673 |

N observed (N expected)

**Table 5.** Side of DVT.

| | Recurrence | | |
|---|---|---|---|
| 1st event | **Left** | **Right** | **Both** |
| Left | 79 (50%, CI95 42%-57%) | 78 (49%, CI95 42%-57%) | 2 (1%) |
| Right | 54 (40%, CI95 32%-48%) | 81 (60%, CI95 50%-66%) | 0 |
| Both | 1 | 0 | 0 |

among those with 1-3 months of anticoagulation therapy. When patients were split into idiopathic and provoked first venous thrombosis the difference remained after 2.5 years.

## Discussion

In this large follow-up study of 4731 patients with a first venous thrombosis followed for a total follow-up time of 24 124 person-years we found 683 certain recurrent events for an incidence rate of 27.9 per 1000 person-years and a cumulative incidence of 3 percent after one year. We found male sex to be a risk factor for recurrence with a 2.2-fold increased risk (95%CI; 1.9-2.6). An idiopathic first thrombosis was associated with a 1.4-fold increased risk (95%CI; 1.2-1.7) which was most pronounced in men. Increasing age was not associated with risk of a recurrent event. When we studied the different durations of anticoagulation therapy we found that most recurrences occurred in patients with less than 3 months of treatment.

To establish the true incidence of recurrence we performed a sensitivity analysis, varying various aspects of the analysis, which led to a range of thrombosis recurrent rates of 27.9-37.0 per 1000 person-years. We found an incidence of 27.9 per 1000 person-years when only certain recurrences were taken into account and an incidence of 37.0 per 1000 person-years when both certain and uncertain recurrences were taken into account. When follow-up was started after discontinuation of treatment the range of thrombosis recurrence rates was 30.6-38.4 per 1000 person-years. The range of incidences of recurrent thrombosis we report is similar but more precise than recurrent incidences previously reported[7,14,21,33,36,38,159]. Additional to small study size, different incidence rates found in the literature may be explained by different definitions of duration of follow-up (starting at time of thrombosis or discontinuation of treatment). Both methods of defining duration of follow-up are justifiable, but they lead to results that should be interpreted differently and cannot be compared with each other. Furthermore, previous studies generally did not take uncertainty of recurrent events into account. In our study we showed incidences of recurrence both starting follow-up after the date of thrombosis and after the date of discontinuation of treatment. To start duration of follow-up at date of first venous



**Table 6.** Number of patients per duration of anticoagulation therapy

| Group of patients | Total N | 1-3 months oac N (%) | 4-6 months oac N (%) | 7-12 months oac N (%) | >12 months oac N (%) |
|---|---|---|---|---|---|
| All without malignancy | 4053 | 1082 (27) | 1756 (43) | 795 (20) | 420 (10) |
| Idiopathic | 1279 | 297 (23) | 549 (43) | 288 (23) | 145 (11) |
| Provoked | 2774 | 785 (28) | 1207 (44) | 507 (18) | 275 (10) |

- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium.
- Provoked venous thrombosis was defined as thrombosis due to surgery, plaster of minor injuries.

thrombosis has the advantage that recurrences during anticoagulation treatment are taken into account (n=42). We chose to show the main results of only those with a certain recurrence, as these are most likely to truly have had a recurrent event. However, we also present a result where uncertain diagnoses were counted as recurrence, and one in which we imputed the recurrence status of patients with an uncertain recurrence.

Recurrent events occurred more than expected at the same site as the first thrombosis, i.e. patients with a PE as first event were more likely to have a PE as recurrent event, and patients with a first DVT had more DVT as recurrence. This may be explained by damage to the veins at the location of the first thrombosis or by a higher awareness of thrombotic symptoms at the location of the first event. However, when a patient had had a first venous thrombosis of the left leg with a recurrence in the leg, the side of recurrence location was random. When the first event occurred in the right leg patients were only slightly more likely to have a recurrent event in the right leg. These results suggest that most recurrences are not due to vascular damage or residual thrombosis after the first venous thrombosis, or that most first DVTs are bilateral.



We attempted to study the association between duration of treatment and the occurrence of recurrent venous thrombosis. Those with a treatment duration approaching 6 months appeared to have the lowest incidence of recurrence. However, as this is an observational study we do not know the indications for the different durations of treatment. To avoid some of the confounding by indication for the duration of treatment we stratified the analysis for those with a first idiopathic and provoked venous thrombosis (figure 3b and 3c) and still observed the highest risk of recurrence for those with 1-3 months of therapy. It should be noted that we have no information on the occurrence of major haemorrhage and therefore cannot balance thrombosis prevention versus bleeding risk.

In this study we found that a first idiopathic venous thrombosis is mainly a risk factor for recurrence in men and not in women. For women more removable provoked risk factors are known and therefore they are at lower risk of recurrence than men. These risk factors are not present in idiopathic patients. Since men with an idiopathic thrombosis were at higher risk of recurrence than women with an idiopathic first event the intrinsic risk of thrombosis for men appears to be higher than for women. Most previous studies did not stratify by sex in the analysis of idiopathic versus provoked first venous thrombosis and the risk of recurrence[36,157,158,161]. Increasing age did not increase the risk of a recurrent event after adjustment for sex. Similar results were obtained from previous studies, including our own.[30,36,127]

A limitation of this study is that it was based in a clinical setting. We did not perform CUS for all patients after the first event to better evaluate a subsequent recurrence. However, we tracked all possible recurrences and had access to three sources of information to decide on the likelihood of a true recurrence. The sensitivity analysis showed little difference

between the minimum and maximum recurrence rate possible (27.9-37.0) per 1000 person-years when follow-up started after thrombosis and 30.6-38.4 per 1000 person-years when follow-up started after discontinuation of treatment) as described in table 1. However, our study with the recurrence definition based on clinical experience gives the optimal estimate of true effects in clinical practice. A second limitation is that we included patients with a first venous thrombosis who were younger than 70 years of age. Therefore, our results are not generalizable to patients with a first venous thrombosis above the age of 70. A third limitation is that for 23% of patients limited follow-up was available. Part of these patients were lost to follow-up due to death. However, from some of them we still knew their recurrence status up to death through registries of the causes of death and information from the anticoagulation clinics. So, finally we did not know the recurrence status of 8% of patients who died, which at most would have led to a slight underestimation of the incidence of recurrent thrombosis. The majority of patients were lost to follow-up due to reasons that are unlikely to be related to the recurrence risk (non-availability of contact details).

In conclusion, in this large study in 4731 patients with a first venous thrombosis we found an overall recurrence rate between three and four percent per year. The recurrence rate was highest during the first year after the first event (i.e. 54 per 1000 person-years) and decreased until it became stable at 25 per 1000 person-years at 4 years after the first venous thrombosis. Age did not affect the risk of a recurrent event. An idiopathic first thrombosis is a risk factor for recurrence only in men, and men had an overall higher risk of recurrence than women. For duration of treatment, sex, type of first event (idiopathic or provoked) and location of first event (DVT or PE) may need to be taken into account. Clinical trials are indicated to test such a strategy.

# 8

# Body height, mobility, and risk of first and recurrent venous thrombosis

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## Summary

Tall people have an increased risk of a first venous thrombosis. Sedentary lifestyle has been shown to act synergistically with body height, especially in long-haul flights. The aim of this study was to estimate the effect of height on the risk of a first and recurrent venous thrombosis and the additional effect of a mobile or immobile lifestyle in the MEGA case-control and MEGA follow-up study. Patients with a first venous thrombosis and controls subjects were included between 1999 and 2004. Patients were followed for recurrence for an average time of 5 years. Self reported height at time of first venous thrombosis was used. The effect of height was estimated in 5 centimeter (cm) categories. Odds ratios and hazard ratios per increase of 5 cm were calculated. For both men and women a height of 165-170 cm was used as the reference category. In 4464 patients who reported their height we found an increased risk of a first and recurrent event with height. For men a more than 3-fold increased risk was found for those taller than 200 cm for both first and recurrent venous thrombosis. For women a 2-fold increased risk was found for those taller than 180 cm for both first and recurrent venous thrombosis. For both men and women an additional effect was observed for sedentary lifestyle. In conclusion, both tall men and women have an increased risk of first and recurrent venous thrombosis, especially in combination with a sedentary lifestyle.

# Introduction

Tall people have an increased risk of a first venous thrombosis[166–169]. Body height affects venous pressure dynamics[170,171], so taller people may have more stasis in the legs which could explain the increased risk. As men are taller than women most previous studies were restricted to men or only found an increased risk for men[166,168].

Prolonged seated immobility such as during work or long haul flights has been found to be a risk factor for a first venous thrombosis[15,16,172]. Prolonged seating induces compression of the poplitial vein and reduces blood flow from the lower leg. This effect will most likely be stronger in tall people who may be seated in a more cramped position leading to more compression of their poplitial vein than in people of average height. The combination of prolonged seating and being particularly tall was indeed found to increase the risk of thrombosis substantially during long haul flights[15,16]. The same was found for short people, where we hypothesized that their feet may not reach the floor in standard seats[15,16]. It is not well known to what extent prolonged immobility during daily life affects the risk of venous thrombosis in tall or short people.

The risk of a recurrent venous thrombotic event is generally high, but low in those with transient risk factors. As height is a non-modifiable risk factor, it could well be that height also affects the risk of a recurrent event, particularly in combination with prolonged seating. Men have a higher risk of recurrent venous thrombosis than women, and we hypothesized that this could be explained by their generally greater height.

The aim of this study was to investigate the risk of a first and a recurrent venous thrombosis in relation to height in men and women separately, as well as the effect of prolonged seated immobility in combination with body height. We studied this in a large unselected population of nearly 5000 patients with a first VT, of whom nearly 700 developed a recurrence, and 5000 control subjects.

# Methods

### Study population

The multiple environmental and genetic assessment (MEGA) study of risk factors for venous thrombosis is a large population based case-control study that included 4956 cases with a first venous thrombosis and 6297 control subjects between March 1999 and September 2004. Cases were included at six anticoagulation clinics, which monitor virtually all outpatient treatment with vitamin K antagonists; control subjects were either partners of the cases (n=3297) or recruited with random digit dialing (n=3000)[7,14].

All participants of the MEGA study filled in an extensive questionnaire on risk factors for venous thrombosis. Body height was reported by 4464 (90%) cases and 5803 (92%) controls. The definition of immobility during the day was based on a combination of two questions: 1)

'How do you spend most of your day?', on which possible answers were: standing, walking, sitting or lying down, and 2) 'how do you classify your daily activities regarding physical activity', on which an answer could be chosen out of four categories from light to heavy. The answers walking and standing and the two heavy categories of physical activity during the day were classified as mobile and all others as not mobile. If the two questions contradicted each other (23%) we used the answer to the question about daily physical activity as we considered this question more specific for prolonged seated immobility. If participants filled in just one of the two questions, only that question was taken into account. The question: 'How do you spend most of your day' was filled in by 3117 (30%) participants, as this question was present in only part of the questionnaires. In total 7414 (72%) participants filled in the question about their daily activity. When both questions were combined information on physical activity was present for 8458 (82%) participants.

Subsequently a follow-up study was performed for the 4731 cases who participated in the MEGA case-control study who also agreed to participate in the follow-up study, with the aim to establish incidence rates of and risk factors for a recurrent event. Questionnaires about recurrent events were sent to all patients known to be alive. In addition, we checked the records of all patients at the anticoagulation clinics to find all possible recurrent events. Recurrences were confirmed with discharge letters using a decision rule which was described before[173]. A total of 631 patients developed a certain recurrence while 184 subjects with uncertain recurrence were censored at time of possible recurrence. Body height as reported at time of first venous thrombosis and the association with prolonged immobility during daily life were studied as risk factors for recurrence. During follow-up 4264 (90%) patients had information about their body height at baseline and 3999 (85%) patients had information about physical activity at baseline.

**Statistical Methods**

Height was divided in categories of five centimeters starting from 155 centimeters up to 200 centimeters. All participants shorter than 155 centimeters were grouped, and formed the lowest height category. All subjects taller than 200 centimeters formed the highest height category. The category of 165-170cm was used as the reference category as this category contained a substantial number of both men and women.

For determining the association between height and first venous thrombosis, odds ratios for the different height categories were calculated as estimates of the incidence rate ratio (relative risk). All odds ratios were adjusted for age to take the matching into account. For determining the association between height and a recurrent event, incidence rates were calculated per height category (number of recurrences per height category per number of person-years per category). Hazard ratios for recurrence per height category compared with those of average height (165-170cm) were calculated. Overall risks of height for a first venous thrombosis in these data have been published earlier so here we do not repeat the

overall analysis but describe the results for first venous thrombosis for men and women separately[167]. For recurrent venous thrombosis, incidence rates and HRs were calculated overall and for men and women separately.

We used 10 cm categories of height to study the combination of height and immobility during daily life. For these analyses we used a height of 160-170 cm as reference category. These analyses were done for both first and recurrent venous thrombosis and for men and women separately.

## Results

For the case-control set up, a total of 4464 patients and 5803 controls reported their body height and were therefore included; 45.9% of patients and 46.2% of controls were men. Median age of the patients was 54.9 ($5^{th}$-$95^{th}$ percentile 31.2-68.4) for men and 45.8 ($5^{th}$-$95^{th}$ percentile 24.0-67.8) for women. Median age of the control subjects was 48.4 ($5^{th}$-$95^{th}$ percentile 26.7-67.1) for men and 48.0 ($5^{th}$-$95^{th}$ percentile 25.0-66.4) for women. Among the 4365 patients who reported body height and participated in the follow-up study, 648 recurrent events were identified during follow-up. The mean duration of follow-up was 5 years. The overall recurrence rate among these patients was 28.5 (95CI 26.4-30.8) per 1000 person-years.



### First venous thrombosis

For both men and women an increasing risk of a first venous thrombosis with higher body height was found, up to a 3.8-fold increased risk (95CI 1.5-9.8) for the tallest men (>201 cm) and a 1.5-fold increased risk (95CI 0.7-3.4) for the tallest women (>185 cm) compared to subjects with a height of 165-170 cm (table 1). For men an increased risk was also found for the shortest participants (<155 cm) compared with subjects with a height of 165-170cm, although numbers were small here (OR 3.7: CI95 0.6-24.0).

Seated immobility was associated with a 1.2-fold (95CI 1.1-1.4) increase in risk of first venous thrombosis for men and a 1.4-fold (95CI 1.2-1.6) increase in risk for women. When seated immobility during daily life was analyzed jointly with body height we found the highest risk in the tallest men (200-tallest) who were not mobile most of the day (OR 4.7 CI95 1.1-20.2) compared with men with a height of 165-170cm who were mobile during the day. This synergistic effect of height and immobility was only present in the tallest category (table 2).

For women in all categories of body height a slightly increased risk of a first venous thrombosis was seen when these women were mainly seated during the day. The largest risk was found for women of 181-190cm who were not mobile (HR 3.1 CI95 1.6-6.1) compared with mobile women of 161-170cm (table 2).

### Recurrent venous thrombosis

For recurrent venous thrombosis we also observed a gradual increase in risk with body height (table 3a), which attenuated somewhat after adjustment for age and sex. When we

**Table 1.** Body height as risk factor for a first venous thrombosis.

| 1st Venous thrombosis | Men (N = 4729) | | | Women (N = 5538) | | |
|---|---|---|---|---|---|---|
| Height (cm) | N Cases | N Controls | $OR_{adj}$ (95% CI)* | N Cases | N Controls | $OR_{adj}$ (95% CI)* |
| Smallest-155 | 3 | 2 | 3.7 (0.6-24.0) | 79 | 113 | 0.9 (0.7-1.2) |
| 156-160 | 5 | 9 | 0.7 (0.2-2.7) | 237 | 370 | 0.9 (0.7-1.0) |
| 161-165 | 39 | 42 | 1.3 (0.8-2.2) | 478 | 700 | 0.9 (0.8-1.0) |
| 166-170 | 136 | 208 | 1(ref) | 740 | 956 | 1 (ref) |
| 171-175 | 307 | 453 | 1.1 (0.9-1.5) | 478 | 549 | 1.1 (0.9-1.3) |
| 176-180 | 541 | 681 | 1.4 (1.1-1.8) | 322 | 353 | 1.1 (0.9-1.4) |
| 181-185 | 453 | 614 | 1.5 (1.1-1.9) | 67 | 71 | 1.1 (0.8-1.6) |
| 186-190 | 357 | 423 | 1.9 (1.4-2.5) | 14 | 11 | 1.5 (0.7-3.4) |
| 191-195 | 134 | 174 | 1.9 (1.4-2.7) | | | |
| 196-200 | 64 | 65 | 2.9 (1.9-4.4) | | | |
| 201- Tallest | 10 | 9 | 3.8 (1.5-9.8) | | | |

cm=centimeters, N=number, OR=Odds ration, 95% CI=95% confidence interval, $OR_{adj}$=adjusted odds ratio.
*Odds ratios were adjusted for age.



**Table 2.** body height and seated immobility in daily life in relation to risk of first venous thrombosis

| 1st Venous thrombosis | | Men (N = 4558) | | | Women (N = 4614) | | |
|---|---|---|---|---|---|---|---|
| Height (cm) | Mobile | Cases (N) | Controls (N) | ORadj* | Cases (N) | Controls (N) | ORadj* |
| Smallest-160 | Yes | 1 | 4 | 0.3 (0.0-2.7) | 91 | 114 | 0.9 (0.6-1.2) |
| Smallest-160 | No | 5 | 5 | 1.7 (0.4-7.6) | 163 | 254 | 1.2 (0.9-1.7) |
| 161-170 | Yes | 54 | 70 | 1 | 373 | 382 | 1 |
| 161-170 | No | 70 | 111 | 1.3 (0.7-2.1) | 658 | 952 | 1.2 (0.9-1.4) |
| 171-180 | Yes | 237 | 302 | 1.2 (0.8-1.9) | 214 | 221 | 1.1 (0.8-1.4) |
| 171-180 | No | 386 | 620 | 1.3 (0.9-2.0) | 489 | 536 | 1.5 (1.2-1.8) |
| 181-190 | Yes | 240 | 251 | 1.9 (1.3-3.0) | 19 | 21 | 1.6 (0.7-3.9) |
| 181-190# | No | 446 | 647 | 1.7 (1.1-2.6) | 54 | 52 | 3.1 (1.6-6.1) |
| 191-200 | Yes | 63 | 57 | 4.1 (2.2-7.5) | | | |
| 191-200 | No | 117 | 162 | 2.1 (1.3-3.3) | | | |
| 201-tallest | Yes | 3 | 2 | 1.9 (0.1-3.8) | | | |
| 201-tallest | No | 6 | 6 | 4.7 (1.1-20.2) | | | |

Cm=centimeters, N=number
*Odds ratio adjusted for age
# for women this category is 180-tallest

stratified on sex we found an increase in risk for both tall men and women. For men of >200cm a HR of 3.7 (95CI 1.4-10.0) for recurrence was found compared with male subjects with a height of 165-170cm; for women of 186-190cm we found a HR of 3.0 (95CI 0.9-9.4) compared with female subjects with a height of 165-170cm (table 3B and C). Short women also had an increased incidence of recurrence: a 1.7-fold (95CI 0.9-3.2) increased risk for the shortest women with a height of 165-170cm as the reference. Overall, the same trends in

**Table 3.** Body height as a risk factor for a recurrent venous thrombosis.

**A: Overall**

| Recurrent venous thrombosis | | | N = 4365 | | |
|---|---|---|---|---|---|
| **Height (cm)** | **N Total** | **N rec** | **IR# (95% CI)** | **HR (95% CI)** | **$HR_{adj}$ (95% CI)*** |
| smallest-155 | 74 | 11 | 33.9 (17.9-59.0) | 1.5 (0.8-2.9) | 1.6 (0.9-3.1) |
| 156-160 | 225 | 15 | 11.9 (6.9-19.2) | 0.6 (0.3-0.9) | 0.6 (0.3-1.0) |
| 161-165 | 487 | 43 | 16.3 (11.9-21.7) | 0.7 (0.5-1.1) | 0.8 (0.5-1.1) |
| 166-170 | 826 | 99 | 21.8 (17.8-26.4) | 1 (ref) | 1 (ref) |
| 171-175 | 763 | 97 | 23.9 (19.5-29.1) | 1.1 (0.8-1.4) | 0.9 (0.7-1.3) |
| 176-180 | 835 | 142 | 32.9 (27.8-38.7) | 1.5 (1.2-1.9) | 1.1 (0.8-1.5) |
| 181-185 | 493 | 91 | 37.7 (30.5-46.1) | 1.7 (1.3-2.9) | 1.2 (0.8-1.6) |
| 186-190 | 362 | 90 | 49.1 (49.7-60.1) | 2.2 (1.7-3.0) | 1.5 (1.0-2.0) |
| 191-195 | 129 | 23 | 33.4 (21.7-49.4) | 1.5 (1.0-2.4) | 1.0 (0.6-1.7) |
| 196-200 | 61 | 15 | 53.0 (30.8-85.5) | 2.4 (1.4-4.1) | 1.6 (0.9-2.9) |
| 201-205 | 9 | 5 | 111.1 (40.7-246.3) | 3.2 (1.2-8.6) | 3.6 (1.4-9.0) |

**B: men**

| Recurrent venous thrombosis | | | N = 1949 | | |
|---|---|---|---|---|---|
| **Height (cm)** | **N Total** | **N rec** | **IR# (95% CI)** | **HR (95% CI)** | **$HR_{adj}$ (95% CI)*** |
| smallest-155 | 2 | 0 | - | - | - |
| 156-160 | 4 | 0 | - | - | - |
| 161-165 | 32 | 6 | 41.9 (17.0-87.3) | 1.2 (0.5-3.0) | 1.2 (0.5-2.9) |
| 166-170 | 122 | 20 | 35.1 (22.0-53.2) | 1 (ref) | 1 (ref) |
| 171-175 | 296 | 49 | 16.6 (12.4-21.7) | 1.0 (0.6-1.6) | 1.0 (0.6-1.7) |
| 176-180 | 519 | 105 | 39.4 (32.4-47.4) | 1.1 (0.7-1.8) | 1.2 (0.7-1.9) |
| 181-185 | 427 | 86 | 42.3 (34.0-51.9) | 1.2 (0.7-2.0) | 1.3 (0.8-2.1) |
| 186-190 | 350 | 87 | 48.8 (39.3-59.9) | 1.4 (0.9-2.3) | 1.5 (0.9-2.4) |
| 191-195 | 127 | 23 | 34.0 (22.1-50.2) | 1.0 (0.5-1.8) | 1.1 (0.6-1.9) |
| 196-200 | 61 | 15 | 53.0 (30.8-85.5) | 1.5 (0.8-2.9) | 1.7 (0.8-3.3) |
| 201-tallest | 9 | 5 | 111.1 (40.7-240.6) | 3.2 (1.2-8.6) | 3.7 (1.4-10.0) |

**C: women**

| Recurrent venous thrombosis | | | N = 2315 | | |
|---|---|---|---|---|---|
| **Height (cm)** | **N Total** | **N rec** | **IR# (95% CI)** | **HR (95% CI)** | **$HR_{adj}$(95% CI)*** |
| smallest-155 | 72 | 11 | 34.8 (18.3-60.5) | 1.7 (0.9-3.3) | 1.7 (0.9-3.2) |
| 156-160 | 221 | 15 | 12.1 (7.0-19.5) | 0.6 (0.4-1.1) | 0.6 (0.3-1.0) |
| 161-165 | 455 | 37 | 14.8 (10.6-20.2) | 0.7 (0.5-1.1) | 0.7 (0.5-1.1) |
| 166-170 | 704 | 79 | 19.6 (15.6-24.4) | 1 (ref) | 1 (ref) |
| 171-175 | 467 | 48 | 18.4 (13.7-24.2) | 0.9 (0.6-1.3) | 0.9 (0.7-1.3) |
| 176-180 | 316 | 37 | 22.4 (16.0-30.5) | 1.1 (0.8-1.7) | 1.2 (0.8-1.8) |
| 181-185 | 66 | 5 | 13.2 (4.8-29.3) | 0.7 (0.3-1.6) | 0.7 (0.3-1.8) |
| 186-tallest | 14 | 3 | 58.8 (15.0-160.1) | 2.9 (0.9-9.1) | 3.0 (0.9-9.4) |

Cm=centimeters, N=number, rec=recurrences, IR=incidence rate, HR=Hazard ratio, 95% CI=95% confidence interval, $HR_{adj}$=adjusted Hazard ratio.
*adjusted for age and sex in table a and age in table b and c, # per 1000 person-years

risk of recurrence related to body height were seen in men and women (figure 1). However, the recurrence rate for women was lower for almost all body heights.

Seated immobility at time of first venous thrombosis was associated with a 1.1-fold (95CI 0.9-1.4) increased risk of recurrence in men and a 1.5-fold (95CI 1.1-2.0) increase in risk in women. When seated immobility was analyzed jointly with body height we saw a slight synergistic effect in the overall analysis (table 4A). However, when we stratified on sex this was attenuated and the additional effects were mainly seen in women (table 4B). For men we only saw an additional effect in the tallest group (>200cm) compared with those with a height of 161-170cm.

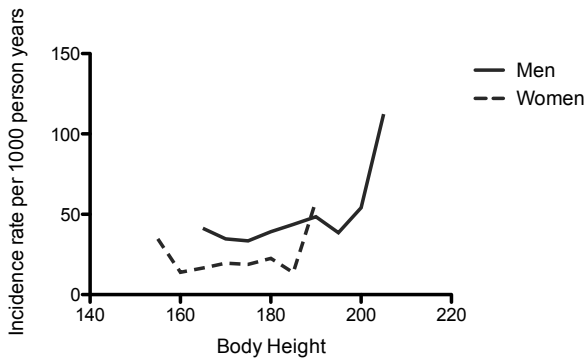


**Figure 1.** Incidence of recurrence per body height for men and women separately.

**Table 4A.** Body height and mobility in daily life and risk of recurrent venous thrombosis.

| **Recurrent venous thrombosis** | | **N=3544** | | | |
|---|---|---|---|---|---|
| **Height (cm)** | **Mobile** | **N total** | **N rec** | **HR (95% CI)** | **HRadj*** |
| Smallest-160 | Yes | 89 | 7 | 0.6 (0.3-1.4) | 0.6 (0.3-1.5) |
| Smallest-160 | No | 154 | 16 | 1.2 (0.7-2.1) | 1.0 (0.6-1.9) |
| 161-170 | Yes | 403 | 47 | 1 | 1 |
| 161-170 | No | 691 | 73 | 1.1 (0.7-1.5) | 1.2 (0.8-1.7) |
| 171-180 | Yes | 440 | 59 | 1.2 (0.8-1.7) | 0.9 (0.6-1.4) |
| 171-180 | No | 848 | 124 | 1.5 (1.1-2.1) | 1.3 (0.9-1.9) |
| 181-190 | Yes | 255 | 55 | 2.2 (1.5-3.2) | 1.4 (0.9-2.2) |
| 181-190 | No | 484 | 105 | 2.2 (1.6-3.2) | 1.5 (1.0-2.2) |
| 191-200 | Yes | 60 | 14 | 2.3 (1.3-4.2) | 1.4 (0.7-2.7) |
| 191-200 | No | 112 | 23 | 2.1 (1.3-3.5) | 1.3 (0.8-2.2) |
| 201-tallest | Yes | 3 | 1 | 3.5 (0.5-25.5) | 2.2 (0.3-16.3) |
| 201-tallest | No | 5 | 3 | 6.4 (2.0-20.5) | 5.1 (1.8-14.6) |

Cm=centimeters, N=number, HR=Hazard ratio, 95% CI=95% confidence interval, $HR_{adj}$=adjusted Hazard ratio, *adjusted for age and sex

**Table 4B.** Body height and mobility in daily life for recurrent venous thrombosis for men and women separately

| Recurrent venous thrombosis | | Men (N = 1840) | | | | Women (N = 2037) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Height (cm)** | **Mobile** | **N total** | **N Rec** | **HR (95% CI)** | **HRadj*** | **N total** | **N Rec** | **HR (95% CI)** | **HRadj*** |
| Smallest-160 | Yes | | - | - | - | 71 | 6 | 0.9 (0.4-2.1) | 0.9 (0.4-2.1) |
| Smallest-160 | No | 6 | 0 | - | - | 132 | 14 | 1.4 (0.8-2.7) | 1.4 (0.7-2.7) |
| 161-170 | Yes | 45 | 11 | 1 (ref) | 1 (ref) | 310 | 29 | 1 (ref) | 1 (ref) |
| 161-170 | No | 96 | 14 | 0.7 (0.3-1.6) | 0.7 (0.3-1.5) | 598 | 64 | 1.4 (0.9-2.1) | 1.4 (0.9-2.1) |
| 171-180 | Yes | 220 | 39 | 0.7 (0.3-1.3) | 0.7 (0.3-1.3) | 190 | 16 | 0.9 (0.5-1.6) | 0.9 (0.5-1.7) |
| 171-180 | No | 539 | 104 | 0.9 (0.5-1.6) | 0.9 (0.5-1.6) | 473 | 57 | 1.6 (1.0-2.5) | 1.7 (1.1-2.7) |
| 181-190 | Yes | 224 | 49 | 0.9 (0.5-1.7) | 0.9 (0.5-1.8) | 16 | 3 | 2.1 (0.6-6.9) | 2.4 (0.7-8.0) |
| 181-190* | No | 503 | 115 | 1.0 (0.5-1.9) | 1.0 (0.6-1.9) | 50 | 4 | 1.0 (0.4-3.0) | 1.2 (0.4-3.5) |
| 191-200 | Yes | 59 | 12 | 0.8 (0.4-1.8) | 0.9 (0.4-2.0) | | | | |
| 191-200 | No | 118 | 24 | 0.9 (0.4-1.8) | 0.9 (0.5-1.9) | | | | |
| 201-tallest | Yes | 2 | 1 | 1.5 (0.2-11.3) | 1.5 (0.2-11.7) | | | | |
| 201-tallest | No | 6 | 4 | 2.9 (0.9-9.2) | 3.3 (1.0-10.5) | | | | |

Cm=centimeters, N=number, HR=Hazard ratio, 95% CI=95% confidence interval, $HR_{adj}$=adjusted Hazard ratio, *adjusted for age
For women this category is 180-tallest

## Discussion

In this study body height was positively associated with the risk for both first and recurrent venous thrombosis, both in men and women. The effect was more pronounced in men, probably because they are on average taller. Prolonged seated immobility further increased the risk of a first venous thrombosis for men in the highest height category and for women in all categories. For recurrent venous thrombosis a similar pattern was observed. We also observed an increased risk of venous thrombosis for small people (<155 cm). For the shortest people an additional effect of seated immobility on the risk was found as well.

Previous studies have shown an increased risk of a first venous thrombosis with increasing body height[166–168] However, these studies have been performed in men only[166,168] or used large categories of body height[167] like quartiles, for which reasons an increase in risk in women has not been described before. The Dutch population is one of the tallest populations in the world, which allowed adequate numbers of tall men and women in the study. Our results on the combined effect of height with immobility during daily life are in line with risks found before for tall and short people during long haul flights.[174]

To our knowledge no previous studies on the effect of body height on recurrent venous thrombosis have been performed. For recurrent venous thrombosis we also found a weak synergistic effect of body height and immobility for women. For men this synergy was only seen for the tallest men. For tall subjects we found a 3- to 4- fold increase in risk of recurrence, which are among the largest HRs found in thrombosis recurrence research.

This study in a large group of patients is the first to show that tall women are at increased risk of venous thrombosis and that body height is a risk factor for recurrent venous thrombosis. The explanation for an increased risk for tall men and women probably lies in their long legs where stasis is more present due to a higher resting venous pressure.[6] Although generally a dose-response relation appears to be present with increasing height and increasing risk, there seems to be a threshold (<155cm) below which the risk of (recurrent) venous thrombosis increases in short people. An explanation may be that these individuals in some seats cannot plant their feet on the floor, which leads to compression of the popliteal vein and more stasis.

Body height cannot fully explain the overall higher risk of recurrent venous thrombosis in men compared to women for two reasons. Firstly, for men and women with the same body height the incidence of recurrence was still 2-fold higher in men than in women (figure 2). Secondly, when we analyzed sex as a risk factor for recurrent venous thrombosis and adjusted the estimate for body height the effect of sex diminished only slightly, from 2.2 to 1.8. So even after adjustment for body height an approximately 2-fold increase in risk for recurrence in men remains.

A limitation of our study is that both body height and mobility were self-reported. However, with respect to body height misclassification would most likely be minor and

random and equally present in cases and controls, which would at most have attenuated the results. Being mobile during the day has not been questioned in great detail in our questionnaires. The small additional increase in risk we observed for seated immobility may well be larger when mobility is assessed in more detail. Only 30% of the participants answered the question on how they spent most of the day. This did most likely not affect our results because we considered the question about physical activity as the most accurate. Another potential limitation is that we assessed body height while leg length may be more informative.[175] As body height already showed an increase in risk the effect of leg length is expected to be even stronger.

In conclusion, in this population based study in 4464 patients with a first thrombosis of whom 631 had a recurrent event, we found an increased risk for both first and recurrent venous thrombosis with increasing body height for both men and women. The effect was more pronounced for subjects who are less mobile during the day.

# 9

# Summary and General Discussion

The aim of this thesis was to identify new risk factors for first and recurrent venous thrombosis of both the upper and lower extremity, and assess the incidence of recurrence and mortality after a first venous thrombosis. An overview was provided of the current literature on risk factors and treatment for a first venous thrombosis of the upper extremity (chapter 2). We investigated the association between levels of coagulation factors, blood group and a first venous thrombosis of the upper extremity (chapter 3), and studied risk factors for a recurrent event in patients with a first venous thrombosis of the upper extremity (chapter 4). Furthermore, we studied the association between venous thrombosis and long-term mortality (chapter 5). In this study we found that patients with thrombosis died more of chronic obstructive pulmonary disease (COPD) than expected from population figures. COPD was found to be a risk factor for a first venous thrombosis in chapter 6. We studied the incidence of recurrent venous thrombosis, as well as sex, age and an idiopathic first venous thrombosis as risk factors for recurrence (chapter 7). Body height was studied as a risk factor for both first and recurrent venous thrombosis in combination with mobility (chapter 8). In this summary chapter results are elaborated on and methodological considerations, clinical relevance and suggestions for further research are described.

## Main findings

In this thesis, results of both the MEGA follow-up study and the MEGA case-control study are presented. The MEGA study is a large case-control study, in which over 5000 patients were included with a first venous thrombosis and over 5000 controls. Subjects were included between March 1999 and September 2004. Patients were included at six anticoagulation clinics in the Netherlands and controls were either partners of patients or were randomly recruited by random digit dialling. All subjects filled in an extensive questionnaire about their history and on potential risk factors for thrombosis. Up to June 2002 blood samples were collected from participants. From June 2002 until September 2004 DNA samples were taken with buccal swabs. In 2006 a pilot for a follow-up of the MEGA study was performed in all patients with a first venous thrombosis of the upper extremity. The actual collection of follow-up data of all patients included in the MEGA study was carried out between June 2008 and June 2009. The aim of the MEGA follow-up study was to assess the incidence of recurrent venous thrombosis, to identify new risk factors for a recurrent venous thrombosis, and to study the association between venous and arterial thrombosis and their common risk factors.

A pilot study for the MEGA follow-up study was performed in all 226 patients with a venous thrombosis of the upper extremity. In this study risk factors for a recurrence after a first venous thrombosis of the upper extremity and differences in risk factors for a first upper extremity venous thrombosis and for subsequent recurrence were found. Women had an increased risk of recurrence after a first venous thrombosis of the upper extremity compared with men. A thrombosis in a different vein than the subclavian vein, high BMI, and malignancy at time of first venous thrombosis increased the risk of recurrence in

patients with a first venous thrombosis of the arm. From chapter 2 we learned that levels of coagulation factors and blood group had not been previously studied in literature as risk factors for venous thrombosis of the arm. We found in our study that high levels of von Willebrand Factor, Factor VIII, and fibrinogen increased the risk of an upper extremity venous thrombosis. Patients with blood group non-O, a genetic cause of high levels of vWF and FVIII had an increased risk as well. Elevated levels of other coagulation factors did not seem to increase the risk of thrombosis of the upper extremity. In chapter 5 we report that venous thrombosis was associated with an increased mortality up to eight years after the thrombotic event. This period of eight years is much longer than described in previous studies. The risk of death was highest in patients with cancer, but also persistently elevated in those without. It was less pronounced in those who had comorbidities at the time of venous thrombosis. In this study we also found that patients with venous thrombosis had a 4-fold increased risk to die of chronic obstructive pulmonary disease (COPD). Subsequently, since we assumed COPD to precede venous thrombosis, we studied COPD as a risk factor for a first venous thrombosis in the MEGA case-control study, reported in chapter 6. COPD was indeed found to be associated with a 3-fold increased risk of a first venous thrombosis. This risk mainly concerned pulmonary embolism and was most pronounced when COPD was severe. In chapter 7 we described the design and first results from the MEGA follow-up study. In the MEGA follow-up study we found that the incidence of recurrence lies between 27.9 and 37.0 per 1000 person-years. This range is similar to that reported in the literature. Men had a higher risk of recurrence than women. The increased risk of recurrence in patients with a first idiopathic venous thrombosis seemed almost restricted to men. In chapter 8 we studied the effect of body height on the risk of a first and recurrent venous thrombosis. Previous studies had only studied first venous thrombosis and reported an increased risk in tall men but not in women. We found an increased risk for both tall and short men and women for a first and recurrent venous thrombosis. For women these risks were slightly higher when these women were not active for a large part of the day.



## Methodological considerations

### Survival bias

The MEGA case-control study could have been affected by survival bias. Survival bias occurs when the exposure is related to survival, and only surviving patients are included in etiologic studies. The mean time between venous thrombosis and inclusion in the MEGA study was 1 month. This time gap was due to the way patients were included, i.e. via the anticoagulation clinics. These monitor outpatient treatment, so patients diagnosed with venous thrombosis, to be registered at an anticoagulation clinic, need to have survived the acute phase of the thrombotic event. This selection of survivors will only have biased the estimates of risk factors for first thrombosis, when these factors were related to mortality as well. For instance, COPD is related to both mortality and venous thrombosis. In this case more patients with venous thrombosis and COPD would die before registration at

the anticoagulation clinic than patients with only venous thrombosis. This would lead to an underestimation of the true effect. Since acute mortality in venous thrombosis is small, we do not expect major effects of this bias, except possibly in patients with malignancies.

**Strength of risk factors for recurrence**

Only a few risk factors are known for a recurrent venous thrombosis and they differ considerably in nature and strength from those for a first venous thrombosis. Part of these differences can be explained because provoking risk factors, such as oral contraceptives, are removed after the first event or because of prophylactic therapy during periods of increased risk such as in case of surgery or pregnancy after the first event. However, not all risk factors are transient or sufficient to warrant prophylaxis, such as malignancy, body height, and genetic risk factors. Furthermore, some risk factors for a first venous thrombosis do not predict recurrence, such as age, and some risk factors selectively affect recurrence, as male sex, as we have shown in chapter 7. When risk factors affect both first and second venous thrombosis the effect on recurrence appears invariably lower than that on first events (e.g. 5 versus 1.3-fold increase for FVL and 7 versus 1.5-fold increase for malignancies). These differences in relative risk can be explained by index event bias or by scale effects, i.e., differences in absolute risks for first and recurrent venous thrombosis.

**Index event bias**

Recurrence research can be affected by a form of selection bias called index event bias. This bias is problematic when etiologic rather than prognostic questions are asked. Due to the selection of cases with a first event, risk factors are differently associated with other risk factors than they are in the general population. For example, one may develop a disease due to either risk factor A or X. In the general population A and X are not associated with each other (figure 1). However, in a group of patients with the disease risk factors A and X will be negatively associated as those with risk factor A are less likely to have X because they developed the disease because of A and vice versa. When for recurrence research patients with a first event are selected, these negative relations exist in this selected population. In theory, when one would study the effect of FVL on recurrence in patients with a first venous thrombosis the effect will be underestimated because in the selected cohort patients will be less likely have other risk factors for thrombosis, compared with the general population. Due to the selection of cases with a first venous thrombosis this association can lead to biased estimates (figure 1). Sometimes risk factors interact with each other, i.e., the joint effect is larger than expected based on the separate effects. When this is the case (and the interaction is supra-multiplicative among patients) among patients the relations between risk factor X and A will be positive and will overestimate the risk of recurrence. Venous thrombosis is a multi-causal disease for which many risk factors interact negatively and positively, and the strengths of these interactions differ among risk factors. Thereby many risk factors and relations between them are unknown. Therefore, it is not possible to predict how this bias would affect the risk factors studied.

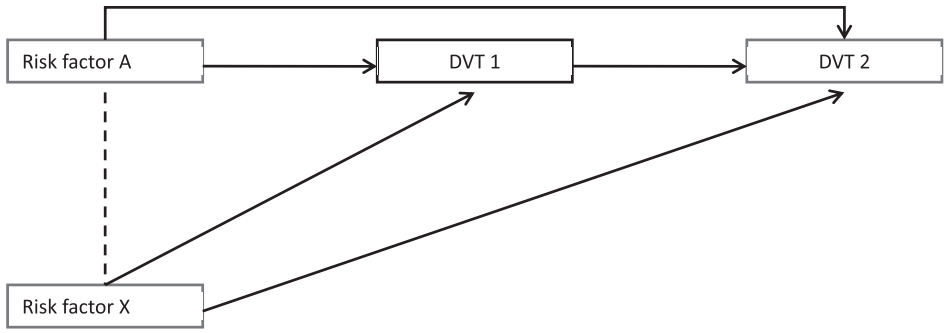


**Figure 1.** Directed Acyclic Graph of index event bias. Due to selection of a collider (DVT1) associations between the risk factors arise that are not causal.

This bias is only a problem when the research question is etiologic or causal. In practice, most recurrence research will be focused on the search for factors that predict the risk of a recurrent event in patients with a first venous thrombosis, to identify those who would benefit most from anticoagulant prophylaxis. However, if targeted interventions on a single risk factor would be possible, e.g., an intervention that would only affect factor V Leiden, the effect of index event bias would be highly relevant.



### Differences in absolute risks

As shown in the table the absolute risk (incidence) of a recurrent venous thrombosis is much higher than of a first event (1 per 1000 versus 30 per 1000 per year). It is relevant to note that these incidences can only be contrasted numerically, for they refer to different populations (e.g., everyone versus those who had a first thrombosis). Individuals who are 'invulnerable' to thrombosis will be in the denominator of risk estimates of a first event, but not of a second event. If there is a difference in the vulnerability of developing the disease in question, the absolute risk for recurrence will be higher in numerical terms than that of a first event. The effect of a risk factor can be expressed as an incidence rate difference (risk difference) or an incidence rate ratio (relative risk). The risk difference is calculated as the absolute difference of two incidence rates, i.e., if a risk factor increases the incidence of first

**Table**

| | | 1st event | | 2nd event | |
|---|---|---|---|---|---|
| Strength | **RR** | **Absolute risk** | **Risk difference** | **Absolute risk** | **Risk difference** |
| Baseline | 1 | 1 per 1000 | | 30 per 1000 | |
| Weak | 2 | 2 per 1000 | 1 per 1000 | 60 per 1000 | 30 per 1000 |
| Moderate | 5 | 5 per 1000 | 4 per 1000 | 150 per 1000 | 120 per 1000 |
| Strong | 10 | 10 per 1000 | 9 per 1000 | 300 per 1000 | 270 per 1000 |

thrombosis from 1 per 1000 person-years to 7 per 1000 person-years, with a risk difference of 6 per 1000 person-years. The relative risk is calculated as the ratio of the incidence rates of those with and those without the risk factor. In the example, the relative risk is 7. The difference in the baseline incidence (in the absence of the risk factor of interest) of first and recurrent events implies that the risk difference and relative risk for first and recurrent event cannot be parallel, i.e., if a factor has the same risk difference for first and recurrent events the relative risk will be largest for first events. This is shown in the hypothetical table, where absolute risks for both a first and recurrent venous thrombosis are shown and the increase in these absolute risks (risk difference) is calculated for constant relative risks of 1, 2, 5 and 10. The absolute risk increases from 1 per 31.5 per year (3% per year) to 1 per 3 (30% per year) for a relative risk of 10 for recurrent venous thrombosis. In other words, when the relative risk is constant. In practice this would mean that for a risk factor with a 10-fold increase in risk for recurrent thrombosis, over 85% of patients with a first venous thrombosis and that risk factor would experience a recurrent event within 5 years.

When we look at the risk differences that are actually observed, these are often larger for recurrent than first thrombosis. So, on an absolute scale, even if relative risks appear smaller, risk factors are often stronger for recurrence than for first events. For example for factor V Leiden, relative risk estimates are 5 for first events and 1.4 for recurrence. This would lead to risk differences of 4 per 1000 (5/1000-1/1000) for first events, and 12 per 1000 for recurrent events (42/1000 – 30/1000). In other words, on an absolute scale the effect of FVL is not smaller for recurrent than first events, but larger.

## Clinical relevance

**Upper extremity venous thrombosis**

Our study on risk factors for recurrence after venous thrombosis of the upper extremity, was the first performed. We showed in chapter 4 that in current practice removal of risk factors, like CVCs, prevents recurrence in these patients. Upper extremity venous thrombosis was strongly related with the presence of malignancies and central venous catheters and was therefore strongly related with death as well. Due to this high mortality among patients with a first venous thrombosis of the upper extremity few patients experienced recurrent events, but the incidence found was as high or higher as for DVT of the leg. Recurrence after venous thrombosis of the upper extremity was related to BMI, location of the first thrombosis and being a woman. Future studies for prevention of recurrence in patients with upper extremity venous thrombosis are most relevant in those patients without catheters and malignancies. For patients with a primary or effort thrombosis of the upper extremity, weight loss and less strenuous exercise with the arms could prevent recurrent events. However, we found that 36% of all recurrences after a venous thrombosis of the upper extremity do not occur in the upper extremities. For these patients the origin might be sought in chronic systemic alterations of the coagulation system.

### Mortality

In chapter 5 we describe an increased risk of death up to eight years after venous thrombosis. This risk was most pronounced in patients with cancer, followed by those with an idiopathic first thrombosis when they were compared to patients with a provoked first thrombosis without malignancy. The resulting decrease in median life expectancy was five years. The clinical implication of this study could be to check or monitor these specific 'healthy' venous thrombosis patients more extensively for other diseases to prevent early death. Candidates for these comorbidities are the additional risks found for several causes of death in chapter 5. Arterial thrombosis has been found in several studies to be related with venous thrombosis. Some studies even suggest venous thrombosis as a risk factor for arterial thrombosis. Possible pathways between these diseases could be atherosclerosis and an inflammatory state or the presence of common risk factors for arterial and venous thrombosis, such as obesity and smoking. Especially the common risk factors can be targeted in clinical practice.

### New risk factors for recurrence

In chapter 8 we found that body height increased the risk of recurrent venous thrombosis. This knowledge provides better insight in the mechanism behind a venous thrombosis. Tall people have taller legs in which stasis can occur more easily. Stasis is one of the three components Virchow described as causes for venous thrombosis. Body height may be good tools for prediction as body height is a fixed factor. This makes body height a perfect candidate for prediction as most other risk factors change over time. However, with fixed factors only a sort of baseline risk of recurrence can be predicted, while the final precipitation of an event must depend on newly acquired factors.

## Future studies

### Difference in risk for men and women

Several studies including ours found differences in risk of recurrence for men and women. In chapter 7 we found a 2-fold increased risk for men compared with women for a recurrent venous thrombosis, which is consistent with the literature on this subject. However, in chapter 4 we found an increased risk for women compared to men for patients with a recurrent event after a first venous thrombosis of the upper extremity. This difference for upper extremity can be explained by the mortality rates found in chapter 4. In this chapter we showed an increased risk of death for all patients; however, this excess risk disappeared for men when patients with malignancy were excluded. The risk remained increased for women. Most patients with malignancy in this study were men. Death due to malignancy is a large competing risk for recurrent venous thrombosis in patients with venous thrombosis of the upper extremity. Most patients with malignancy die within a year and are therefore no longer at risk for recurrence. As this was mainly present in men only women remain at risk for recurrence and therefore a higher risk of recurrence for women compared to men was found. The observation that men

have a two-fold higher risk of recurrence than women after a venous thrombosis of the leg is still not understood. Future studies into the origin of this difference may give more insight in new risk factors and the etiology behind venous thrombosis.

**Prediction models**

Future studies need to be more focused on prediction of recurrence. When the chance of a recurrence can be predicted with some accuracy, recurrence itself and mortality due to bleeding and recurrent events could be largely avoided by targeted prophylaxis. At this moment the focus of most prediction models is to predict recurrent events in patients with a first idiopathic thrombosis. However, with this method a large proportion of patients is ignored. Only one third of thrombotic events are idiopathic and 10 percent of patients with a provoked first venous thrombosis experience a recurrent event within 5 years. This indicates that for a large group of patients removing the known provoking factor is not sufficient to prevent recurrence. Therefore, in future studies the prognosis after provoked thrombosis should be taken into account and possibly contrasted with idiopathic thrombosis to find specific new risk factors for both first and recurrent venous thrombosis. Future prediction models should be time-dependent, for it may matter whether recurrence is predicted shortly after the first event, or after a longer period. The first moment to predict future risk is immediately after the event, but the best moment may be at the time of discontinuation of anticoagulant treatment, which varies between patients. In the studies currently in the literature most parameters are known at time of thrombosis but not at time of discontinuation of treatment. However, the risk profile is likely to change in the time directly following a first thrombosis, e.g. with respect to in oral contraceptive use or smoking habits.

Additional to changing risk profiles, prediction of recurrence is difficult because many patients develop a recurrent event due to different risk factors than present at their first event. This can be shown by the theory of 'causal pies' (figure 2). Every person has different combinations of risk factors that may cause thrombosis. Only when all parts of a pie are present a thrombosis will occur. However, these pies differ between patients, and patients will have several pies that are partly or almost full, and many of the pieces are unknown.


**Figure 2.** Possible causal pies of thrombosis

Predictions would be made on the first completed causal pie a patient had, which we in most cases do not know fully. However, the pie that will cause a recurrent event can in theory contain completely different risk factors than the pie that caused the first event. Therefore, it is difficult to predict which pie will be next to become full for each person. To a large extent, prediction will therefore depend on causes that are part of many causal pies (persistent ones) or that complete many pies (newly acquired ones).

## Conclusions

In this thesis we identified several new risk factors for both first and recurrent venous thrombosis. These factors are useful for prediction models and may improve individualised treatment of patients.

# 10

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# Nederlandse samenvatting

In dit proefschrift worden resultaten van de MEGA en MEGA follow-up studie besproken. In deze onderzoeken zijn nieuwe risicofactoren gevonden voor eerste en recidief veneuze trombose. In hoofdstuk 2 wordt de literatuur met betrekking tot veneuze trombose van de arm besproken. In hoofdstuk 3 is onderzoek gedaan naar stollingsfactoren en bloedgroep als risicofactoren voor een veneuze trombose van de arm. Hierbij werd gevonden dat verhoogde concentraties van factor VIII, Van Willebrand factor, fibrinogeen en bloedgroep niet-O het risico op een trombosearm verhogen. Deze factoren komen overeen met factoren die het risico op een trombose been verhogen. Er zijn echter een aantal factoren beschreven die het risico op een trombosebeen verhogen, waarvoor wij geen relatie vonden met het risico op een trombosearm. In hoofdstuk vier werd onderzoek gedaan naar risicofactoren voor een recidief trombose bij patiënten met een eerste trombose van de arm. Hier werd gevonden dat vrouw zijn, een hoog BMI, maligniteiten en een trombose in een andere vene dan de subclavia een verhoogd risico geven op een tweede trombose. In hoofdstuk vijf wordt de mortaliteit op de lange termijn na een veneuze trombose beschreven. In deze studie werd gevonden dat patiënten met een veneuze trombose tot acht jaar na de trombose een verhoogde kans op overlijden hebben ten opzichte van de bevolking. Dit risico was het sterkst in patiënten die ten tijde van trombose geen bekende comorbiditeiten hadden, behalve patiënten met kanker, die verreweg het hoogste risico op overlijden hadden. In deze studie werd ook gevonden dat patiënten met trombose een vier keer verhoogd risico hebben om te overlijden aan COPD. In hoofdstuk 6 werd onderzocht of COPD ook een risicofactor is voor het krijgen van een eerste veneuze trombose. Hierbij werd gevonden dat COPD voornamelijk een risicofactor is voor longembolieën en in mindere mate voor trombose van het been. Het risico voor een longembolie neemt daarbij ook nog toe met de ernst van de COPD. COPD zou hiermee een risicofactor kunnen zijn voor het ontstaan van een trombus in de long. In het MEGA vervolgonderzoek vonden we een incidentie tussen de 28 en 37 per 1000 persoonsjaren voor een recidief veneuze trombose. Deze range komt overeen met de bestaande literatuur. Daarnaast werd gevonden dat mannen een hoger risico op een recidief veneuze trombose hebben dan vrouwen. Een idiopathische eerste trombose verhoogde ook het risico op een recidief veneuze trombose maar voornamelijk in mannen. Eerdere studies beschreven lengte als risicofactor voor trombose voornamelijk in mannen. In dit proefschrift werd de relatie tussen lengte en eerste en recidief trombose onderzocht in zowel mannen als vrouwen. Voor zowel eerste als recidief trombose verhoogde lang zijn (meer dan 1.85m voor vrouwen en meer dan 2.00m voor mannen) het risico. Ook voor 'korte' mensen, kleiner dan 1.55m, werd een verhoogd risico op trombose gevonden.

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# Curriculum Vitae

Linda Flinterman is op 16 januari 1984 geboren te Delft. In 2002 behaalde zij het VWO diploma aan het Kalsbeek College te Woerden. Aansluitend begon zij aan de studie Biomedische Wetenschappen aan de Universiteit Leiden. Hierbij liep zij stage bij de afdeling Klinische Epidemiologie van het Leids Universitair Medisch Centrum en de afdeling Medische Pharmacologie van het Leiden/Amsterdam Center for Drug Research (LACDR). In augustus 2007 behaalde zij haar Master diploma.

Hierna is zij als promovenda aangesteld op de afdeling Klinische Epidemiologie van het Leids Universitair Medisch Centrum onder leiding van Prof. dr Frits Rosendaal, Dr Astrid van Hylckama Vlieg en Dr Suzanne Cannegieter. Tijdens het promotietraject volgde zij verscheidene epidemiologische cursussen waaronder de Boerhaave cursus "Klinische Epidemiologie" op Schiermonnikoog (2008), de NIHES cursus "Causal Inference" van prof Miguel Hernán in Rotterdam (2010) en de cursus "Causal Inference in Epidemiology" aan de London School of Hygiene and Tropical Medicine (2010).

Zij hield presentaties op nationale en internationale congressen en ontving een Young Investigator Award van de International Society on Thrombosis and Haemostasis (2009) en de Wetenschapsprijs van de Nederlandse Vereniging voor Trombose en Hemostase (2011). In 2011 ontving zij een Bontius Fellowship van de Bontius Stichting voor onderzoek naar de relatie tussen veneuze en arteriële trombose.

Van december 2011 tot februari 2013 is zij werkzaam als geweest bij de afdeling Epidemiologie aan de Universiteit van Aarhus in Denemarken. Onder leiding van Prof. Kim Overvad verrichtte zij onderzoek naar de relatie tussen arteriële en veneuze trombose. Momenteel werkt ze als projectcoördinator van het Zorgprogramma voor Preventie en Herstel, op de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC in Rotterdam, onder leiding van Prof. Ewout Steyerberg.