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# Chapter *2*

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

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## Abstract

**Background**
The reported incidence of recurrent venous thrombosis (VT) varies widely.

**Objectives**
The aim of this study was to estimate the incidence of a recurrent event and the effect of location, age, and sex in a large cohort of patients with a first VT.

**Patients**
We followed 4731 patients with a first VT between 1999 and 2004 (MEGA study) until 2008-2009. Recurrences were adjudicated from self-reported information in questionnaires, anticoagulation clinics, and discharge letters. We calculated incidence rates and hazard ratios (HR) to estimate the effect of various factors on recurrence.

**Results**
673 patients (14.2%) had a recurrent event. The overall incidence rate was 27.9 per 1000 person years (95%CI, 25.8-30.0). The cumulative incidence at 5 years was 11.3%. An idiopathic first thrombosis was a risk factor for recurrence in men and women. Men had a higher risk of recurrence than women regardless of location or the presence of a provoking factor (HR overall: 2.2 (95%CI, 1.9-2.6). Age did not affect recurrence risk.

**Conclusions**
This study provides precise and valid estimates of recurrence risk, which is substantial at about 3% per year. For duration of treatment, sex, type of first event and location of first event may need to be taken into account.

## Introduction

Venous thrombosis is a multi-causal disease that occurs in 1-3 per 1000 persons per year.[1,2] 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% within five years after the first event.[3-7] Incidence rates of recurrence also vary between studies, from 25 to 46 per 1000 person-years.[5,7] Sources of this variation include definition of recurrence, setting and size of study (clinical versus research setting) and starting point of follow-up.

In contrast to a first event, only few risk factors are known to be associated with the risk of recurrent thrombosis, such as male sex, the presence of a malignancy, and an idiopathic first venous event.[3,5,7-14] Age, which is the strongest risk factor for a first event does not, or only slightly, increase the risk of recurrence.[5,9-13] 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 drawback of a major bleeding risk, which, if it were to be given indiscriminately, 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.[15-18]

A recent study showed that recurrent events do not occur at random sites.[19] The ability to predict the location of recurrence may influence the duration of treatment especially when a pulmonary embolism (PE) as recurrent event is more likely than a deep vein thrombosis (DVT) of the leg.

To address all questions mentioned above, we performed a large follow-up study of almost 5000 patients with a first venous thrombosis. In this study, we estimated risk of recurrence, the separate associations of age, sex, and an idiopathic first thrombosis with the risk of recurrence, 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[20,21], 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. From the cases, patients with a deep venous thrombosis of the leg, pulmonary embolism (PE), or both were included and patients with a venous thrombosis of the upper extremity were excluded from this analysis (follow-up data reported previously [20]). Of 4956 patients eligible for follow-up 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 Medical 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 questions: 1)"Did you have a recurrent event?" and 2)"By which doctor was it diagnosed?" Questionnaires were sent by mail between June 2008 and July 2009. When questionnaires were not returned, 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 included for their first event and, in case they moved house, at the clinic near their new address. Information on 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 or the clinic.

*Definition of recurrence*
A decision rule regarding certainty of diagnosis was made according to the information collected for each patient. Reported recurrences were classified into certain and uncertain recurrences. In this study 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 criteria.
1. A discharge letter was present concluding a diagnosis of recurrence, based on 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 location of either first or second thrombosis was not known, an event was still classified as certain if at least three months had passed since the first thrombosis.

2. A discharge letter was not available (e.g., when the treating physician was unknown) but both the anticoagulation clinic and the patient reported a recurrence at a clearly different location than the first event (contralateral leg, 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 PE or DVT at least six months after the first event.

Uncertain recurrences were defined by four criteria, one of which had to apply:
4. 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.
5. A discharge letter was not available but both the patient and the anticoagulation clinic reported a recurrence within a year after the first event.
6. Information was only available from either the patient or the anticoagulation clinic.
7. A registered cause of death from PE or DVT within six months after the first event.

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

In order to find a range of incidences which includes the true incidence of recurrence, we calculated, as a sensitivity analysis, incidences for all possible recurrences combined (certain and uncertain) and separately for certain recurrences with both starting points of follow-up. Additionally we refined our incidence estimation 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 thrombosis.[14,19]

Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster cast, hormone use (oral contraceptives and hormone therapy) or pregnancy,
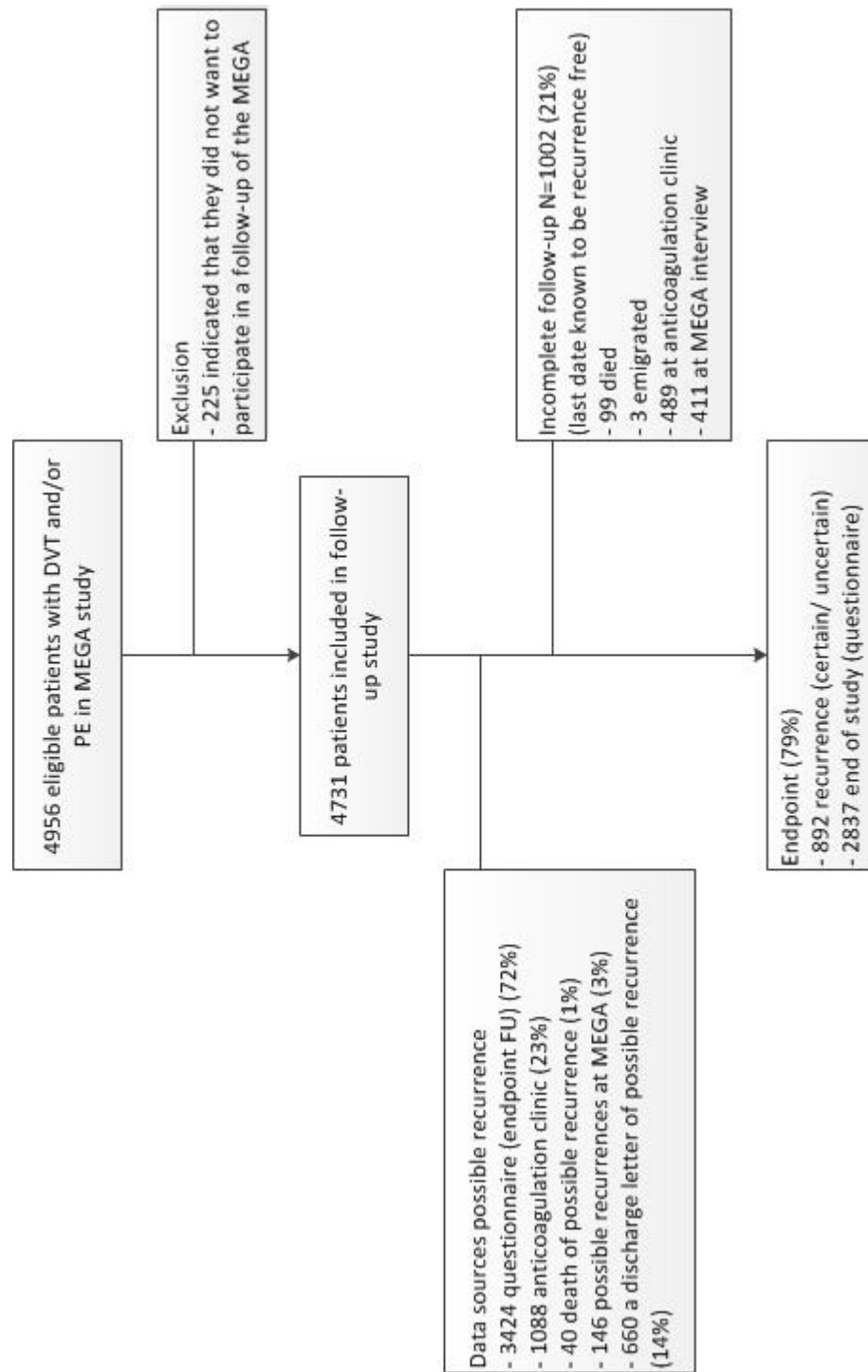
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Exclusion
- 225 indicated that they did not want to participate in a follow-up of the MEGA

4956 eligible patients with DVT and/or PE in MEGA study

4731 patients included in follow-up study

Incomplete follow-up N=1002 (21%)
(last date known to be recurrence free)
- 99 died
- 3 emigrated
- 489 at anticoagulation clinic
- 411 at MEGA interview

Endpoint (79%)
- 892 recurrence (certain/ uncertain)
- 2837 end of study (questionnaire)

Data sources possible recurrence
- 3424 questionnaire (endpoint FU) (72%)
- 1088 anticoagulation clinic (23%)
- 40 death of possible recurrence (1%)
- 146 possible recurrences at MEGA (3%)
- 660 a discharge letter of possible recurrence (14%)

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

all within three months before the event, or puerperium or active malignancy at the time of the event. Kaplan-Meier curves adjusted for competing risks were estimated for men, women, and patients with an idiopathic and provoked first venous thrombosis separately. Incidence rates were calculated for men, women, and idiopathic and provoked cases separately in different age categories to study risk patterns for these three factors.

For the analysis on risk factors and optimal duration of anticoagulation, only certain recurrences were used and uncertain recurrences were censored at the time of reported recurrence. Hazard ratios (HR) were estimated for all potential risk factors, and all HRs were adjusted for age and sex when applicable. All HRs were estimated with follow-up starting at time of first venous thrombosis. The effect of male sex was also studied in a restricted analysis excluding women who used hormones at time of 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 10-year age categories. These effects were studied in all patients and in patients without cancer and life-long anticoagulants separately. These restrictions were done to determine the effect of these risk factors in those without another strong risk factor of thrombosis (cancer) and in those who cannot be treated longer 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 HRs for site of recurrence per site of first thrombosis.

For the analysis of the effect of duration of anticoagulation therapy, patients with malignancies at the time of thrombosis were excluded. Duration of anticoagulation therapy was calculated in months. Survival curves were made for patients who used anticoagulation therapy for 3, 4-6, 7-12, and >12 months. Survival curves were adjusted for competing risks due to death and included only recurrences that occurred after discontinuation of anticoagulant therapy.

Analyses were performed with SPSS version 21.0 (Chicago, Ill) and STATA SE version 12 (Stata Corporation, College Station, Texas) for Windows.

## Results

*Population*
Mean age of patients at time of first venous thrombosis was 48 years and 54% of 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. Total volumes of follow-up were 24 124 and 20 031 person-years respectively. In total 79% of patients (n=3729) had a complete follow-up of whom 2837 filled in the questionnaire and 892 were followed until recurrence. 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 later point in time during follow-up (n=411) (Figure 1).

*Recurrences*
We obtained information about recurrence status from 3757 patients. 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 either post-thrombotic syndrome or suspected recurrences that were subsequently excluded by ultrasound or CT-scan. Therefore, 892 recurrences could be further classified. Of these, 673 patients were classified to have a certain recurrence according to the criteria listed in the Methods section. 593 patients fulfilled criterion 1) for certain recurrence. Fifty-eight patients were identified as a certain recurrence with criterion 2) and 22 patients with criterion 3). 219 patients had an uncertain recurrence of which 32 fulfilled criterion 4), 19 criterion 5), 159 criterion 6), and 9 criterion 7).

*Incidence of recurrence*
When follow-up started at time of first venous thrombosis, we found an incidence of 27.9 per 1000 person-years (95%CI, 25.8-30.0) when only certain recurrences were taken into account. When certain and uncertain recurrences were counted as recurrent events, as a sensitivity analysis, we found an incidence of 37.0 per 1000 person-years (95%CI, 34.6-39.4) (Table 1). These incidence rates corresponded to a 5-year cumulative incidence 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 (95%CI, 28.1-33.0) when only certain recurrences were taken into account and 38.8 (95%CI, 36.1-41.6) per 1000 person-years when both certain and uncertain recurrences were taken into account. When recurrence status was imputed in the group who had uncertain recurrences the incidence of recurrence became 29.4 (95%CI, 27.4-31.7) per 1000 person-years when follow-up started at time of first venous thrombosis and 32.0 (95%CI, 29.6-34.6) when follow-up started after discontinuation of treatment (Table 1).

Recurrence rate was highest during the first 1.5 years, i.e., 54 per 1000 (95%CI, 45-65) person-years at 1 year and 42 per 1000 (95%CI, 33-52) person-years at 1.5 years, and decreased to 25 per 1000 (95%CI, 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 incidences of recurrence stratified by age, sex, and whether the first venous thrombosis was idiopathic or not. Incidence rates were in all instances higher for men than women. No clear effect of age was seen in any of the categories.

Men had a 2.2-fold (95%CI, 1.9-2.6) increased rate of recurrence compared with women (Figure 3, Table 3). After exclusion of women who used hormones, or were pregnant at time of first thrombosis the relative rate increased to a 2.8-fold (95%CI, 2.2-3.6) increased rate in men. Age at time of first venous thrombosis was not associated with an increased risk of recurrence (Table 3).

Patients with a first idiopathic thrombosis had a 2.0-fold (95%CI, 1.7-2.3) increased rate of recurrence compared with patients with a provoked first thrombosis. However, after adjustment for sex this rate ratio diminished to 1.4 (95%CI, 1.2-1.7).

Incidence of recurrent thrombosis was higher in men than in women, regardless whether the first event was provoked or idiopathic, i.e., the incidence after a provoked first event in men: 35.5 per 1000 person-year (95%CI, 29.4-39.5) and in women: 16.5 per 100 person-years (95%CI, 14.2-18.8) and the incidence after an idiopathic first event in men: 47.6 per 1000 person-years (95%CI, 41.7-53.5) and in women: 28.2 per 1000 person-years (95%CI, 20.1-36.3). The increased rate of recurrent thrombosis after an idiopathic first event was present in both men (HR 1.4 (95%CI, 1.1-1.6)) and women (HR 1.7 (95%CI, 1.3-2.5))(Figure 2). Exclusion of patients with cancer and life-long treatment did not lead to more than trivial changes in these estimates (Table 3).

*Location of recurrent and first thrombosis*
Sixty-two percent of recurrences were DVTs, 31% were PEs, 5% had DVT+PE, and 1% of recurrences were in a different location (upper extremity, portal vein, intestines or sinus) (Table 4a). Recurrences occurred more than expected at the same location as the first event (Table 4a). Patients 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 PE. Patients with a first PE were 1.9-fold (95%CI, 1.4-2.8) more likely to suffer a recurrent PE than those with a first DVT or with a DVT+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%, 95%CI, 50%-66%) than a recurrent event in the left leg (Table 4b).

*Anticoagulation therapy for the initial event*
For this analysis, 575 patients with malignancy were excluded as these patients often

**Table 1. Recurrence rates**

**Start follow-up after 1st thrombosis**

| Type of recurrence | N | Person years | Incidence (CI95) | 5 years cum incidence | N men | Incidence men (CI95) | N women | Incidence women (CI95) |
|---|---|---|---|---|---|---|---|---|
| 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 after discontinuation of treatment**

| Type of recurrence | N | Person years | Incidence (CI95) | 5 years cum incidence | N men | Incidence men (CI95) | N women | Incidence women (CI95) |
|---|---|---|---|---|---|---|---|---|
| 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 (years) | Men all | | | Men, first Idiopathic VT | | | Women all | | | Women, first idiopathic VT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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, plastercast or hormone use (oral contraceptives and hormone replacement therapy), and pregnancy within three months before the event, and without active malignancies or puerperium

**Table 3. Risk factors for recurrent venous thrombosis**

| 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 1$^{st}$ 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, plastercast 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.
*Adjusted for age and sex when applicable.

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. Most patients received 4-6 months of anticoagulation treatment after the first venous thrombosis (Figure 3). Patients 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 (30% vs. 25%). Figure 3 shows the cumulative incidence of recurrence over time for four different duration periods of anticoagulation. This Figure shows that the curves for the different durations of anticoagulation therapy run parallel indicating that the risk of recurrence is equal after discontinuation of anticoagulation regardless of duration.

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

| | Recurrence | | | | |
|---|---|---|---|---|---|
| 1$^{st}$ 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 4b. Side of DVT.**

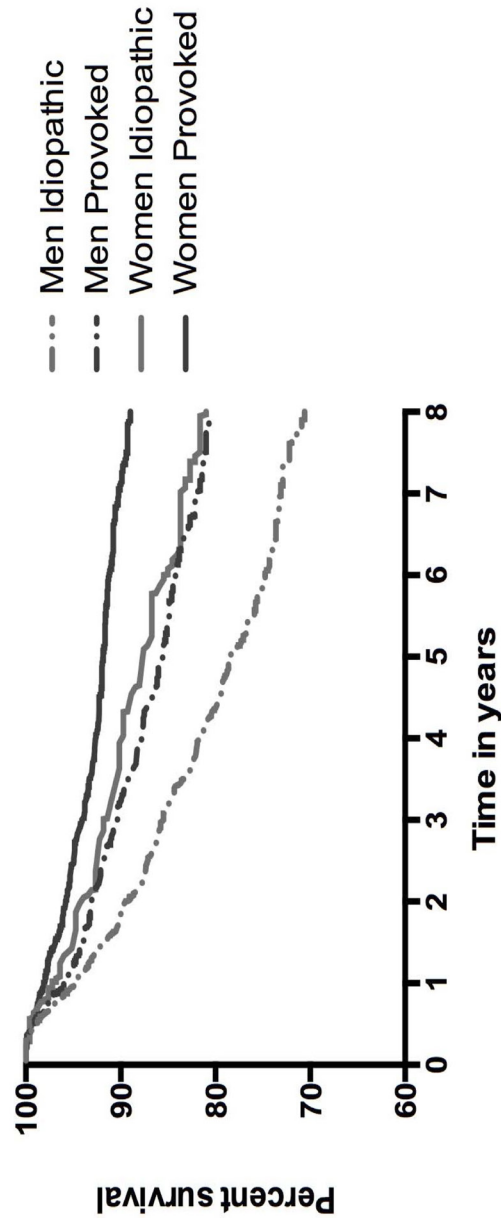| | Recurrence | | |
|---|---|---|---|
| 1$^{st}$ event | Left | Right | Both |
| Left | 79 (50%, CI95 42%-57%) | 78 (49%, CI95 42%-57%) | 2 (1%) |
| Right | 54 (40%, CI95 32%-48%) | 81 (60%, CI95 50%-66%) | 0 |
| Both | 1 | 0 | 0 |

**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 cast 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 caster or minor injuries, oral contraceptive use, hormone replacement therapy use, pregnancy and puerperium.
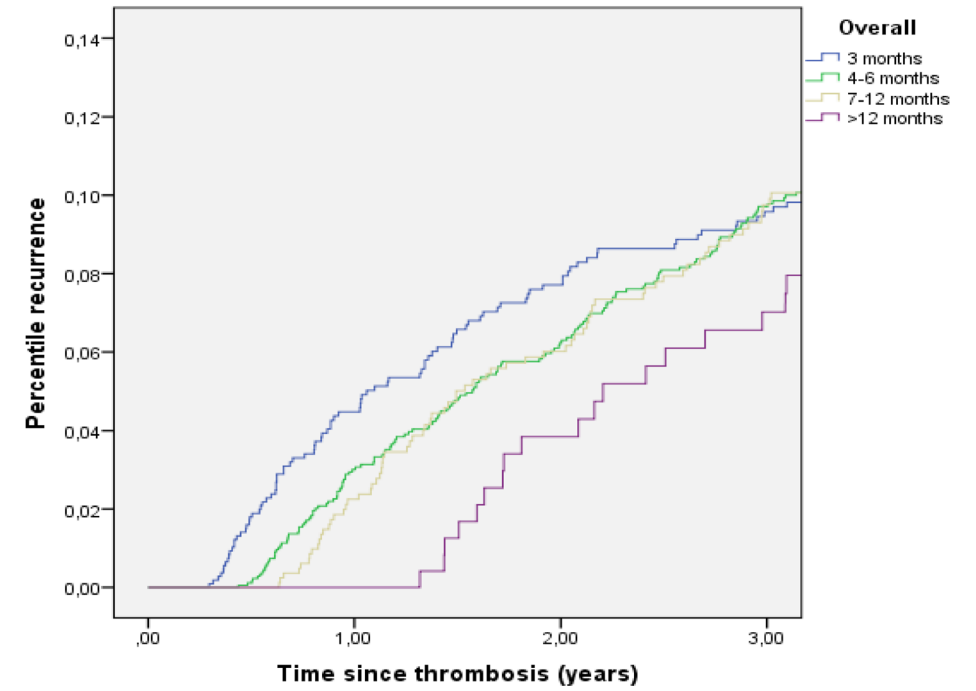


**Figure 3. Cumulative risk of recurrence for different durations of treatment when follow-up started at time of first venous thrombosis.**

| Total N | 1-3 months oac N (%) | 4-6 months oac N (%) | 7-12 months oac N (%) | >12 months oac N (%) |
|---|---|---|---|---|
| 3603 | 1027 (29) | 1637 (45) | 724 (20) | 215 (6) |

- Idiopathic thrombosis was defined as venous thrombosis without surgery, trauma, plaster cast 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 caster or minor injuries.

## 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% after one year. We found male sex to be a risk factor for recurrence with a 2.2-fold increased rate (95%CI, 1.9-2.6). Overall, an idiopathic first thrombosis was associated with a 1.4-fold increased rate (95%CI, 1.2-1.7). Increasing age was not associated with recurrence risk. When we studied different durations of anticoagulation therapy we found no difference in recurrence risk after discontinuation.

To establish the true incidence of recurrence we performed a sensitivity analysis. We found an incidence of 27.9 per 1000 person-years when only certain recurrences were taken into account and 37.0 per 1000 person-years when both certain and uncertain recurrences were taken into account. The range of incidences of recurrent thrombosis we report is similar but more precise than incidences previously reported. [3-6,11,21,22] Additional to small study sizes, the variation in incidence rates found in the literature may be explained by different definitions of start of follow-up (starting at time of thrombosis or at discontinuation of treatment). Both methods of defining start of follow-up are justifiable, but lead to results that should be interpreted differently. To start follow-up at date of first event has the advantage that recurrences during anticoagulation are taken into account. Furthermore, previous studies generally did not take (un)certainty of recurrences 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. 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 results where uncertain diagnoses were counted as recurrence, and in which recurrence status of patients with an uncertain recurrence was imputed. By showing all possible ways of estimating incidence rates, our results can easily be compared with those of other studies.

Recurrent events occurred more often than expected just by chance at the same site as the first thrombosis, i.e., patients with a first PE 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 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 was random. These results suggest that most recurrences are not due to vascular damage or residual thrombosis but may be the result of a more general hypercoagulable state.

When studying the effect of treatment duration, we observed parallel running survival curves. The curves ran parallel because we considered for this analysis only recurrences that occurred after discontinuation of anticoagulation therapy. Obviously, with increasing duration of anticoagulation, discontinuation occurred later during follow-up. This finding implies that the risk of recurrence is not higher after three months of treatment than with longer periods, which is in line with findings from a recent meta-analysis by Boutitie et al.[23]

As has been consistently shown in other studies, we found a two-fold higher risk of recurrence in men than women. For women more modifiable 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. However, men with an idiopathic thrombosis were still at higher risk of recurrence (incidence: 47.6 per 100 person-years; 95%CI, 41.7-53.5) than women with an idiopathic first event (incidence: 28.2 per 1000 person-years; 95%CI, 20.1-36.3), indicating that men have a higher intrinsic risk of thrombosis. Such an intrinsic higher risk in men has also recently been demonstrated by a study of our group where we showed that the risk of a first event is also twice as high in men when hormonal risk factors are taken into account.[23] Most previous studies did not stratify by sex in the analysis of idiopathic versus provoked first venous thrombosis and the risk of recurrence.[5,9,10,13] 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.[5,17,18]

The MEGA follow-up study is the largest single study on risk of recurrent venous thrombosis. While varying estimates of recurrence risk have been reported in literature, the large number of patients and the long duration of follow-up resulting in the identification of almost 700 recurrences, allowed us to estimate the risk of recurrence with great precision, overall and in several subgroups.

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 as described in Table 1. However, an advantage of this clinical setting is that our study gives the optimal estimate of true effects in clinical practice. A second limitation is that we included only patients with a first event who were younger than 70 years of age. Therefore, our results are not generalizable to patients with a first venous thrombosis above 70 years. A third limitation is that for 21% of patients limited follow-up was available. Some 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 anticoagulation clinics. Therefore, in the end 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).

Currently, most guidelines indicate that patients with a provoked first thrombosis may be treated with three months of anticoagulation while those with an unprovoked first event benefit from a longer treatment duration.[24,25] The results of the current study indicate that sex of the patients should be included in the guidelines as all men are at increased risk of recurrence regardless of the type of thrombosis or presence of a provoking factor. Therefore, while women with a provoked event may be treated with anticoagulants for a duration of three months, a longer duration of treatment should be considered in men and in women with an unprovoked first event. Furthermore, as the likelihood of a same type of recurrent event is higher, patients with a first PE may need to be distinguished from those with a first DVT with respect to duration and intensity of treatment, considering that a recurrent PE is a more severe event than a DVT. Future studies should examine this.

In conclusion, in this large study of 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 recurrence risk. An idiopathic first thrombosis is a risk factor for recurrence in men and women, 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.

## References

1. Oger E. Incidence of Venous Thromboembolism: A Community-based Study in Western France. *Thromb Haemost* 2000;83:657–660.
2. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J . Incidence and mortality of venous thrombosis : a population-based study. *J Thromb Haemost* 2007;5:692–699.
3. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Lotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007;92:199–205.
4. Young L, Ockelford P, Milne D, Rolfe-Vyson V, McKelvie S, Harper P. Post-treatment residual thrombus increases the risk of recurrent deep vein thrombosis and mortality. *J Thromb Haemost* 2006;4:1919–1924.
5. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, Clinical Factors, and Recurrent Venous Thrombotic Events. *JAMA* 2005;293:2352–2361.
6. Hansson PO, Sörbo J, Eriksson H. Recurrent Venous Thromboembolism After Deep Vein Thrombosis. *Arch Intern Med* 2000;160:769–774.
7. Eichinger S, Weltermann A, Mannhalter C, Minar E, Bialonczyk C, Hirschl M, Schönauer V, Lechner K, Kyrle PA. The Risk of Recurrent Venous Thromboembolism in Heterozygous Carriers of Factor V Leiden and a First Spontaneous Venous Thromboembolism. *Arch Intern Med* 2002;162: 2357–2360.
8. Murin S, Romano PS, White RH. Comparison of Outcomes after Hospitalization for Deep Venous Thrombosis or Pulmonary Embolism. *Thrombosis* 2002;88:407–414.
9. Baglin TP, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, Palareti G, Poli D, Tait RC, Iorio A. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost* 2010;8:2436–2442.
10. Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP. Comparison of 3 and 6 Months of Oral Anticoagulant Therapy Pulmonary Embolism and Comparison of 6 and 12 Weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001;103:2453–2460.
11. Kearon C, Gent M, Hirsch J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *NEJM* 1999;340:901–907.
12. Schulman S, Rhedin A, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljunberg B, Walter H, Viering S, Nordlander S, Leijd B, Jönsson K, Hjorth M, Linder O, Boberg J. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *NEJM* 1995;332:1661–1665.
13. The columbus investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *NEJM* 1997;337:657–662.
14. Kniffin W, Baron JA, Barrett J, Birkmeyer J, Anderson FA. The Epidemiology of Diagnosed Pulmonary Embolism and Deep Venous Thrombois in the Elderly. *Arch Intern Med* 1994;154:861–866.
15. Baglin TP, Luddington R, Brown K, Baglin CA. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003;362:523–526.
16. Palareti G, Legnani C, Cosmi B, Valdré L, Lunghi B, Bernardi F, Coccheri S. Predictive Value of D-Dimer Test for Recurrent Venous Thromboembolism After Anticoagulation Withdrawal in Subjects With a Previous Idiopathic Event and in Carriers of Congenital Thrombophilia. *Circulation* 2003;108:313–318.

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17. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The Risk of Recurrent Venous Thromboembolism in Men and Women. *NEJM* 2004;350:2558–2563.
18. Baglin TP, Luddington R, Brown K, Baglin CA. High risk of recurrent venous thromboembolism in men. *J Thromb Haemost* 2004;2:2152–2155.
19. White RH, Dager WE, Zhou H, Murin S. Racial and gender differences in the incidence of recurrent venous thromboembolism. *Thromb Haemost* 2006;96:267–273.
20. Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Doggen CJ. Recurrent thrombosis and survival after a first venous thrombosis of the upper extremity. *Circulation* 2008;118:1366-1372.
21. Blom JW, Doggen CJM, Ossanto S, Rosendaal FR. Malignancies, Prothrombotic Mutations and the Risk of Venous Thrombosis. *JAMA* 2005;293:715–722.
22. Bezemer ID, Bare LA, Doggen CJM, Arellano AR, Tong C, Rowland CM, Catanese J, Young BA, Reitsma PH, Devlin JJ, Rosendaal FR. Gene Variants Associated With Deep Vein Thrombosis. *JAMA* 2008;299:1306–1314.
23. Boutitie F, Pinede L, Schulman S, Agnelli G, Radkob G, Julian J, Hirsch J, Kearon C. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ* 2011;342:1–9.
24. NHG-standard Deep Venous Thrombosis (2008). *NHG.* https://www.nhg.org/standaarden/samenvatting/diepe. Accessed January 2014.
25. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic Therapy for VTE disease, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e419S-94S.