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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\textsuperscript{2,3,116}. Venous thrombosis is associated with considerable morbidity and mortality. About 10-20\% of patients develop a recurrence within five years\textsuperscript{2,24,30} and up to 50\% develop post-thrombotic syndrome within several months after the thrombotic event\textsuperscript{129}. The mortality rate after venous thrombosis is about 20\% within one year\textsuperscript{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\textsuperscript{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\textsuperscript{5,7}. 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\textsuperscript{5}. 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\textsuperscript{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.

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
Long-term survival after venous thrombosis

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).

![Figure 1. Kaplan Meier survival curves for patients and controls](image-url)
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, ‡ 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 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    |   |   |   |   |   |   |   |   |         |
| 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. 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. 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. 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. 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.
