Chapter

Risk of recurrent venous thrombosis related to past provoking risk situations: follow-up of a cohort study

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**ABSTRACT**

**Objective:** Strategies targeting at classifying the risk for recurrent venous thrombosis (VT) are needed. We previously hypothesized, by studying a cohort of patients, that those who had ‘survived’ risk situations for VT without developing it would, after a first VT, have a low recurrence risk. Therefore, we re-evaluated the same cohort, now with a longer follow-up.

**Methods:** Patients, after a first confirmed VT event, were followed for an average of 43 months after suspension of anticoagulation. Patients with indication for indefinite anticoagulation were not included. The primary end point was objective recurrent VT.

**Results:** Recurrent VT was recorded in 9% of 378 eligible patients. Patients with a provoked first event and positive past risk situations for VT had an incidence rate of recurrence of 1.26 (95% CI, 0.60-2.31) per 100 patient-years. The incidence rate ratio (IRR) of this subgroup compared to patients with a provoked event without other past risk situations for VT was 0.8 (95% CI 0.2-2.9). This IRR was 2.8 (95% CI, 1.2-6.5) in patients with an unprovoked event and positive past risk situations and 7.1 (95% CI, 3.0-17.1) in patients with an unprovoked event and no past risk situations. When only idiopathic first events were evaluated the IRR was 2.5 (95% CI, 1.1-5.9) for patients without past risk situation compared with those with these history.

**Conclusions:** In this study asking a patient about past exposure to risk factors for VT long before the occurrence of a first VT occurred, could be used to classify patients with a first unprovoked VT at higher risk for recurrence of VT.
INTRODUCTION

Venous thrombosis (VT) occurs in 1-2 per 1000 persons per year [1]. Approximately 30% of patients with VT will experience a recurrent event within the subsequent 5 years [2]. It has been recognized that the presence of a transient or reversible risk factor at the time of VT is associated with a decreased risk of recurrence after anticoagulant therapy is stopped [3]. Therefore, a relatively short period of anticoagulant treatment with vitamin K antagonists is advised for those patients [4]. However, because about 50% of events occur without a clear provoking risk factor, many patients may need long-term or even indefinite anticoagulation after the occurrence of a first event. This treatment may lead to serious side effects such as major bleeding [5]. Therefore, the challenge is to identify new subgroups of patients with unprovoked VT who have a low rather than high risk of recurrence. This would allow shortening the duration of the anticoagulant treatment in these patients.

The thrombosis potential model takes into consideration that the thrombosis potential will drop sharply after the occurrence of a provoked event and that such an individual will not readily cross the thrombosis threshold again, consequently leading to a reduced risk for recurrence [6,7]. Considering this model, we previously hypothesized that those who had ‘survived’ many risk situations without developing VT would, after a first VT, have a low recurrence risk [8]. We observed that the risk for recurrence seemed related with the presence of past risk situations for VT, but as our total event rate for recurrence was low (N=25) and our follow up was relatively short, we could not rule out a possible chance finding. For this reason, we re-evaluated the same cohort of 378 patients, now with a median follow-up of 13 more months.
METHODS

The subjects of the cohort were described previously [8]. The study started in April 2000. Patients were seen in our outpatients’ clinic (Hematology Unit, University Hospital, Universidade Federal de Minas Gerais, Belo Horizonte) or contacted by phone at least once a year. All but 62 patients were contacted by phone or had a clinical evaluation at July 1st 2011. Patients were not systematically screened with ultrasonography since we were only interested in symptomatic recurrent VT. All patients were advised to seek the outpatients’ clinic in case of suspected DVT or PE. A standardized questionnaire with study questions was completed by a professional healthcare assistant in each patient visit. All eligible patients for this study provided written informed consent, and the study was approved by the local ethics committees.

Definitions

The duration of anticoagulation for provoked VT was 3-6 months and for unprovoked VT 6-12 months. Some patients were treated with anticoagulants for longer or shorter time duration mainly because of individual patient preferences. The first episode of VT was considered established if proximal DVT was confirmed by compression ultrasound, and PE by ventilation/perfusion lung scanning or spiral computer tomography scanning. Recurrence was considered established if it was demonstrated by objective techniques at another site than the first event, or at the same site if previously repeated tests showed no residual VT. If the recurrence of DVT was at the same site and we had not previously repeated tests to analyze if there was residual VT, we only considered recurrence when the compressive ultrasound (CUS) showed new thrombus formation in combination with clinical symptoms that were absent previously. Only the objectively demonstrated PE was considered a recurrence. If these criteria were not fulfilled, anticoagulant treatment was withheld and the event was not classified as a recurrent VT. VT (either first or recurrent) was defined as provoked if it had occurred at or within 3 months after exposure to exogenous risk factors including surgery (with more than 30 minutes of duration), trauma leading to hospitalization, immobilization for more than 3 days (hospitalization for clinical reasons), limb immobilization in a plaster cast for more than 7 days, pregnancy, puerperium (until 2 months after delivery), use of oral contraceptives or hormonal replacement therapy (at the time of thrombosis), presence of autoimmune diseases, or active malignancy. In the absence of these risk factors, VT was classified as unprovoked.
During the medical visit, patients were asked about past risk situations for VT at any time of life. The questions were related to use of oral contraceptives or hormonal replacement therapy, pregnancies, surgeries, immobilization with plaster cast in the lower limbs or any hospital admission for clinical reasons for more than 3 days. If they answered positive on any of these risk situations that occurred at least 3 months or more before the event occurred, they were considered as positive for past risk situations for VT. Patients were submitted to CUS or ventilation/perfusion lung scanning or spiral computer tomography scanning around the end of anticoagulation use, and were separated in two groups: those with complete recanalization and those with incomplete or absent recanalization, according to the result of the image test. A family history was considered positive when the patient had one or more first degree relatives (parents, sibling and/or offspring) with VT documented by image tests and/or with history of vitamin K antagonist use due to VT. Follow up period started after vitamin K antagonist were withdrawn and finished at 01.07.2011 or last consultation or death, whichever occurred first.

Statistical analysis

Observation time started after vitamin K antagonists were withdrawn and ended at the time of the recurrence or at the last consultation. Incidence rates of recurrent thrombotic events were calculated as the number of events over the accumulated observation time. Incidences and 95% confidence intervals (95% CI) were calculated under the Poisson distribution assumption. Stratified analyses were used to assess the risk of thrombotic events recurrence by age, sex, idiopathic or provoked first thrombotic event, status of image test around the end of anticoagulation (recanalization), family history of VT and presence or absence of past risk situations for VT. Including patient time before patients were enrolled (i.e. patients who stopped anticoagulant treatment before the first appointment with the researcher) could be problematic as this may create a survivor bias [9]. Therefore, we performed 3 sensitivity analyses to take observation time into close account (Figure 1). Statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago ILL).
RESULTS

The study cohort comprised 378 patients: 291 (77%) were female, 253 (67%) had a provoked VT, the median age at time of the first event was 36 years, 109 (29%) had a distal VT, 175 (46%) had a proximal VT, 71 (19%) had a PE and 22 (6%) had DVT and PE together (these patients were analyzed in the PE group). Oral contraceptives, hormone replacement therapy, pregnancy or puerperium were the most prevalent provoked risk factors appearing 189 times (in 65% of the female population). Ultrasound/duplex was the diagnostic image method in 284 (75%) patients, ventilation/perfusion lung scan in 54 (14%) patients and spiral computer tomography scanning in 40 (11%) patients. Family history for VT was present in 95 patients (25%) and positive past risk situations (patients who experience a well-known risk situation for VT in the past and did not develop thrombosis at that moment) were present in 251 patients (66%). Recurrent VT occurred in 35 patients (9%), trigger factors were present in 6 (17%) patients and the thrombotic event was unprovoked in 29 (83%). The median age at recurrence was 49 years. At a median of 7 months after their initial first event, patients were consulted by the researcher. Only two patients died during the follow up and the causes were unknown. The median follow-up time was 43 months.

Patients with a provoked first event and positive past risk situations had an incidence rate of recurrence of 1.26 (95% CI, 0.60-2.31) per 100 patient-years (Table 1). The incidence rate ratio of patients with a provoked event without other past risk situations for VT compared to patients with a provoked first event and positive past risk situations was 0.8 (95% CI 0.2-2.9). This incidence rate ratio was 2.8 (95% CI, 1.2-6.5) in patients with an unprovoked event and positive past risk situations and 7.1 (95% CI, 3.0-17.1) in patients with an unprovoked event and no past risk situations versus patients with a provoked first event and positive past risk situations. The incidence rate ratio was 2.5 (95% CI, 1.1-5.9) for patients without past risk situation compared with those with these history when only idiopathic first events were evaluated. Sensitivity analyses taking period of follow up into account showed similar findings; i.e. previous risk situations affected recurrent VT risk only in patients with unprovoked first event.

Male sex was associated with an increased risk for recurrence (incidence rate ratio 5.5; 95% CI, 2.8-10.8), as was unprovoked first VT (incidence rate ratio, 4.1; 95% CI, 2.1-8.1). Residual vein thrombosis was a risk factor for recurrence (incidence rate ratio, 2.2; 95% CI, 0.9-5.4), although presented broad confidence intervals (Table 2). Patients with a positive family history had an incidence rate ratio for recurrence of 1.3 (95% CI, 0.6-2.6) compared with patients with a negative family history of VT. Patients older than 40 years with an unprovoked first event had an incidence rate ratio of 0.9 (95% CI, 0.4-2.1) for recurrence compared with patients younger than 40 with an unprovoked first event.
DISCUSSION

We have re-evaluated a cohort of 378 patients with a first confirmed VT event for recurrent VT and concluded that previous risk situations for VT affected recurrence risk only in patients with an unprovoked first event. To our knowledge, this is the first approach to explore past risk situations as a risk factor for VT.

This incidence rate ratio for recurrence was 2.8 in patients with an unprovoked event and positive past risk situations and 7.1 in patients with an unprovoked event and no past risk situations when compared with patients with a provoked first event and positive past risk situations. Thus, collecting information about risk situations for VT that took place long before the occurrence of a first thrombotic event seems to add information about the risk for recurrence when the event was unprovoked.

Results from this cohort study are in agreement with other studies, in which patients with first provoked VT have a lower risk of recurrence than those with unprovoked events [10,11]. Risk situations for VT that occurred in the past yet did not result in VT at that time were noted in 66% of patients. The high rate of positive responders to this question provided a large group that, according to our hypothesis, could also be at lower risk of recurrence compared to those who experienced their first event without ever having had a venous thrombotic risk situation. However, we could only observe this when the first event was unprovoked.

The young age of patients enrolled in our study (median age 36 years) clearly shows that the cohort does not represent a normal distribution of patients with first VT, as the median age at onset of a first venous thrombotic event in the community is 62 years [12]. To test whether selection bias influenced our relative risk estimates, we created subgroups to compare whether our results are similar to cohorts that included consecutive patients from normal populations [2,3]. It turned out that these risk estimates were similar to those of general populations.

In our study, we also found that the risk of recurrent VT was higher in men than in women, as has been shown by others [13,14]. Furthermore, age an important risk factor for a first episode of VT, was not a risk factor for recurrence in this study. This has also been reported by other studies [13,15]. Residual vein thrombosis seems to be a risk factor for recurrence [16]. This finding was confirmed in our study although it had broad confidence interval (incidence rate ratio 2.2; 95% CI, 0.9-5.4). Nevertheless, the point estimate is similar to a larger study (n= 538) that also explored this question [16,17]. Even though, the difficulty in the standardization of residual thrombosis is always a problem in these studies and our study.
Few studies have reported on positive family history as a risk factor for recurrence, but the few that did report no influence on recurrence risk [18]. This is also in agreement with our findings.

Some methodological aspects of our study warrant further comments. First, although the absolute risk of VT recurrence was high in our study (2.09 per 100 person years), it is similar to absolute risks of recurrence found in the community [11,13]. Second, as the total number of recurrences was low (n=35), it was difficult to carry out a multivariate analysis. However, stratified analysis demonstrated results that were in agreement with the literature. Third, patients with distal vein thrombosis were included in this study although they seem to have a lower probability of recurrence [19,20]. Finally, because the subgroup analyses performed in this study revealed similar findings to general population studies, we believe that the main results of the present study (i.e. that past VT risk situations decrease recurrent VT risk) are generalizable to other cohorts. Nevertheless, at least one other cohort study should confirm our findings before implications from a clinical level can be inferred from our findings, and such study should also include patients more representative for a general population.

In conclusion, in this study asking a patient about past exposure to risk factors for VT long before the occurrence of a first VT occurred, could be used to classify patients with a first unprovoked VT at higher risk for recurrence of VT.
REFERENCE LIST


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<tr>
<th>First event Type</th>
<th>Past risk factor situation</th>
<th>Observational years</th>
<th>Median age at first event</th>
<th>Number of events</th>
<th>IR per 100 PY (95% CI)</th>
<th>IRRatio (95% CI)</th>
<th>IRRatio † (95% CI)</th>
<th>IRRatio * (95% CI)</th>
<th>IRRatio # (95% CI)</th>
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<td>Provoked</td>
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<td>796</td>
<td>35</td>
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† Model A
* Model B
# Model C

IR denotes, incidence rate; PY, patient years; CI, confidence interval.
Table 2: Venous thrombosis in different subgroups

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<th>Observational years</th>
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<th>Number of events</th>
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<th>IRRatio (95% CI)</th>
<th>IRRatio † (95% CI)</th>
<th>IRRatio * (95% CI)</th>
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<td>Female (n=291)</td>
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<td>15</td>
<td>1.11 (0.62-1.83)</td>
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<td>Male (n=87)</td>
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<td>20</td>
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<td>Provoked (n=253)</td>
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<td>13</td>
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<td>Unprovoked (n=122)</td>
<td>485</td>
<td>45</td>
<td>22</td>
<td>4.54 (2.84-6.87)</td>
<td>4.1 (2.1-8.1)</td>
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<td>Complete (n=131)</td>
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<td>6</td>
<td>1.11 (0.41-2.41)</td>
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<td>2.42 (1.38-3.93)</td>
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<td>Absent (n=275)</td>
<td>1195</td>
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<td>23</td>
<td>1.92 (1.22-2.89)</td>
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<tr>
<td>Present (n=95)</td>
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<td>11</td>
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<td>&lt; 40 (n=43)</td>
<td>164</td>
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<td>&gt;40 (n=79)</td>
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† Model A
* Model B
# Model C
‡ Data were missing for some patients in these subgroups.
IR denotes, incidence rate; PY, patient years; CI, confidence interval.
The sensitivity analysis was aimed to take observation time into account. In model A, observation time started at enrollment (and when vitamin K antagonists were withdrawn) and ended at time of recurrence or last appointment. In model B, the follow-up time started when vitamin K antagonists were withdrawn and ended at the time of recurrence or July 1st 2011, whichever occurred first. In model C the follow-up time started at the time of enrollment (and when vitamin K antagonists were withdrawn) and ended at the time of recurrence or July 1st 2011, whichever occurred first.