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Title: Venous and arterial thromboembolism: prevention and prognosis  
Issue Date: 2015-10-27
Chapter 7

Risk of atherothrombotic events in patients after proximal deep-vein thrombosis

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Blood Coagul Fibrinolysis 2014; 14: epub ahead of print
ABSTRACT

Introduction
Several studies showed elevated incidences of atherothrombotic events (ATE) in patients with unprovoked venous thromboembolic events (VTE). This association remains understudied in patients presenting with deep vein thrombosis (DVT). We evaluated the incidence of ATE in patients with DVT and compared it to patients with provoked DVT and controls without DVT.

Methods
Patients with compression ultrasonography (CUS) proven unprovoked DVT, provoked DVT, and symptomatic patients, in whom DVT was excluded by CUS, were followed and scored for the occurrence of ATE.

Results
170 patients with provoked, 74 patients with unprovoked DVT and 991 patients without DVT were included. During follow-up 128 ATE occurred (incidence 6.5/100 patient-years). Adjusted hazard ratio (HR) was not different between patients with DVT and without DVT (1.4; 95%CI 0.76-2.4). In contrast, patients with unprovoked DVT suffered ATE more frequent than provoked DVT patients (3.16; 95%CI 1.1-9.1) and control patients (HR 2.8; 95%CI 1.3-5.7). Notably, when fully adjusted for known ATE risk factors the risk differences between controls, provoked and unprovoked DVT patients diminished: HR 1.1 (95%CI 0.47-2.5) and 1.7 (95%CI 0.80-3.6) respectively.

Conclusion
Our study showed that risk of ATE in patients with unprovoked DVT was higher than in patients with provoked DVT or control patients. Interestingly, after full adjustment for multiple known risk factors, the significant difference between unprovoked DVT patients and provoked DVT patients or control patients diminished. This implicates that the correlation between ATE and DVT is non-causal and the measured cardiovascular risk factors are confounders in this correlation.
INTRODUCTION

Several studies have observed an increased risk of atherothrombotic events (ATE) after a diagnosis of venous thromboembolism (VTE) of unknown origin (unprovoked) (1-4). A meta-analysis by Becattini et al. (5), showed an incidence rate ratio (IRR) of 1.87 for the risk of ATE in patients with unprovoked VTE when compared to healthy controls and an IRR of 1.86 for the risk of ATE in unprovoked VTE when compared to patients with VTE of known origin (provoked). Three of the studies included in this meta-analysis concerned patients with pulmonary embolism (PE) (3, 6, 7), while only one study examined the incidence of ATE after deep vein thrombosis (DVT) (3). In the latter population-based cohort study, the relative risk for overall ATE in the first year after VTE was higher in unprovoked PE patients than in unprovoked DVT patients (2.84 vs 1.87) when compared to population controls and when population controls were compared to provoked PE and provoked DVT, the relative risk was 2.28 and 1.82 respectively (8). Importantly, in that study, the incidence of ATE in patients with DVT had been compared with the incidence in population controls without VTE, who may have a lower a priori risk for arterial disease than patients with established VTE. Moreover, due to the study design, Sorensen et al. were unable to adjust for patients’ characteristics and known individual cardiovascular risk factors. Therefore, our goal was to further explore the association between DVT and ATE by including a control population with more similar baseline characteristics than population controls and to collect their individual cardiovascular risk factors. Therefore we selected a group of consecutive patients presenting to our hospital who were clinically suspected of having DVT, but in whom DVT was ruled out by compression ultrasonography (CUS) as a control group. In this prospective cohort study, we assessed and compared the incidence of ATE in patients with a first episode of CUS confirmed proximal DVT with the ATE incidence of patients in whom DVT was suspected but ruled out. Further, we repeated this analysis for patients with provoked and unprovoked DVT separately.

METHODS

Study design
A prospective cohort study was conducted to define the risk of ATE and the event-free survival in patients with a first unprovoked and/or provoked proximal DVT compared to control patients without a medical history of VTE in whom DVT was suspected but ruled out. Primary study endpoints were new episodes of confirmed VTE and ATE, the latter defined as myocardial infarction, ischemic stroke, transient ischemic attack, intermittent claudication, carotid endarterectomy, unstable angina, coronary artery bypass grafting,
peripheral arterial angioplasty, bypass or death of unknown cause in the period from diagnosis of DVT until 31-12-2010.

**Patients**

All in- and out-patients in our hospital with clinically suspected DVT between July 2002 and December 2005 were eligible for inclusion. Their medical charts were searched for the occurrence of study endpoints at the end of the follow-up period. Whenever a patient had died before December 2010, the pathology report, whenever available, was examined for date and cause of death. This was double checked with data from the Office of National Statistics of the Netherlands. The surviving patients were contacted by mail and requested to complete a questionnaire with questions regarding medical history, smoking status, medication use and current clinical condition. In case the resubmitted questionnaires contained missing data, we contacted the patients by telephone. Patients who did not respond to our first request were sent a reminder. If patients could not be reached, the last medical report of their treating general practitioner was used to complete our database. In case of a reported episode of VTE or ATE during the follow-up period, information regarding diagnosis, treatment regimen and treatment time was collected. The study protocol was reviewed and approved by the Institutional Review Board of the Leiden University Medical Centre (LUMC).

**Patients with a first acute DVT**

The diagnosis of proximal DVT was based on non-compressibility in the popliteal, femoral and/or iliac veins on compression ultrasonography (CUS). Data on risk factors for DVT were derived from the original medical charts. Unprovoked DVT was defined as DVT occurring in the absence of risk factors: active malignancy, immobility for more than three days or a recent long flight (at least 4 hours), recent surgery or fracture of lower extremity, pregnancy or peri-partum period, hormone replacement therapy and use of oral contraception. Patients diagnosed with acute DVT were initially treated according to hospital policy with low-molecular-weight heparin (LMWH) followed by oral vitamin K antagonists (VKA) for at least 3 months for patients with provoked DVT and at least 6 months for patients with unprovoked DVT. Because therapy with VKA reduces the risk for myocardial infarction patients with an alternative indication for VKA therapy, in whom these anticoagulants could not be withdrawn after a 6-month treatment period, were excluded from this analysis.

**Patients in whom DVT was suspected but ruled out**

The control population consisted of patients in whom a first DVT was clinically suspected but ruled out by serial CUS or CUS with a normal D-dimer test. They were not treated
with anticoagulant drugs. As with the proven DVT patients, those with an alternative indication for oral anticoagulation were excluded from this analysis.

**Statistical analysis**

Baseline characteristics are given as mean ± standard deviation (SD). Nominal data are presented as the number of patients (N) and the percentage in the study cohort (%). The incidence of ATE in patients with provoked and unprovoked DVT compared to patients in whom a DVT was clinically suspected but ruled-out by CUS was assessed. Cumulative event rates were estimated using a Kaplan-Meier life-table. To rule out the effect of VKA on the incidence of ATE, the start date was set at the day of VKA cessation. Hazard ratios (HR) were calculated using a Cox proportional hazard model. These were adjusted for known confounders including sex, age, malignancy, positive smoking status, hypertension, diabetes and hypercholesterolemia and a previous history of ATE. Patients with (recurrent) thrombosis or non-vascular death were censored in the analysis. Analysis was performed using SPSS version 14.0 (SPSS Inc, Chicago, IL).

**RESULTS**

**Patients**

In a total of 1425 patients, the presence of acute DVT was suspected during the inclusion period. Because of a prior history of acute VTE, 190 (13%) patients were excluded from further analysis. From the remaining 1235 patients, 244 (20%) were diagnosed with and treated for DVT, leaving 991 patients (80%) without DVT as control population. Alternative diagnosis in these latter patients without DVT included Baker’s cyst, thrombophlebitis, cellulitis, erysipelas, intramuscular bleeding and varicose veins.

Baseline characteristics of the study population are depicted in Table 1. There were significantly more females in the provoked DVT and control groups than in the unprovoked DVT group. Provoked DVT patients were significantly younger than the other study patients and a history of ATE was significantly less prevalent in unprovoked DVT patients. There was no difference within the study groups for the presence of diabetes, hypercholesterolemia and smoking. The total number of patient-years (py) was 5882 in the entire population, 5169 py in the control patients, 482 py in the patients with provoked DVT and 231 py in the patients with unprovoked DVT. The median follow-up was 6 years.

**Atherothrombotic Events**

A total of 128 fatal and non-fatal ATE occurred during the study period in a total of 384 person years (incidence 6.5/100 py). No significant difference was found in event free
survival between all DVT patients compared to control patients without DVT (figure 1) (HR 1.4; 95%CI 0.80-2.5). When adjusted for age, sex, smoking, active malignancy, hypertension, diabetes, hypercholesterolemia and a history of a prior ATE, the HR remained non-significant (1.4; 95% CI 0.76-2.4).

After categorizing the DVT group in patients with unprovoked and patients with provoked DVT, the incidence of ATE in patients with unprovoked DVT was 18/100 py (10 events in 41.6 py), 3.4/100 py in patients with provoked DVT (12 events in 16.4 py) and 6.3/100 py in control patients (106 events in 325.8 py) without DVT. A significant difference was found in the unadjusted event free survival between control patients and patients with unprovoked DVT (HR 2.8; 95% CI 1.3-5.7, figure 2) and the event free survival between unprovoked and provoked DVT patients (H.R.3.16; 95% CI 1.1-9.1, figure 2). The event free survival between patients with provoked DVT patients and control patients was not different (H.R. 0.87; 95% CI 0.38-2.0).

When fully adjusted for known risk factors (age, sex, smoking, active malignancy, hypertension, diabetes, hypercholesterolemia and a history of a prior ATE), the difference in event free survival between controls, provoked and unprovoked DVT patients almost disappeared (provoked vs. control 1.1; 95% CI 0.47-2.5; unprovoked vs. control 1.7; 95%CI 0.80-3.6; unprovoked vs. provoked 1.6; 95% CI 0.52-4.6).

**Venous thromboembolic events**

A total of 46 fatal and non-fatal VTE occurred during the follow-up period. Fifteen control patients without DVT endured a new VTE in a total of 58.9 py (incidence 1.1/100 py). Recurrent VTE occurred in 14 unprovoked DVT patients (total of 29.4 py, incidence 12.7/100 py) and in 17 provoked DVT patients (total of 31.8 py, incidence 6.6/100 py). The

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### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=1235)</th>
<th>Control patients (n=991)</th>
<th>Patients with provoked DVT (n=170)</th>
<th>Patients with unprovoked DVT (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female, %)*</td>
<td>725 (59)</td>
<td>598 (60)</td>
<td>102 (60)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Age (years ± SD)*</td>
<td>56 ± 17</td>
<td>57 ± 18</td>
<td>53 ± 17</td>
<td>59 ± 16</td>
</tr>
<tr>
<td>History of ATE (n,%)*</td>
<td>142 (12)</td>
<td>124 (13)</td>
<td>15 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Active malignancy (n,%)*</td>
<td>221 (19)</td>
<td>157 (16)</td>
<td>64 (38)</td>
<td>-</td>
</tr>
<tr>
<td>Smoking (n,%)</td>
<td>187 (15)</td>
<td>148 (15)</td>
<td>27 (16)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Diabetes (n,%)</td>
<td>110 (9)</td>
<td>96 (10)</td>
<td>7 (4)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Hypertension (n,%)*</td>
<td>375 (30)</td>
<td>309 (31)</td>
<td>39 (23)</td>
<td>27 (37)</td>
</tr>
<tr>
<td>Hypercholesterolemia (n,%)</td>
<td>195 (16)</td>
<td>163 (16)</td>
<td>18 (11)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Number of patient years in follow-up</td>
<td>5882</td>
<td>5169</td>
<td>482</td>
<td>231</td>
</tr>
</tbody>
</table>

*Significantly different; DVT=Deep Vein Thrombosis; SD=Standard Deviation; ATE=Atherothrombotic Event
risk for VTE in follow-up was significantly higher in patients with unprovoked DVT than in control patients (Relative Risk (RR) 12.5; 95% confidence interval 6.3-25) and in patients with provoked DVT than in patients without DVT (RR 6.61; 95% CI 3.4-13). The risk for recurrent thrombosis in unprovoked DVT patients was nearly significant higher than in patients with provoked DVT (RR 1.89; 95% CI 0.99-3.6).

Deaths
A total of 355 study patients died during the follow-up period. The majority (154 patients, 43%) died of cancer, 30 patients (8.5%) died of a myocardial infarction, 24 patients (6.8%) suffered a fatal stroke, 8 patients (2.3%) had fatal PE. The remaining 139 patients (39.2%) died of other reasons, including infections and traumatic events.

![Figure 1. Carotid artery intima-media thickness and blood pressure class](image)

**DISCUSSION**

The results of our study indicate that the risk of ATE in patients with unprovoked DVT was higher than in patients with provoked DVT and in control patients in whom DVT was clinically suspected but ruled-out by CUS. Interestingly, after full adjustment for multiple known risk factors, the significant difference between unprovoked DVT patients and provoked DVT patients or control patients diminished considerably. By demonstrating this, our study extends earlier observations and implicates that the correlation between ATE and DVT is non-causal and that the measured cardiovascular risk factors are confounders in this correlation.
Our study design and study population was different from previous reports analyzing the incidence of ATE after VTE. Only one previous study examined solely the incidence of ATE in DVT patients and compared it to control patients without VTE (3). They found that patients with a DVT had an increased risk for the development of ATE, which was most pronounced during the first year but persisted after 20 years of follow-up. However, this study was performed in a population-based cohort from a nationwide database and nationwide patients were used as controls, which may have a lower a-priori risk for ATE than patients with proven VTE. The inclusion of patients in whom DVT was clinically expected but ruled out by CUS resulted in a control group with more comparable baseline characteristics. In addition, our study is the first study in patients, presenting with proximal DVT of the leg, in which it was possible to adjust for known individual cardiovascular risk factors and to exclude patients using vitamin K antagonists from the analysis.

Our study group has earlier evaluated the risk for ATE after PE, and identical control patients –i.e. in whom PE was suspected but ruled out- were selected to adjust for confounding factors (7). Though our unadjusted results are very comparable to this earlier study, there is an interesting contrast to the PE cohort with regard to the influence of classical ATE risk factors on the adjusted hazard ratio’s for ATE. While the unadjusted as well as adjusted hazard ratios for ATE in unprovoked PE patients were significantly higher compared to provoked PE and control patients, correction of the hazard ratios for traditional ATE risk factors in the DVT cohort resulted in loss of all significant differences. Two possible explanations for this difference between DVT and PE patients seem obvious. First, since the number of patients in the unprovoked DVT cohort is relatively limited, our study could be underpowered for an analysis that includes almost 10 different correction factors. A second possible explanation could be that risk factors -and therefore the pathophysiological mechanism- for PE and DVT are not uniform. For instance, a previous study has shown that, when compared to non-carriers, the relative risk for the occurrence of DVT was 7.0 in factor V Leiden carriers while the relative risk for the occurrence for PE was 2.812. This paradox has also been found in use of oral contraceptives and pulmonary diseases, including asthma, COPD and pneumonia (14-16). In addition, ATE after PE may occur following another more direct mechanism. One could hypothesize that the presence of a thrombus in the pulmonary artery and direct cardiac stress by the pulmonary embolus could lead to cytokine release and local inflammatory reaction which enhances the progression of already present atherosclerotic plaques (17). However, there are no currently published studies that reject or prove this hypothesis. A direct causal effect of DVT on future occurrence of ATE is difficult to explain. Considering this, the large influence of traditional cardiovascular risk factors on the hazard ratios for ATE in patients with unprovoked versus provoked DVT patients and controls might in-
dicate that these risk factors contribute to both ATE as well as VTE, especially in patients with unprovoked DVT.

Strengths of this study include the fact that we used data from the general practitioner and the Office of National Statistics of The Netherlands in addition to the medical record of our hospital and the questionnaire to score our study endpoints. Therefore no patients were lost to follow-up. Second, we used well defined and serious medical events as study endpoints, which are likely to be recorded and therefore we believe we did not miss out any ATE in follow-up. Third, we had an adequately long follow-up period, with a total number of 5882 patient years. Limitations of our study were, despite the large consecutive sample size, a relatively small number of patients with unprovoked DVT. Second, possible confounding factor including the classical ATE risk factors were only assessed at baseline. Therefore our analyses were not corrected for patients receiving preventive medication for ATE after study inclusion.

In conclusion, our data indicates that patients after unprovoked DVT are at increased risk of ATE compared to patients after provoked DVT and control patients without DVT, as was previously shown in patients with unprovoked PE. However, full adjustment for several well established ATE risk factors diminished these findings. These results raise the question whether the known risk factors for ATE and VTE attribute equally in PE and DVT patients and contradict a causal relation between ATE and VTE. Large prospective trials are needed to identify the underlying mechanism in both PE and DVT patients for developing ATE complications and to identify an adequate treatment regimen for future arterial and venous complications in patients presenting with a first VTE. This treatment could include vitamin-K antagonists, direct factor Ila or Xa inhibitors, aspirin or statins.
REFERENCES


