Recurrent Venous Thromboembolism After Deep Vein Thrombosis

Incidence and Risk Factors

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**Background:** The recurrence rate after deep vein thrombosis (DVT) is high and the risk factors for recurrent thromboembolic events have only been investigated on a small scale.

**Objectives:** To estimate the cumulative incidence of recurrent venous thromboembolic events after a first or a second DVT and to identify possible risk factors for recurrent venous thromboembolism.

**Methods:** We prospectively followed up 738 consecutive patients with an objectively verified symptomatic DVT for 3.7 to 8.8 years. Medical records and death certificates for all patients were reviewed during follow-up and recurrent DVT and pulmonary embolism were registered.

**Results:** The 5-year cumulative incidence of recurrent venous thromboembolic events was 21.5% (95% confidence interval [CI], 17.7%-25.4%) after a first DVT and 27.9% (95% CI, 19.7%-36.1%) after a second DVT. The 5-year cumulative incidence of fatal pulmonary embolism was 2.6% (95% CI, 1.1%-4.1%) after a first DVT. Proximal DVT (relative risk [RR], 2.40; 95% CI, 1.48-3.88; \(P<.001\)), cancer (RR, 1.97; 95% CI, 1.20-3.23; \(P<.001\)), and history of a venous thromboembolism (RR, 1.71; 95% CI, 1.16-2.52; \(P<.01\)) predicted an independently increased risk of recurrent events in multivariate survival analysis. Postoperative DVT (RR, 0.27; 95% CI, 0.13-0.55; \(P<.001\)) and a long duration of oral anticoagulation therapy (RR, 0.95; 95% CI, 0.92-0.98; \(P<.01\)) involved a smaller risk of recurrent events. Sex, age, initial antithrombotic therapy, or immobilization did not affect the risk of a recurrent event.

**Conclusions:** The recurrence rate after a symptomatic DVT is high. Patients with proximal DVT, diagnosed cancer, short duration of oral anticoagulation therapy, or a history of thromboembolic events had a higher risk of recurrent events, while patients with postoperative DVT had a lower recurrence rate. This knowledge could help identify patients who might benefit most from prolonged prophylactic treatment in various risk situations.

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Deep vein thrombosis (DVT) is a common disease that occurs in most medical disciplines. The estimated yearly incidence of symptomatic DVT of the lower extremities is 0.5 to 1.6 per 1000 urban inhabitants.\(^1\)\(^-\)\(^3\) This is probably an underestimation of the true incidence, as many venous thromboembolic events (VTEs) are asymptomatic.

The short-term outcome for patients with acute DVT of the leg has been studied extensively, while the long-term clinical course is less well investigated. Recent studies have indicated a high incidence rate for recurrent VTE after a first DVT.\(^4\)\(^-\)\(^7\) Preventive actions are important, since a recurrence of DVT, especially in the ipsilateral leg, may increase the risk of a postthrombotic syndrome\(^7\) and recurrent pulmonary embolism (PE) may be fatal.\(^8\)

The optimal duration for prophylactic anticoagulation therapy after DVT is still controversial and the risk of recurrent events must be balanced against the risk of bleeding during anticoagulation therapy.\(^9\) It would be of great clinical importance if we could identify more effectively patients with the highest risk of a recurrent DVT or PE. Previous studies of patients with recurrent VTEs have been limited in sample size and follow-up time. The known risk factors for a recurrent event are idiopathic thrombosis,\(^4\)\(^,\)\(^7\) cancer,\(^7\)\(^,\)\(^10\) and a short duration of oral anti-coagulant therapy.\(^6\) Two studies have indicated a higher recurrence rate among younger subjects compared with older patients with DVT.\(^3\)\(^,\)\(^10\)
PATIENTS AND METHODS

STUDY POPULATION

The present study consists of consecutive patients who were hospitalized and treated for DVT at the Medical Department, Sahlgrenska University Hospital-Ostra, Göteborg, Sweden. Patients were included during a 5-year period from March 1988 to April 1993. The inclusion criteria were an objectively verified, symptomatic DVT in the leg or arm, diagnosed by phlebography or by color duplex ultrasonography. All phlebographies were performed in a standard fashion as ascending contrast venography.11 Nonionic, low osmolar contrast media (100 mL of iopromide or iohexol) were used. A diagnosis of DVT was based on direct criteria (constant filling defects or visualization of the top of the thrombosis). Diagnoses of a DVT with ultrasound were performed using an ultrasonographer (Acuson 128; Acuson Corporation, Mountain View, Calif) and were based on the lack of apposition on the venous wall during compression maneuvers. The presence or absence of venous flow augmentation was assessed by color-flow images and Doppler waveform analysis.

Thromboses of the legs were categorized in 6 levels according to the upper extension of the thrombus: level 1, thromboses in the calf muscle veins; level 2, in at least 1 branch of the 3 paired deep calf veins (anterior tibial vein, posterior tibial vein, or fibular vein); level 3, in the popliteal vein; level 4, in the femoral veins; level 5, in the iliac vein; and level 6, in the inferior caval vein. A thrombosis was defined as “distal” (level 1 or 2) or “proximal” (level 3 or above).

ANTITHROMBOTIC THERAPY

Patients were treated with anti-thrombotic therapy according to local clinical practice. The standard initial treatment was unfractionated heparin intravenously in combination with oral anticoagulation for at least 5 days and until the target range of the prothrombin time was achieved. Patients with a large proximal DVT (levels 5 and 6) were considered for surgical thrombectomy or thrombolytic therapy followed by treatment with unfractionated heparin. Thrombolytic therapy was given in the form of streptokinase intravenously either by continuous infusion for 1 to 3 days, or as ultra-high doses (3-9 million international units) of streptokinase given during a 2-hour infusion.12 Some patients were initially treated with recombinant hirudin (HBW 023) in a clinical trial.13 Oral anticoagulation using either dicumarol (Apekumarol; Ferrosan, Malmö, Sweden) or warfarin sodium (Waran; Nycomed, Oslo, Norway) was usually started at the same time as the initial antithrombotic therapy. Oral anticoagulation was monitored at a central unit located at one of the two hospitals in Göteborg. The target range for the international normalized ratio was 2.0 to 3.0. The duration of oral anticoagulation therapy was determined by the treating physicians on follow-up visits. Most patients were followed up at the thromboembolic unit (Sahlgrenska University Hospital-Ostra). Local clinical practice during the study period was 3 months of prophylactic anticoagulation treatment after a distal DVT and 6 months after a proximal or first recurrent DVT.

FOLLOW-UP

Patients who died before discharge from the hospital, or within the first month after a diagnosis of DVT, were excluded from the follow-up study, as were temporary visitors and emigrants. All the medical records were individually and systematically reviewed by one of us (J.S.) and all the recurrent events were registered. A registry of all the hospital discharge diagnoses from all the hospitals in Sweden were also used to identify patients who were hospitalized outside Göteborg and treated for a DVT (International Classification of Diseases, Ninth Revision [ICD-9] code14 451B) or pulmonary embolism (code 413B), up to December 31, 1996. Death certificates were obtained from a Registry of the National Bureau of Statistics in Sweden for all except 2 of the patients who died during follow-up. A recurrent event was defined as an objectively verified hospital discharge diagnosis of DVT or PE or as a fatal PE found at autopsy. Medical records were reviewed for all recurrent events. The clinical follow-up rate during a period of 3.7 to 8.8 years according to recurrent VTEs and death was therefore close to 100%.

STATISTICAL ANALYSIS

All the analyses were performed using SAS software (SAS Institute, Cary, NC). A Kaplan-Meier life-table method was used to calculate the cumulative incidence of recurrent VTEs.15 A second or third recurrent event after the index DVT was not included in the cumulative incidence analyses, except when analyzing the cumulative incidence of fatal PE. The hazard ratio for a recurrent VTE was calculated using a stepwise Cox proportional hazards model.

The aim of the present study was to estimate the cumulative probability of recurrences after a first or second DVT and to identify possible risk factors for these recurrences.

RESULTS

STUDY POPULATION

Seven hundred sixty consecutive patients with a symptomatic DVT were included during the study period. Twenty-two patients were excluded from further analyses as they died during the in-hospital stay or within 1 month of the diagnosis of DVT.

One hundred thirty-six patients had 1 prior VTE, and 11 patients had 2 prior VTEs before the current event. Of these 147 patients, 108 had a prior DVT, 19 had a prior PE, and 20 patients had both DVT and PE prior to the current event. Therefore, 591 patients were discharged alive from the hospital after a first symptomatic DVT, 136 patients with a symptomatic DVT as a second VTE, and 11 patients with a DVT as a third VTE.

CLINICAL CHARACTERISTICS

Table 1 shows the clinical characteristics of patients with DVT as a first or recurrent event. The mean age was 66 years (range, 17-95 years). There were 360 men and 378
women in the study. A DVT in the left leg or arm was more frequent than in the right (415 vs 322), while 1 patient had a DVT in both legs. The DTVs were diagnosed by phlebography in 702 patients (95.1%). There were 237 distal and 482 proximal DVTs in the leg, while 19 patients had a thrombosis in an arm vein. One hundred twenty-eight patients (17.3%) had known cancer when they had a DVT in an arm vein. One hundred and thirty-two patients (17.1%) were pregnant or within 2 weeks post partum. These patients were classified in the immobilized group in the multivariate analysis.

ANTITHROMBOTIC THERAPY

Table 2 shows the antithrombotic treatment among patients with a first or recurrent DVT. Unfractionated heparin was used intravenously as the initial treatment in 570 patients (76.1%). Heparin was used intravenously as the initial treatment in 644 patients (87.3%), thrombolytic therapy in 43 patients (6.0%), surgical thrombectomy in 9 patients (1.3%), and thrombectomy in 10 patients (1.4%). There were 237 distal and 482 proximal DVTs in the leg, while 19 patients had a thrombosis in an arm vein. One hundred twenty-eight patients (17.3%) had known cancer when they had a DVT in an arm vein. One hundred and thirty-two patients (17.1%) were pregnant or within 2 weeks post partum. These patients were classified in the immobilized group in the multivariate analysis.

Table 1. Clinical Characteristics of Patients With Symptomatic Deep Vein Thrombosis (DVT) as a First or Recurrent Venous Thromboembolic Event

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First DVT (n = 591)</th>
<th>Recurrent DVT (n = 147)</th>
<th>All DVT (N = 738)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>66 (17-92)</td>
<td>67 (20-95)</td>
<td>66 (17-95)</td>
</tr>
<tr>
<td>Men/women</td>
<td>279/312</td>
<td>81/66</td>
<td>360/378</td>
</tr>
<tr>
<td>Side of DVT</td>
<td>256/334/1</td>
<td>66/81/0</td>
<td>322/415/1</td>
</tr>
<tr>
<td>(right/left/bilateral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic method, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebography</td>
<td>559 (94.6)</td>
<td>143 (97.3)</td>
<td>702 (95.1)</td>
</tr>
<tr>
<td>Ultrasound/duplex</td>
<td>32 (5.4)</td>
<td>4 (2.7)</td>
<td>36 (4.9)</td>
</tr>
<tr>
<td>Upper level of DVT, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle vein</td>
<td>50 (8.5)</td>
<td>12 (8.2)</td>
<td>62 (8.4)</td>
</tr>
<tr>
<td>Deep calf vein</td>
<td>138 (23.4)</td>
<td>37 (25.2)</td>
<td>175 (23.7)</td>
</tr>
<tr>
<td>Popliteal vein</td>
<td>57 (9.6)</td>
<td>19 (12.9)</td>
<td>76 (10.3)</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>221 (37.4)</td>
<td>57 (38.8)</td>
<td>278 (37.7)</td>
</tr>
<tr>
<td>Iliac vein</td>
<td>103 (17.4)</td>
<td>21 (14.3)</td>
<td>124 (16.8)</td>
</tr>
<tr>
<td>Caval vein</td>
<td>4 (0.7)</td>
<td>0</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Arm vein</td>
<td>18 (3.1)</td>
<td>1 (0.7)</td>
<td>19 (2.6)</td>
</tr>
<tr>
<td>Potential risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>112 (19.0)</td>
<td>16 (10.9)</td>
<td>128 (17.3)</td>
</tr>
<tr>
<td>Surgery, any</td>
<td>101 (17.1)</td>
<td>15 (10.2)</td>
<td>116 (15.7)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>17 (2.9)</td>
<td>1 (0.7)</td>
<td>18 (2.4)</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>56 (9.5)</td>
<td>7 (4.8)</td>
<td>63 (8.5)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (4.7)</td>
<td>7 (4.8)</td>
<td>35 (4.7)</td>
</tr>
<tr>
<td>Immobilization or pregnancy</td>
<td>94 (15.9)</td>
<td>12 (8.2)</td>
<td>106 (14.4)</td>
</tr>
</tbody>
</table>

Three hundred thirty-three patients (45.1%) were treated with oral anticoagulation medication for 3 months or less, 234 patients (31.7%) for 4 to 6 months, and in 150 patients (20.3%), the treatment period was more than 6 months (Table 2).

FOLLOW-UP AFTER A FIRST DVT

All the patients were discharged alive from the hospital. During follow-up, 109 (18.4%) of the 591 patients had a second VTE. Two of the patients had a fatal PE as a third event. There were 84 recurrent DTVs and 14 nonfatal PEs during 2342 observation-years at risk and 13 fatal PEs during 2639 observation-years. The estimated incidence rate of recurrence per 1000 observation-years was 35.9 for DVT, 6.0 for nonfatal PE, 4.9 for fatal PE, and 46.5 for any VTE. Nine patients (1.5%) had recurrent events during ongoing oral anticoagulation (8 DVT and 1 fatal PE). Two hundred forty-six patients (41.6%) died during follow-up. The autopsy rate was 23.6% for all deaths and 62% for patients with a fatal PE. A total of 58 autopsies were performed and 8 of these patients (13.8%) were found to have PE as the primary cause of death.

The cumulative incidence of a recurrent VTE was 7.0% (95% confidence interval [CI], 4.8%-9.1%) after 1 year, 12.1% (95% CI, 9.3%-14.9%) after 2 years, 15.0% (95% CI, 11.8%-18.1%) after 3 years, 17.9% (95% CI, 14.5%-21.3%) after 4 years, and 21.5% (95% CI, 17.7%-25.4%) after 5 years of follow-up (Figure). The cumulative incidence of fatal PE was 2.6% (95% CI, 1.1%-4.1%) after 5 years of follow-up. There were 5 fatal
bleeding events during follow-up. One of these patients was still receiving oral anticoagulation at the time of death.

**FOLLOW-UP AFTER DVT AS A SECOND VTE**

Among the 136 patients with 1 prior VTE, 37 patients developed a second recurrent event (26 DVTs, 9 nonfatal PEs, and 2 fatal PEs) during 618.5 observation-years, while patients with a postoperative DVT had a fatal PE as a fourth event during follow-up. The cumulative incidence of a second VTE was 7.6% (95% CI, 0.27-1.64; P = .007) after orthopedic surgery and 0.67 (95% CI, 0.27-1.64; P = .38) within 3 months after any other surgery.

This large-scale follow-up study of consecutive patients with objectively verified, symptomatic DVT in a leg or an arm showed an increasing cumulative incidence of recurrent VTE from 7.0% after 1 year to 21.5% after 5 years of follow-up for patients with a first DVT and from 7.6% after 1 year to 27.9% after 5 years of follow-up among patients with DVT as a second VTE. In a multivariate survival analysis, we found proximal DVT, cancer, history of VTE, short duration of oral anticoagulation therapy, and nonpostoperative DVT to be independent risk factors for recurrent events.

Previous studies have found rates of recurrent DVT and PE similar to those in the present study. Prandoni et al followed up 355 consecutive patients with a DVT as a first VTE during a 5- to 8-year follow-up period. In that study, the cumulative incidence rate to 6 weeks and 6 months of oral anticoagulant therapy. They found the 2-year cumulative recurrent rate to be 18.1% among patients treated for 6 weeks and 9.5% among patients treated for 6 months. We also found an association between the duration of oral anticoagulant therapy and the rate of recurrent events in the present study.

In the DURAC study, Schuneman et al randomized patients with a first DVT or PE to 6 weeks or 6 months of oral anticoagulant therapy. They found the 2-year cumulative recurrent rate to be 18.1% among patients treated for 6 weeks and 9.5% among patients treated for 6 months. We also found an association between the duration of oral anticoagulant therapy and the rate of recurrent events in the present study.

In the DURAC study, the recurrence rate during 4 years of follow-up after a second VTE was 20.7% for patients assigned to 6 months therapy with oral anticoagu-
studies. The corresponding recurrence rate after a second DVT was 23.5% in the present study.

Two previous studies have indicated a higher recurrence rate among young patients. White et al used a large computer register of almost 37,000 patients hospitalized for DVT in California to study rehospitalization for VTE during 6 months of follow-up. They found young age, malignancy, surgery, trauma, dementia, and long initial hospital stay to be associated with a higher rate of rehospitalization. Beyth et al followed up 124 patients with a first or recurrent DVT for 6 to 8 years. They found recurrent events to be more common among patients aged 65 years and younger. The recurrence rate was also higher among patients with a history of VTE in univariate analysis. Whether their findings persisted in multivariate analysis was not shown. We found no such association between the age of the patient and the rate of recurrences in the present study. The finding that a history of VTE was associated with a higher recurrence rate matches our results, as well as the findings of previous studies.

We found no significant difference in recurrence rate during follow-up between patients with a DVT in the leg or in the arm. There were, however, only 19 cases of arm vein thrombosis included, and our study is too small to address whether arm vein thromboses are associated with a lower recurrence rate compared with DVT in the leg.

In the present study, the estimated incidence rate of fatal PE was 4.9 per 1000 patient-years at risk. A recently published meta-analysis including 25 studies, each with a follow-up time of 3 to 23 months, found the rate of fatal PE to be 3 (95% CI, 1-8) per 1000 observation-years following 3 months of anticoagulant therapy.

The follow-up rate was close to 100% in the present study, which strengthens the results. Patients who died during their hospital stay or during the first month of follow-up were excluded from the analyses, as we wanted to study the long-term risk of recurrent events. So, all the patients were discharged alive. There is always a risk of overdiagnosing or underdiagnosing venous thromboembolism and PE in particular. However, this problem is the same for any clinical study that attempts to estimate the incidence of PE. In the present study, all the recurrent nonfatal PEs were diagnosed by perfusion-ventilation lung scan and none was verified with pulmonary angiography. Of the fatal PEs, 8 of 13 were verified at autopsy. The low autopsy rate (23.6%) would tend to underestimate the risk of fatal PE, which is shown in earlier autopsy studies.

The main limitation of the present study is that neither the initial treatment nor the duration of oral anticoagulation therapy was randomized. Instead, oral anticoagulation therapy was prolonged when the treating physician suspected a high risk of recurrent events. In other words, patients with a history of venous thromboembolism were assigned to oral anticoagulation of longer duration (Table 2), which is probably the reason why these patients were found to have a higher rate of recurrent events during follow-up in the multivariate but not the univariate analysis. The comparatively low relative risk associated with short duration of anticoagulation could also have been biased by the fact that the duration of oral anticoagulation therapy was not randomized.

Patients with cancer had a higher risk of recurrent events and patients with a postoperative DVT had a lower risk of recurrent events in multivariate analyses. The same findings have been reported previously. When subgrouping the postoperative patients, the lowest risk of recurrent events was found after orthopedic surgery. Even though the difference between these and other postoperative patients was not statistically significant, the observation is interesting as others have found orthopedic surgery to be more likely to cause postoperative DVT than other types of surgery. It is reasonable to believe that the risk of recurrent events is low if the first VTE occurs under the influence of a strong risk factor that ceases to exist, while the risk of recurrent events is higher when the risk factor for a first event still exists (such as cancer). We also found patients with proximal DVT to be at higher risk of recurrences compared with patients with a distal DVT. The reason for this is not clear. A proximal DVT might cause more damage to the vascular valves and therefore more postthrombotic problems, leading to local rheological changes that could facilitate recurrent events. However, this explanation does not explain recurrences in the contralateral leg. Another possible explanation could be the fact that a defect in the coagulation or fibrinolytic system could cause a first DVT to become more proximally extended. Inherited or acquired thrombophilia would make a patient more inclined to experience recurrent events.

Regrettably, coagulation and fibrinolytic data are not included in the present study.

In conclusion, a large-scale prospective study of recurrent venous thromboembolism with a follow-up rate close to 100% has been conducted. The rate of recurrent VTEs after a DVT is high. In addition to known risk factors for recurrent events, such as idiopathic VTE, history of VTE, and cancer, we have found that patients with proximal DVT have a higher risk of recurrent events compared with patients with a distal DVT. The rate of recurrent VTE without oral anticoagulation must be balanced against the risk of bleeding events during oral anticoagulation therapy. A higher recurrence rate among patients with proximal DVT or cancer may justify prolonged prophylactic therapy in high-risk situations, ie, surgery and immobilization.

We believe that it is necessary to differentiate between the duration of anticoagulation therapy, by taking account of the individual risk of recurrent events as well as the risk of severe bleeding events. An approach of this kind should be tested in further large-scale prospective studies.

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