Symptomatic Pulmonary Embolism and the Risk of Recurrent Venous Thromboembolism

Sabine Eichinger, MD; Ansgar Weltermann, MD; Erich Minar, MD; Milena Stain, MD; Verena Schönauer, MD; Barbara Schneider, PhD; Paul Alexander Kyrle, MD

Background: In patients with a first symptomatic pulmonary embolism (PE), the risk of recurrence is unknown. We therefore investigated the risk of recurrence among patients with spontaneous symptomatic PE and among those with deep vein thrombosis (DVT) without symptoms of PE.

Methods: After discontinuation of secondary thromboprophylaxis for a first venous thromboembolism (VTE), we prospectively observed 436 patients for an average of 30 months. Patients with secondary VTE, natural inhibitor deficiencies, lupus anticoagulant, cancer, long-term antithrombotic therapy, vena cava filters, or pregnancy were excluded. The study outcome was objectively documented recurrent symptomatic VTE.

Results: Recurrent VTE was seen among 28 (17.3%) of 162 patients with symptomatic PE and among 26 (9.5%) of 274 patients with DVT without symptoms of PE. Compared with patients with DVT, the relative risk of recurrent VTE among patients with symptomatic PE was 2.2 (95% confidence interval, 1.3-3.7; P = .005). The relative risk was not affected by age, sex, presence of factor V Leiden or prothrombin G20210A, hyperhomocysteinemia, or high factor VIII levels. Compared with patients with DVT without symptoms of PE, patients with symptomatic PE had an adjusted relative risk of PE at recurrence of 4.0 (95% confidence interval, 1.3-12.3; P = .03).

Conclusion: Patients with a first symptomatic PE not only have a higher risk of recurrent VTE than those with DVT without symptoms of PE, but are also at high risk of symptomatic PE at recurrence.

Arch Intern Med. 2004;164:92-96

PULMONARY EMBOLISM (PE) IS a frequent and potentially fatal disease with an incidence of 1 in 1000 persons per year.1-3 Approximately 10% of the patients die of heart failure and cardiac shock within hours.4 Twenty-five percent of the patients do not survive the first year,5,6 but many deaths during this time are related to underlying conditions, such as cancer or chronic heart disease, rather than to recurrent PE.7,8 The prognosis of patients with PE without a predisposing illness might be more favorable, but the risk of recurrent venous thromboembolism (VTE) among these patients has never been investigated, to our knowledge.

Recurrent VTE can be prevented by treatment with oral anticoagulants.9,10 Since these drugs may cause bleeding,11-13 determining the optimal duration of anticoagulation entails balancing the risk of hemorrhage against the risk of recurrence. Pulmonary embolism is regarded as the consequence of deep vein thrombosis (DVT) rather than a separate clinical entity. Most trials on the risk of recurrent VTE therefore did not distinguish between patients with DVT and those with PE.9,10,14,15 Since the risk of recurrence is thus unknown in patients with PE, the decision as to how long these patients should receive anticoagulation is subject to individual preference rather than objective guidelines.

We observed 436 patients with a first spontaneous VTE and compared the risk of recurrence between patients with symptomatic PE and those with DVT without symptoms of PE.

METHODS

PATIENT POPULATION

Between July 1, 1992, and June 30, 2002, 1056 consecutive patients (older than 18 years) with DVT of the leg and/or PE, who had been treated with oral anticoagulants for at least 3 months, were eligible. A total of 392 patients were excluded because of surgery, trauma, or preg-
nancy within the previous 3 months; previously recurrent VTE; deficiency of antithrombin, protein C, or protein S; presence of the lupus anticoagulant; cancer; requirement for long-term antithrombotic treatment; or a venous cava filter. All patients had been treated with unfractionated or low-molecular-weight heparin in therapeutic dosages. Twenty-one patients with PE had received thrombolytic therapy.

Patients entered the study at the time of discontinuation of oral anticoagulants and were then seen at 3-month intervals during the first year and every 6 months thereafter. They received written information on the symptoms of VTE and were instructed to report if such symptoms occurred.

The study was approved by the ethics committee of the Vienna University Hospital, Vienna, Austria, and all patients provided written informed consent before inclusion.

**DIAGNOSIS OF VTE**

The diagnosis of DVT was established by a positive finding on venography or color duplex sonography (in case of proximal DVT). To be considered positive, the venograms had to meet at least 1 of the following direct or indirect criteria: a constant filling defect seen on 2 views; an abrupt discontinuation of the contrast-filled vessel at a constant level of the vein; and the absence of filling in the entire deep vein system (without compression), with or without venous flow through collateral veins. With color duplex ultrasonography, at least 1 of the 2 following criteria for DVT had to be met: visualization of an intraluminal thrombus in a deep vein and incomplete compressibility or absence of compressibility.

A diagnosis of PE was considered if the patient had typical symptoms (chest pain, dyspnea, cough, hemoptysis, and/or syncope). The diagnosis of PE was then confirmed either by a positive finding on ventilation-perfusion scanning according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis or by spiral computed tomography demonstrating 1 or several low-attenuation areas that partly or completely filled the lumen of an opacified vessel.

**STUDY END POINTS**

The end point of the study was recurrent symptomatic DVT confirmed by venography or color duplex sonography (in case of proximal DVT of the contralateral leg) or recurrent symptomatic PE confirmed by ventilation-perfusion scanning and/or spiral computed tomography according to the aforementioned criteria. The DVT was considered to have recurred if the patient had a thrombus in the leg opposite from that affected by the previous thromboembolic event; a thrombus in another deep vein in the same leg as the previous event; or a thrombus in the same venous system as the previous event, with proximal extension of the thrombus (if the upper limit of the original thrombus had been visible) or with a constant filling defect surrounded by contrast medium (if the original thrombus had not been visible). The diagnosis was established by an adjudication committee consisting of independent clinicians and radiologists.

**LABORATORY ANALYSIS**

Blood was collected, after fasting, into 1:10 volume of 0.11 mM trisodium citrate and immediately centrifuged for 20 minutes at 2000g. The plasma was stored at −80°C. Genomic DNA was isolated from leukocytes by standard methods.

Screening for factor V Leiden and for prothrombin G20210A was carried out as described. Determination of antithrombin, protein C, protein S, total homocysteine, and factor VIII was performed as previously reported. The diagnosis of a lupus anticoagulant was based on the criteria of the International Society of Thrombosis and Haemostasis. The technicians were unaware of the patient characteristics at all times.

**STATISTICAL ANALYSIS**

Times to recurrence (uncensored observations) or follow-up times in patients without recurrence (censored observations) were analyzed by survival time methods. The probability of recurrence was estimated according to Kaplan-Meier. To test for homogeneity between strata, we applied the log-rank and the generalized Wilcoxon test. The data were adjusted for age, sex, factor V Leiden, prothrombin G20210A, hyperhomocysteinemia, or high factor VIII level (dichotomized at the 95th percentile of the reference range), and high factor VIII level (dichotomized at a plasma level of 234%). Categorical data were checked for homogeneity by means of contingency table analyses ($\chi^2$ test). Simple descriptive statistics were computed to provide a clear presentation of the data. For numerical operations, an SAS software package (SAS Institute Inc, Cary, NC) was used. Values are given as mean±SD.

**RESULTS**

Of 464 patients, 162 patients had PE and 302 patients had DVT. Symptoms of PE were chest pain in 104 patients (64%), dyspnea in 116 patients (72%), cough or hemoptysis in 37 patients (23%), and syncope in 27 patients (17%). Twenty-eight patients with DVT were excluded because they had symptoms of PE but objective testing was not performed. The characteristics of the remaining 436 study patients (274 with DVT without symptoms of PE and 162 with symptomatic PE) are shown in Table 1. There was no significant difference between patients with symptomatic PE and patients with DVT without symptoms of PE with regard to age, sex distribution, the presence of factor V Leiden or prothrombin G20210A, hyperhomocysteinemia, or high factor VIII level. Patients with symptomatic PE had a shorter observation time and received anticoagulants significantly longer than patients with DVT.

One hundred twenty-three patients left the study. Seven did so because they were given a diagnosis of cancer and 82 because they required antithrombotic therapy for reasons other than VTE. Twenty-eight patients (6%) were lost to follow-up. Six patients died, but recurrent VTE was the cause of death in none of them. The patients’ data were censored at the time of exclusion or death.

Recurrent VTE (39 DVT without symptoms of PE, 15 symptomatic PE) occurred in 54 patients (12.4%). Thirty-nine patients with recurrence were male and 15 patients were female. The proportion of patients with high factor VIII levels was higher among patients with recurrence than among patients without recurrence (11 patients [20%] and 37 patients [9%], respectively; $P = .01$). There was no significant difference between patients with and without recurrence with regard to age (50±16 years and 47±18 years, respectively), the presence of factor V Leiden (16 patients [30%] and 135 patients [33%], respectively) or prothrombin G20210A (9 patients [17%] and 37 patients [9%], respectively), or the proportion of patients with hyperhomocysteinemia (16 patients [30%] and 243 patients [23%], respectively).
Our prospective study demonstrates that the risk of recurrent VTE is significantly higher among patients with symptomatic PE than among patients with DVT without symptoms of PE. In a prospective study of 436 patients, the risk of recurrence was more than twice as great among patients with a first spontaneous symptomatic PE as among those with DVT without symptoms of PE. Most important, patients with symptomatic PE had a 4-fold higher risk of symptomatic PE at recurrence than patients with DVT.

Our findings are in agreement with those of the Columbus Investigators, who compared the efficacy of low-molecular-weight and unfractionated heparin in patients with VTE. At 3 months, the rate of recurrence was higher among patients with PE (5.9%) than among patients with DVT (4.8%). That study, however, was neither intended nor powered to compare the rate of recurrence between patients with PE and DVT.

The observation of a high risk of PE at recurrence among patients with an incident symptomatic PE corroborates findings of 2 recent studies. In a meta-analysis, Douketis and coworkers found a higher rate of fatal recurrent PE in patients with PE (1.4%) than the rate of a fatal first PE after treatment for DVT (0.3%). In a retrospective cohort study, the initial clinical manifestation of VTE strongly predicted the same clinical presentation among patients rehospitalized for recurrent thromboembolism. Among patients with PE who developed recurrence, 70% were diagnosed as having PE and 30% were diagnosed as having venous thrombosis alone, whereas among patients with venous thrombosis and recurrence, only 15% were diagnosed as having PE and 85% had venous thrombosis.

The different rates of recurrence among patients with symptomatic PE and those with DVT without symptoms of PE do not result from an incidentally unbalanced distribution of thrombotic risk factors among the 2 groups. We have excluded patients with potent risk factors for recurrence, such as previous thrombosis, cancer, or the lupus anticoagulant, as well as low-risk patients with thrombosis related to surgery, trauma, or pregnancy. We excluded neither patients with high factor VIII level, who have a high risk of recurrence, nor carriers of factor V Leiden or prothrombin G20210A, in whom we reported a risk of recurrence similar to that in

### Table 1. Baseline Characteristics of the 436 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVT Without Symptoms of PE (n = 274)</th>
<th>Symptomatic PE (n = 162)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at venous thromboembolism, mean ± SD, y</td>
<td>48 ± 18</td>
<td>46 ± 18</td>
<td>.20</td>
</tr>
<tr>
<td>Sex, No. (%) female</td>
<td>158 (58)</td>
<td>91 (56)</td>
<td>.80</td>
</tr>
<tr>
<td>Duration of oral anticoagulant therapy, mean ± SD, mo</td>
<td>8 ± 7.5</td>
<td>11.2 ± 18.9</td>
<td>.001</td>
</tr>
<tr>
<td>Factor V Leiden, No. (%)</td>
<td>95 (36)</td>
<td>42 (27)</td>
<td>.06</td>
</tr>
<tr>
<td>Prothrombin G20210A, No. (%)</td>
<td>25 (9)</td>
<td>16 (10)</td>
<td>.80</td>
</tr>
<tr>
<td>Hyperhomocysteinemia, No. (%)</td>
<td>61 (24)</td>
<td>47 (31)</td>
<td>.10</td>
</tr>
<tr>
<td>High factor VIII (&gt;234%), No. (%)</td>
<td>30 (11)</td>
<td>15 (10)</td>
<td>.60</td>
</tr>
<tr>
<td>Observation time, mean ± SD, mo</td>
<td>32 ± 27</td>
<td>26 ± 27</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

### Kaplan-Meier estimates of the risk of recurrent venous thromboembolism in patients with symptomatic pulmonary embolism (PE) or deep vein thrombosis (DVT) without symptoms of PE.

Kaplan-Meier analysis showed a significant divergence between the rate of recurrence among patients with symptomatic PE and among patients with DVT without symptoms of PE. At 24 months, the likelihood of recurrence among patients with symptomatic PE compared with 7% (95% confidence interval, 3%-11%) among patients with DVT (P = .004). A first symptomatic PE conferred a relative risk of recurrence of 2.2 (95% confidence interval, 1.3-3.7; P = .005) (Table 2) and remained an independent risk factor for recurrence after adjustment for age, sex, the presence of factor V Leiden or prothrombin G20210A, hyperhomocysteinemia, or high factor VIII level (relative risk, 2.2; 95% confidence interval, 1.3-3.7; P = .005).

Patients with symptomatic PE had a high risk of a subsequent symptomatic PE. Compared with patients with DVT without symptoms of PE, the relative risk of PE at recurrence among patients with a first symptomatic PE was 4.0 (95% confidence interval, 1.3-12.3; P = .03) after adjustment for other potentially confounding thrombotic risk factors.

### Table 2

<table>
<thead>
<tr>
<th>No. of Patients at Risk</th>
<th>Symptomatic PE</th>
<th>DVT Without Symptoms of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic PE</td>
<td>DVT Without Symptoms of PE</td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>274</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>101</td>
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<td></td>
<td>69</td>
<td>140</td>
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<tr>
<td></td>
<td>43</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>73</td>
</tr>
</tbody>
</table>

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The duration of secondary thromboprophylaxis in patients with symptomatic PE was significantly longer than that in patients with DVT without symptoms of PE (11 vs 8 months on average, respectively). This difference can be explained by individual treatment preferences of the supervising physician. Since a longer duration of oral anticoagulation is associated with a lower rate of recurrence, the difference between the 2 groups with respect to the risk of recurrence might have been even greater in the case of a shorter duration of anticoagulation in the patients with PE.

In approximately 40% of the patients with proximal DVT, perfusion scan findings consistent with PE can be found in the absence of clinical symptoms.29 In our study, visualization techniques were not performed on a routine basis, but only in patients who presented with symptoms suggestive for PE. Therefore, some of our patients categorized as having DVT also had asymptomatic PE. Our patient classification would have affected our results only if asymptomatic PE would confer a lower risk of recurrence, which is very unlikely. Assuming that patients with asymptomatic PE have a higher risk of recurrence than patients with DVT without PE, the difference in the rate of recurrence between patients with PE (regardless of the presence or absence of symptoms) and patients with DVT without symptoms of PE would have been even greater. Nevertheless, the risk of recurrence among patients with asymptomatic PE ought to be investigated.

Our findings have 2 major clinical implications. To identify patients at high risk of recurrent VTE, a careful clinical examination of patients with DVT with regard to the presence of symptoms suggestive of PE is of utmost importance. Recurrent VTE is associated with serious clinical consequences: it is fatal in approximately 5% of the patients,24,29 and it is associated with the postthrombotic syndrome in one third of patients.30 Since the risk of recurrence and, thus, its complications can be reduced by treatment with anticoagulants, the results of our study indicate that prospective trials are warranted to investigate the optimal duration of secondary thromboprophylaxis in patients with PE.

Accepted for publication February 21, 2003.

This study was supported by grant 1980 from the Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, Vienna, Austria.

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**Correction**

In the Original Investigation by Civitelli et al titled “Alveolar and Postcranial Bone Density in Postmenopausal Women Receiving Hormone/Estrogen Replacement Therapy: A Randomized, Double-blind, Placebo-Controlled Trial,” published in the June 24, 2002, issue of the ARCHIVES (2002; 162:1409-1415), the dosage of cholecalciferol was incorrectly given as “800 IU/d,” instead of the correct dosage “400 IU/d.”