D-Dimer Levels and Risk of Recurrent Venous Thromboembolism

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Context  Widespread screening of patients with venous thromboembolism (VTE) for thrombophilic risk factors has become common clinical practice. Because of the increasing number of risk factors, assessing the risk of recurrence in an individual patient is intricate; therefore, a laboratory method that measures multifactorial thrombophilia is required.

Objective  To prospectively study the relationship between the risk of recurrent VTE and D-dimer, a global marker of coagulation activation and fibrinolysis.

Design, Setting, and Participants  Prospective cohort study of 610 patients older than 18 years who were treated with oral anticoagulants for at least 3 months with a first spontaneous VTE, in whom D-dimer levels were measured shortly after discontinuation of oral anticoagulation. The study was conducted at the Department of Internal Medicine I, University Hospital, Vienna, Austria. Patients entered the study at time of discontinuation of oral anticoagulants and were observed at 3-month intervals during the first year and every 6 months thereafter from July 1992 to October 2002.

Main Outcome Measure  Objectively documented symptomatic recurrent VTE.

Results  A total of 79 (13%) of 610 patients had recurrent VTE with a mean observation time of 38 months. Patients with recurrence had significantly higher D-dimer levels compared with those without recurrence (553 ng/mL vs 427 ng/mL, P = .01). Compared with patients with D-dimer levels of 750 ng/mL or higher, the relative risk (RR) of recurrence was 0.6 (95% confidence interval [CI], 0.3-1.4), 0.6 (95% CI, 0.3-1.2), and 0.3 (95% CI, 0.1-0.6) in patients with D-dimer levels of 500 to 749 ng/mL, 250 to 499 ng/mL, and less than 250 ng/mL, respectively. The cumulative probability of recurrent VTE at 2 years was 3.7% (95% CI, 0.9%-6.5%) among patients with D-dimer levels of less than 250 ng/mL compared with 11.5% (95% CI, 8.0%-15.0%) among patients with higher levels (P = .001). Patients with D-dimer levels of less than 250 ng/mL had a 60% lower RR of recurrence compared with patients with higher levels (RR, 0.4; 95% CI, 0.2-0.8).

Conclusion  Patients with a first spontaneous VTE and a D-dimer level of less than 250 ng/mL after withdrawal of oral anticoagulation have a low risk of VTE recurrence.

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Table 1. Thrombotic Risk Factors and Relative Risk of Recurrent VTE After Therapy With Anticoagulants Among 610 Patients With a First Spontaneous VTE by D-Dimer Level

<table>
<thead>
<tr>
<th>D-Dimer Level, ng/mL</th>
<th>&lt;250</th>
<th>250-499</th>
<th>500-749</th>
<th>≥750</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>209</td>
<td>254</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Thrombotic risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>51 (24)</td>
<td>82 (33)</td>
<td>32 (41)</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>12 (6)</td>
<td>23 (9)</td>
<td>10 (13)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>High factor VIII*</td>
<td>7 (3)</td>
<td>23 (9)</td>
<td>13 (17)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>No. of recurrences, No. (%)</td>
<td>16 (7.7)</td>
<td>39 (15.6)</td>
<td>11 (14.3)</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Univariate RR (95% CI)</td>
<td>0.3 (0.1-0.6)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.6 (0.3-1.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)†</td>
<td>0.3 (0.1-0.8)</td>
<td>0.6 (0.3-1.3)</td>
<td>0.9 (0.4-2.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; VTE, venous thromboembolism.
*High factor VIII indicates levels of more than 234 IU/dL.
†Adjusted for age, sex, factor V Leiden, factor II G20210A, and high factor VIII.

Outcome Measure
The study end point was recurrent symptomatic deep vein thrombosis or recurrent symptomatic pulmonary embolism, confirmed by venography, color duplex sonography (in case of proximal vein thrombosis of the contralateral leg), ventilation-perfusion scanning, and/or spiral computed tomography.

Laboratory Analysis
Laboratory testing was performed 3 weeks after discontinuation of oral anticoagulants. D-dimer levels were measured by an enzyme-linked immunosassay (Asserachrom D-dimer, Boehringer Mannheim, Germany). Antithrombin, protein C, protein S, factor VIII, and the lupus anticoagulant were determined as reported. Screening for factor V Leiden and factor II G20210A was carried out as described. Recurrent VTE in Relationship With D-Dimer Levels
A total of 79 (13%) of 610 patients had recurrent VTE (deep-vein thrombosis [n=54] and pulmonary embolism [n=25]). Patients with recurrent VTE had significantly higher D-dimer levels than those without recurrence (553 ng/mL vs 427 ng/mL, respectively, P=.01). To assess the risk of recurrence for different ranges of D-dimer levels, we arbitrarily stratified patients into 4 groups. The distribution of thrombotic risk factors, such as factor V Leiden, factor II G20210A, and high factor VIII (dichotomized at a plasma level of 234 IU/dL), and the relative risk (RR) of recurrence according to the 4 ranges of D-dimer levels are shown in Table 1. Compared with the reference group (patients with D-dimer levels ≥750 ng/mL), the RR of recurrence was lower among patients with D-dimer levels of 250 to 499 ng/mL (RR, 0.6; 95% CI, 0.3-1.4), among patients with D-dimer levels of 250 to 499 ng/mL (RR, 0.6; 95% CI, 0.3-1.2), and was significantly lower among patients with D-dimer levels of less than 250 ng/mL (RR, 0.3; 95% CI, 0.1-0.6), respectively. Adjustment for potential confounding variables, including age, sex, factor V Leiden, factor II G20210A, and high factor VIII, did not substantially influence the result.

A total of 209 (34%) of 610 patients had D-dimer levels of less than 250 ng/mL. Recurrent VTE was observed in 16 (7.7%) of 209 patients with D-dimer levels of less than 250 ng/mL. Patients with D-dimer levels of less than 250 ng/mL were significantly younger and had significantly less thrombotic risk factors, such as factor V Leiden or high factor VIII, compared with patients with higher levels (Table 2). No difference...
between the 2 groups was observed with regard to the mean duration of anticoagulation (7.8 and 8.3 months, respectively; \( P = .30 \)).

The cumulative probability of recurrent VTE at 2 years was 3.7% (95% CI, 0.9%-6.5%) among patients with D-dimer levels of less than 250 ng/mL compared with 11.5% (95% CI, 8.0%-15.0%) among patients with higher levels (\( P = .001 \), Figure). Among patients with D-dimer levels of less than 250 ng/mL, the RR of recurrence was 0.4 (95% CI, 0.2-0.8), which translates into a 60% lower RR compared with patients with higher levels.

COMMENT

Our study showed that patients with a first spontaneous VTE and a D-dimer level of less than 250 ng/mL 3 weeks after discontinuation of oral anticoagulation are at low risk of recurrence. These patients, who represent approximately one third of the total cohort, had a probability of recurrent VTE at 2 years as low as 3.7% with an upper limit of the 95% CI of 6.5%. Compared with patients with D-dimer levels of 250 ng/mL or higher, those patients with lower levels had a 60% lower RR of recurrence, which was independent of other potentially confounding variables.

During the last years, several new thrombotic risk factors have been identified. \(^{13,16}\) Subsequently, the risk of recurrence associated with these thrombophilic conditions was investigated with the intention to optimize secondary thromboprophylaxis. Many researchers have shown that heterozygous carriers of factor V Leiden\(^ {17-20}\) or the prothrombin mutation\(^ {21,22}\) do not have a higher risk of recurrence than patients without the mutation. Conversely, patients with combined defects,\(^ {16,20}\) hyperhomocysteinemia,\(^ {23}\) and those with high factor VIII\(^ {19}\) have a high risk of recurrence. As a consequence, extensive thrombophilia screening has become common practice. However, assessing the overall risk of recurrence in an individual patient is intricate as many patients carry more than 1 thrombotic risk factor and the effect of compound defects tends to be multiplicative rather than additive.\(^ {24}\)

To overcome this limitation, a simple laboratory test that measures multifactorial thrombophilia is required.

Our data clearly showed that in patients with a first VTE the use of a single laboratory test (ie, D-dimer) allows a global assessment of their thrombotic tendency and a stratification into high-risk and low-risk patients with regard to the risk of recurrence. In a study from Italy, a high negative predictive value for VTE recurrence was reported.\(^ {9}\) This study differs from our study in many important aspects, including the diagnosis of the first VTE (which is uncertain in the Italian study), patient characteristics (almost 50% of the Italian patients had VTE secondary to removable risk factors), patient number (396 vs 610), and total duration of follow-up (628 vs 1945 patient-years).

In conclusion, measuring D-dimer levels allows identification of a subset of patients with thrombosis with a very low risk of recurrence. In these patients, extensive screening for thrombophilic risk factors may be unnecessary.

**Table 2. Baseline Characteristics of the 610 Patients With a First Spontaneous VTE and D-Dimer Levels Less Than or More Than 250 ng/mL After Therapy With Anticoagulants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>D-Dimer Level, No. (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>( &lt;250 \text{ ng/mL} ) (n = 209)</td>
<td></td>
</tr>
<tr>
<td>Age ( &lt;45 \text{ y} )</td>
<td>117 (56)</td>
<td>223 (56)</td>
</tr>
<tr>
<td>Type of thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal leg veins</td>
<td>63 (30)</td>
<td>146 (36)</td>
</tr>
<tr>
<td>Distal leg veins</td>
<td>49 (23)</td>
<td>91 (23)</td>
</tr>
<tr>
<td>Axillary veins</td>
<td>16 (8)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>81 (39)</td>
<td>153 (38)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>51 (25)</td>
<td>140 (35)</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>12 (6)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>High factor VIII*</td>
<td>7 (3)</td>
<td>51 (13)</td>
</tr>
</tbody>
</table>

Abbreviation: VTE, venous thromboembolism.

*High factor VIII indicates levels of more than 234 IU/dL.

**Figure.** Kaplan-Meier Method Estimates of the Risk of Recurrent VTE According to the Plasma Level of D-Dimer

The probability of recurrent venous thromboembolism (VTE) was lower among patients with D-dimer levels of less than 250 ng/mL than among patients with higher levels (\( P = .001 \) by the Wilcoxon rank sum test and log-rank test).

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D-DIMER LEVELS AND RECURRENT VENOUS THROMBOEMBOLISM

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Statistical expertise: Schneider, Weltermann.

REFERENCES

The gifts of nature are infinite in their variety, and mind differs from mind almost as much as body from body.
—Quintillian (c 35–c 95 AD)