BRIEF REPORT

D-Dimer Levels and Risk of Recurrent Venous Thromboembolism

Sabine Eichinger, MD
Erich Minar, MD
Christine Bialonczyk, MD
Mirko Hirschl, MD
Peter Quehenberger, MD
Barbara Schneider, PhD
Ansgar Weltermann, MD
Oswald Wagner, MD
Paul A. Kyrle, MD

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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THE OPTIMAL DURATION OF SECondary thromboprophylaxis among patients with venous thromboembolism (VTE) is unknown. The risk of recurrence is minimal during oral anticoagulation but increases as soon as anticoagulation is stopped.[1-4] The price for decreasing the risk of recurrence by prolonging anticoagulation is an increased frequency of bleeding. Screening for risk factors might be helpful to identify patients in whom the risk of bleeding is outweighed by the risk of recurrence. This approach is hampered because many patients have more than 1 thrombophilic condition. To tackle the problem of evaluating the overall risk of recurrence, a single laboratory test that measures multifactorial thrombophilia is required.

D-Dimer is a global indicator of coagulation activation and fibrinolysis. D-dimer level is measured in plasma by use of well-standardized assays that are widely used for the diagnosis of acute VTE.[5,6] A high D-dimer level (>70th percentile of controls) is independently associated with a 2.2-fold increased risk for a first venous thrombosis.[7] In a population-based cohort study, D-dimer was positively related to the occurrence of a future first thrombosis.[8] With regard to recurrent VTE, Palareti et al[9] reported a 2.5-fold higher risk of recurrence among patients with VTE and D-dimer levels higher than 500 ng/mL after discontinuation of oral anticoagulation compared with patients with lower levels. We measured D-dimer levels in 610 patients with a first spontaneous VTE and assessed the relationship between the risk of recurrent VTE and the levels of D-dimer.

METHODS

Participants and Study Design

Between July 1992 and October 2002, 2044 consecutive patients with VTE (es-

Author Affiliations: Department of Internal Medicine I (Drs Eichinger, Weltermann, and Kyrle), Ludwig-Boltzmann Institute (Dr Kyrle), Department of Internal Medicine II (Dr Minar), Clinical Institute of Medical and Chemical Laboratory Diagnostics (Drs Quehenberger and Wagner), and Institute of Medical Statistics (Dr Schneider), University of Vienna, Austria; and Wilhelminenspital (Dr Bialonczyk) and Hanuschkrankenhaus (Dr Hirschl), Vienna, Austria.
Corresponding Author and Reprints: Sabine Eichinger, MD, Department of Internal Medicine I, University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria (e-mail: sabine.eichinger@akh-wien.ac.at).

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

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

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.

tablished by venography, color duplex sonography [in case of proximal vein thrombosis], ventilation-perfusion scanning, or spiral computed tomography) older than 18 years, who had been treated with oral anticoagulants for at least 3 months, were eligible. A total of 1434 patients were excluded because of more than 1 previous VTE (n=332); surgery, trauma, or pregnancy within the previous 3 months (n=393); deficiency of a natural coagulation inhibitor (n=59); the lupus anticoagulant (n=32); cancer (n=282); or long-term antithrombotic treatment (n=336). The study was conducted at the Department of Internal Medicine I, University Hospital, Vienna, Austria. The study was approved by the local ethics committee and all patients gave written informed consent to participate. Patients entered the study at the time of discontinuation of oral anticoagulants and were observed at 3-month intervals during the first year and every 6 months thereafter.

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.[10]

Laboratory Analysis

Laboratory testing was performed 3 weeks after discontinuation of oral anticoagulants. D-dimer levels were measured by an enzyme-linked immunoassay (Asserachrom D-dimer, Boehringer Mannheim, Germany). Antithrombin, protein C, protein S, factor VIII, and the lupus anticoagulant were determined as reported.[10] Screening for factor V Leiden and factor II G20210A was carried out as described.[11,12]

Statistical Analysis

Times to recurrence (uncensored observations) or follow-up times in patients without recurrence (censored observations) were analyzed by using survival-time methods.[13] The probability of recurrence was estimated according to Kaplan-Meier method.[14] To test for homogeneity between strata, we applied the log-rank and the generalized Wilcoxon rank sum test. Categorical data were checked for homogeneity by using contingency table analyses (χ^2 test). SAS version 8.02 (SAS Institute, Cary, NC) was used for all analyses and $P<.05$ was considered statistically significant.

RESULTS

Clinical Characteristics

The study population consisted of 610 patients with a first spontaneous VTE. After discontinuation of oral anticoagulants, the patients were followed up for a mean of 38 months. A total of 175 patients were excluded during the course of the study because they were diagnosed with cancer (n=11), required antithrombotics for reasons other than VTE (n=105), became pregnant (n=17), or were lost to follow-up (n=37). One patient died of gastric cancer, 1 of septicemia, and 3 patients of heart failure. These patients were followed up until the time of exclusion or death, when the data were censored (mean follow-up, 14 months).

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 500 to 749 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; $P=.30$).

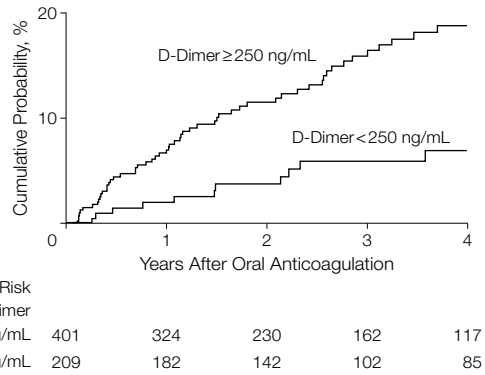
The cumulative probability of recurrent VTE at 2 years was 3.7% (95% CI, 0.9%-6.5%) among patients with D-dimer levels of less than 250 ng/mL compared with 11.5% (95% CI, 8.0%-15.0%) among patients with higher levels ($P=.001$, FIGURE). Among patients with D-dimer levels of less than 250 ng/mL, the RR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

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

Characteristics	D-Dimer Level, No. (%) <250 ng/mL (n = 209)	D-Dimer Level, No. (%) ≥250 ng/mL (n = 401)	*P* Value
Women	117 (56)	223 (56)	.90
Age <45 y	146 (70)	116 (29)	<.001
Type of thromboembolism			
Proximal leg veins	63 (30)	146 (36)	.10
Distal leg veins	49 (23)	91 (23)	.80
Axillary veins	16 (8)	11 (3)	.005
Pulmonary embolism	81 (39)	153 (38)	.90
Factor V Leiden	51 (25)	140 (35)	<.001
Factor II G20210A	12 (6)	38 (10)	.10
High factor VIII*	7 (3)	51 (13)	<.001

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).

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.[15,16] 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[2,17-20] or the prothrombin mutation[21,22] do not have a higher risk of recurrence than patients without the mutation. Conversely, patients with combined defects,[19,20] hyperhomocysteinemia,[23] and those with high factor VIII[10] 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.

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Acquisition of data: Minar, Bialonczyk, Hirschl, Quehenberger, Wagner.

Analysis and interpretation of data: Eichinger, Quehenberger, Schneider, Weltermann, Kyrle.
Drafting of the manuscript: Eichinger, Weltermann, Kyrle.
Critical revision of the manuscript for important intellectual content: Minar, Bialonczyk, Hirschl, Quehenberger, Schneider, Wagner.
Statistical expertise: Schneider, Weltermann.
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> 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)