

D-dimer levels < 250 ng/mL after oral anticoagulation predicted a low risk for recurrent venous thromboembolism

Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA*. 2003;290:1071-4.

QUESTION

In patients who have had a first unprovoked venous thromboembolism (VTE), are levels of D-dimer measured after withdrawal of oral anticoagulant therapy (OAT) associated with risk for recurrent VTE?

DESIGN

Inception cohort followed for a mean of 38 months.

SETTING

A university hospital in Vienna, Austria.

PATIENTS

610 patients > 18 years of age (mean age 48 y, 56% women) with a first unprovoked, objectively documented VTE who received OAT for ≥ 3 months. Exclusion criteria were recent (within 3 mo) surgery, trauma, or pregnancy; natural coagulation inhibitor deficiency; lupus anticoagulant; cancer; or long-term antithrombotic treatment.

ASSESSMENT OF PROGNOSTIC FACTORS

3 weeks after stopping OAT, laboratory testing was done to determine the levels of D-dimer (measured by an enzyme-linked immunoassay [Asserachrom D-dimer, Boehringer Mannheim, Mannheim, Germany]), antithrombin, protein C, protein S, factor

VIII, the lupus anticoagulant, factor V Leiden, and factor II G20210A. Levels of D-dimer were classified as < 250, 250 to 499, 500 to 749, and ≥ 750 ng/mL. Associations between the prognostic factors and times to recurrence were assessed using univariate and multivariate survival analysis.

MAIN OUTCOME MEASURES

Objectively documented recurrent symptomatic VTE (deep venous thrombosis or pulmonary embolism).

MAIN RESULTS

13% of patients had recurrent VTE. The mean level of D-dimer was greater in patients with recurrent VTE than in those without recurrent VTE (553 vs 427 ng/mL, $P = 0.01$). The rate of VTE recurrence was lower in patients with D-dimer levels < 250 ng/mL than in those with D-dimer levels

≥ 250 ng/mL (Table). At 2 years, the cumulative probability of recurrent VTE was lower among patients with D-dimer levels < 250 ng/mL than those with higher levels (3.7% vs 11.5%, $P = 0.001$). Patients with D-dimer levels 250 to 749 ng/mL did not differ from those with D-dimer levels ≥ 750 ng/mL for rate of VTE recurrence (Table).

CONCLUSION

In patients who have had a first unprovoked venous thromboembolism (VTE), D-dimer levels < 250 ng/mL after stopping oral anticoagulant therapy were associated with a low risk for recurrent VTE.

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Association between D-dimer levels and risk for recurrent venous thromboembolism (VTE) after a first spontaneous VTE at mean follow-up of 38 months*

Outcome	D-dimer levels (ng/mL)	Event rates	Univariate RR (95% CI)	Multivariate RR (CI)†
Recurrent VTE	< 250 vs ≥ 750	7.7% vs 18.6%	0.3 (0.1 to 0.6)	0.3 (0.1 to 0.8)†
	250 to 499 vs ≥ 750	15.6% vs 18.6%	0.6 (0.3 to 1.2)	0.6 (0.3 to 1.3)
	500 to 749 vs ≥ 750	14.3% vs 18.6%	0.6 (0.3 to 1.4)	0.9 (0.4 to 2.0)
	< 250 vs ≥ 250	7.7% vs 15.7%	0.5 (0.3 to 0.8)	0.4 (0.2 to 0.8)†

*RR = relative risk. Multivariate RR was adjusted for age, sex, factor V Leiden, factor II G20210A, and high factor VIII. †Association statistically significant.

COMMENTARY

Patients with a first episode of unprovoked VTE are at greater risk for recurrence than those who have transient risk factors (1). The minimum duration of OAT for such patients is 6 months (1), but ongoing debate exists about whether indefinite OAT is required. For those who remain on OAT, no advantage of lowering the intensity of warfarin from the standard international normalized ratio range of 2.0 to 3.0 exists (2). Recent research has focused on identifying patients at greater risk for recurrence in whom indefinite OAT is warranted (1). It is generally accepted that patients with a lupus anticoagulant or antiphospholipid antibody should remain on indefinite OAT, whereas the presence of the factor V Leiden and prothrombin gene mutations are not consistently good predictors of recurrent VTE. For patients with deep venous thrombosis, persisting abnormalities on compression ultrasonography appear to confer a greater risk for recurrence (3).

The study by Eichinger and colleagues adds to the evidence that patients with persistent elevation of D-dimer levels are at greater risk for recurrence than those who have normal D-dimer levels (4). In this study and others, D-dimer was measured after stopping OAT, which is, unfortunately, not as convenient as measuring D-dimer and assessing other risk factors before stopping OAT. However, the timing of D-dimer testing may be important for predicting recurrence (5). Accurate risk stratification after a first unprovoked VTE will probably require a combination

of measurements, including repeated ultrasonography, D-dimer, and others (1). This study helps to point us in the right direction.

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