

THERAPEUTICS

An abnormal D-dimer test result indicated that anticoagulation should be continued

Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355:1780-9.

Clinical impact ratings: Hematol/Thrombo ★★★★★★

QUESTION

In patients with a first episode of venous thromboembolism (VTE) who had received vitamin-K antagonists for ≥ 3 months, does an abnormal D-dimer test result 30 days after discontinuation of anticoagulation predict VTE recurrence?

METHODS

Design: Randomized controlled trial (PROLONG study).

Allocation: Concealed.*

Blinding: Blinded (outcome assessors {and monitoring committee}†).*

Follow-up period: Up to 18 months (mean 1.4 y).

Setting: 30 clinical centers in Italy.

Patients: 619 patients 18 to 85 years of age (mean age 63 y, 52% men) who had a first episode of symptomatic, unprovoked VTE, including proximal deep venous thrombosis of the legs, pulmonary embolism, or both; had received a vitamin-K antagonist (warfarin [Coumadin, Bristol-Myers Squibb] or acenocoumarol [Sintrom, Novartis Pharma]) for ≥ 3 months with a target international normalized ratio (INR) of 2.5 (range 2.0 to 3.0); and had D-dimer testing 30 days after anticoagulation was discontinued. Exclusion

criteria were serious liver disease, renal insufficiency, indications or contraindications for anticoagulation, or limited life expectancy.

Intervention: Patients with an abnormal D-dimer level were allocated to discontinue anticoagulation (*n* = 122) or to resume anticoagulation with vitamin-K antagonists (INR 2.0 to 3.0) (*n* = 105). 392 patients with normal D-dimer levels discontinued anticoagulation.

Outcomes: Composite endpoint of confirmed recurrent VTE and major bleeding events.

Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

More patients with abnormal D-dimer levels who did not resume anticoagulation had confirmed recurrent VTE or major bleeding events than did those who resumed anticoagulation (Table). The rate of recurrent

VTE in patients with normal D-dimer levels was lower than that in patients with abnormal D-dimer levels without anticoagulation (*P* = 0.02) and did not differ from that in patients who resumed anticoagulation.

CONCLUSION

In patients who had a first episode of symptomatic, unprovoked venous thromboembolism and received a vitamin-K antagonist for ≥ 3 months, an abnormal D-dimer test result 30 days after discontinuation of anticoagulation indicated that resumption of the therapy should be considered.

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*See Glossary.

†Information provided by author.

Discontinuing vs resuming anticoagulation after 3 months of vitamin-K antagonist therapy in patients with venous thromboembolism (VTE) and abnormal D-dimer levels‡

Outcome	Discontinue anticoagulation	Resume anticoagulation	RRI (95% CI)	NNH (CI)
Composite endpoint§	15% (18/120)	2.9% (3/103)	306% (23 to 1104)	12 (4 to 153)

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from control event rate and hazard ratio in article.

§Recurrent VTE (15% vs 1.9%) or major bleeding (0% vs 1.0%).

COMMENTARY

Patients with unprovoked VTE represent a difficult clinical problem. The optimum duration of oral anticoagulation for such patients remains controversial because the risk–benefit ratio of ongoing oral therapy is disputed. Current research therefore focuses on risk factors that predict recurrent VTE; identifying such risk factors might suggest populations in whom anticoagulation should be continued. The study by Palareti and colleagues provides evidence in this regard: Patients with an elevated D-dimer level 1 month after stopping anticoagulation had a higher risk for recurrent VTE than did patients who restarted the therapy at 1 month. Patients with a normal D-dimer assay result and patients who restarted anticoagulation in the setting of an abnormal D-dimer level had similar rates of recurrent VTE.

Although informative, the study should not establish a practice standard. First, it is a single study that requires confirmation. Second, a more “practitioner-friendly” risk-stratification system would identify risk factors for recurrence at the time discontinuation of anticoagulation is being considered rather than after it has been stopped. Such risk factors might include biomarker levels (including markers of hypercoagulability and D-dimer) and the degree of residual venous obstruction. Such studies are under way. Third, D-dimer assays are not interchangeable,

so the validity of these findings must be confirmed for each D-dimer assay in clinical use. The study used a qualitative (positive/negative) D-dimer test, but growing numbers of laboratories use quantitative (numeric) D-dimer tests. Finally, some patients in the study received as little as 3 months of anticoagulation. That duration is less than currently recommended (1) and may have inflated the risk for recurrent VTE.

Despite these limitations, this study is an important step in the refinement of anticoagulation care for patients with VTE. Identifying patients at high risk for recurrent VTE will minimize the risks for both recurrent VTE (in patients who continue anticoagulation) and bleeding (in patients who discontinue anticoagulation because of low risk for recurrence).

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Reference

1. Büller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:401S-28S.