



CLINICAL INQUIRY

Utility of Plasma D-dimer in Decision to Continue Anticoagulation Therapy Following Idiopathic Venous Thromboembolism

Paula Knabe, D.O., Melissa Yeats, M.D., J. Zachary Schaftel, M.D., Kelly Lambright, M.D.,
Michael Scheve, D.O., Carolyn Glendinning, M.D., Kyle Schwindt, D.O.
University of Kansas School of Medicine-Wichita
Via Christi Family Practice Residency, Wichita, KS

Clinical Question

In patients with a history of idiopathic venous thromboembolism (VTE), is plasma D-dimer helpful in evaluating the risk of recurrence to determine whether oral anticoagulation therapy (OAT) is appropriate beyond the standard 3-6 months of therapy?

Evidence-Based Answer

A single normal D-dimer at the time of the standard oral anticoagulation therapy (OAT) treatment period of 3-6 months is insufficient to predict recurrence of venous thromboembolism (VTE) because OAT may suppress D-dimer levels even in individuals at risk for recurrence (Strength of Recommendation (SOR) B). A negative D-dimer one month after discontinuation of OAT has a high negative predictive value for recurrent VTE, and supports the decision to permanently discontinue treatment (SOR A). Elevated D-dimer levels, either at the end of the recommended course of OAT or upon repeat in one month if the initial level is normal, predict recurrence of VTE and support the decision to resume OAT (SOR A).

Methodology

The relevant literature was obtained through a PubMed search using the following keywords simultaneously: venous thromboembolism, anticoagulation, D-dimer, and duration. Inclusion criteria for articles were that they be randomized control trials, prospective cohort studies, or meta-analyses, published over the past 12 years, and in English.

Evidence Summary

Several studies supported the above recommendations. A prospective 21-month study that included 599 subjects with a previous idiopathic VTE episode showed that a negative D-dimer measured at one month following therapy cessation had a high negative predictive value (over 92%) for VTE recurrence.¹ A second prospective study involving 396 subjects showed a similar result with a negative predictive value over 95%.² Furthermore, in a randomized controlled trial (the PROLONG study), patients with an elevated D-dimer result one month after stopping OAT had a significantly increased risk of VTE recurrence.³ The authors recommended that OAT be restarted in individuals with an elevated D-dimer.

A 2003 prospective cohort study of 610 adults addressed the differing levels of risk based on the magnitude of an abnormal D-dimer.⁴ The results showed a significantly increased risk of VTE at two-years post-OAT cessation for individuals with a D-dimer level of more than 750 ng/ml measured three weeks following cessation of OAT compared with those with a level of less than 250 ng/ml (11.5% vs 3.7%). A meta-analysis of randomized controlled trials and prospective cohort studies demonstrated an almost 3-fold recurrence risk increase when the D-dimer is positive following at least three months of anticoagulation.⁵ A meta-analysis of four studies and over 1500 patients found a two-fold increase in risk of VTE recurrence during the follow-up period when a D-dimer level was abnormal.⁶ Cosmi et al.⁷ published a prospective cohort study that showed similar results and that an abnormal D-dimer was an independent risk factor for VTE recurrence.

An extension to the PROLONG study showed that there was a significant reduction in VTE recurrence up to approximately 2.5 years with a negative D-dimer.⁸ There also was a significant decrease in VTE risk if OAT is restarted and continued during this period. This study also showed that the risk of a major bleeding episode due to OAT is greater than the risk of recurrent VTE, which needs to be considered carefully in each clinical situation. A prospective cohort study from 2008 followed 861 patients and showed elevated D-dimer to be an independent risk factor for recurrent VTE.⁹ The PROLONG II study found that a persistently negative D-dimer for one year after cessation of OAT signified an almost 10-fold decrease in the relative risk of VTE recurrence within a mean of 10-11 months following OAT cessation.¹⁰ Finally, a recently published study of 1010 patients with either idiopathic or low-risk factor VTE showed that serial measurement of a D-dimer both at the time of stopping OAT and at intervals for the three months following cessation was effective at identifying patients at low risk of recurrence.¹¹

Conclusions

Evidence supports the use of D-dimer testing to determine the risk of VTE recurrence in patients with first episode of idiopathic VTE when OAT is discontinued following the standard 3-6 months of therapy. Based on the studies reviewed, it is reasonable that OAT be discontinued after 3-6 months to be followed-up with D-dimer testing at a one-month interval. An elevated D-dimer at that time raises significant concern for recurrence, prompting the physician and patient to weigh the risks and benefits of restarting OAT. There are unfortunately few trials that compare the risk of life-threatening VTE to risk of a life-threatening bleeding episode, therefore, more data on the comparative risk of a life-threatening OAT bleeding event during prolonged treatment for VTE should be collected before determining the final OAT treatment period. From the available data at this time, it is reasonable to use a non-elevated D-dimer result one month following the standard treatment period for idiopathic VTE to identify low-risk patients in whom OAT should not be resumed.

References

- ¹ Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003; 108(3):313-318. PMID: 12847064.
- ² Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: High negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost* 2002; 87(1):7-12. PMID: 11848459.

- ³ Paraleti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Eng J Med* 2006; 355(17):1780-1789. PMID: 17065639.
- ⁴ Eichinger S, Minar E, Bialonczyk C, et al. D-dimer and risk of recurrent venous thromboembolism. *JAMA* 2003; 290(8):1071-1074. PMID: 12941680.
- ⁵ Verhovsek M, Douketis JD, Yi Q, et al. Systematic Review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med* 2008; 149(7):481-490. PMID: 18838728.
- ⁶ Bruinstroop E, Klok FA, Van de Ree MA, Oosterwijk L, Huisman MV. Elevated D-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: A meta-analysis. *J Thromb Haemost* 2009; 7(4):611-618. PMID: 19175498.
- ⁷ Cosmi B, Legarni C, Cini M, Favaretto E, Palareti G. D-dimer and factor VIII are independent risk factors for recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis. *Thromb Res* 2008; 122(5):610-617. PMID: 18304616.
- ⁸ Cosmi B, Legarni C, Tosetto A, et al. Use of D-dimer testing to determine duration of anticoagulation, risk of cardiovascular events and occult cancer after a first episode of idiopathic venous thromboembolism: The extended follow-up to the PROLONG study. *J Thromb Thrombolysis* 2009; 28(4):381-388. PMID: 19288181.
- ⁹ Eichinger S, Hron G, Kollars M, Kryle P. Prediction of recurrent venous thromboembolism by endogenous thrombin potential and D-dimer. *Clin Chem* 2008; 54(12):2042-2048. PMID: 18948369.
- ¹⁰ Cosmi B, Legarni C, Tosetto A, et al. Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: The PROLONG II prospective study. *Blood* 2010; 115(3):481-488. PMID: 19965693.
- ¹¹ Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. *Blood* 2014; 124(2):196-203. PMID: 24879813.

Keywords: venous thromboembolism, anticoagulants, D-dimer, therapy

Appendix
(Adapted from American Family Physician^{*})

<i>Strength of recommendation</i>	<i>Basis for recommendation</i>
A	Consistent, good-quality patient-oriented evidence ^{**}
B	Inconsistent or limited-quality patient-oriented evidence ^{**}
C	Consensus, disease-oriented evidence ^{**} (usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening)

^{*}<http://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf>

^{**}Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life.

Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).