D-Dimer Can Predict Risk of Recurrent Venous Thromboembolism Regardless of Patient Age, Timing of Testing, or Characteristics of Assay

Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. Ann Intern Med 2010;153:523–31.

Study Overview

Objective. To determine whether characteristics of patients or D-dimer testing affected the ability of D-dimer to predict risk for recurrent venous thromboembolism (VTE) in patients after a first unprovoked VTE.

Design. Patient-level meta-analysis using data from 7 prospective studies that measured the association of post-anticoagulation D-dimer with risk of recurrent VTE.

Setting and participants. 1818 patients across the 7 studies (randomized controlled trials and cohort studies). Unprovoked VTE was defined as the presence of a VTE in the absence of major risk factors for VTE such as trauma, cancer, recent immobility of surgery, or pregnancy. The development of a VTE in the presence of a thrombophilia or in the setting of taking hormone therapy was considered an unprovoked VTE. Subjects with antiphospholipid antibody syndrome or antithrombin deficiency were excluded from the analysis.

Main outcome measure. Risk of recurrent VTE by D-dimer result (positive vs. negative).

Main results. The mean age of all pooled subjects was 58.9 years (SD, 17.1), with a mean age-range among the 7 studies of 49.8 to 66.9 years. Mean BMI among pooled subjects (BMI only available for 4 of 7 studies) was 28.1 kg/m^2 (SD, 6.3), with a range across studies of 26.8 to 32.3 kg/m^2. 51% of all subjects were men. Mean duration of follow-up across all subjects was 26.9 months after the cessation of anticoagulation, and the post-anticoagulation D-dimer measures were conducted after 38.5 days on average. D-Dimer results were positive for 45.4% of subjects. The annual risk of recurrent VTE was 3.7 per 100 patient-years (95% confidence interval [CI], 3.2–4.3 per 100 patient-years) for subjects with a negative D-dimer and 8.8 per 100 patient-years (95% CI, 6.2–11.3) with a positive D-dimer. Controlling for patient age, sex, hormone therapy use, BMI, timing of post-anticoagulation D-dimer testing, and presence of inherited thrombophilia, a positive D-dimer was associated with a hazard ratio of 2.59 for recurrent VTE (95% CI, 1.90–3.52). Results were similar across all studies included in the meta-analysis, suggesting no study-specific or D-dimer assay–specific associations. Varying the cut point at which the D-dimer test was considered positive (500 µg/L vs. 250 µg/L) also had no effect on the relationship between D-dimer result and risk for recurrent VTE. The only other significant predictor of an increased risk for recurrent VTE was male sex. The development of a VTE among women taking hormone therapy was associated with a lower risk for recurrence compared with

women who were not taking hormone therapy at the time of their first VTE.

Conclusion. A positive D-dimer predicts a significantly elevated risk for recurrent VTE, regardless of the timing of the test, age of the patient, or the specific assay or cut point used.

Commentary

Unprovoked VTE is common, and the annual risk of recurrence is high [1]. Guidelines have called for lifelong anticoagulation for patients after a first unprovoked VTE, especially if bleeding risk is low [2]. However, many patients may desire a trial off anticoagulation, and patients at higher risk of bleeding require a more thorough determination of the risks and benefits of prolonged anticoagulation. D-dimer has emerged as a test that can help determine the risk for recurrent VTE [1,3,4]. D-dimer is a fibrin degradation product, and elevated levels suggest a continued prothrombotic state. Positive D-dimer results are associated with an up to 15% annual VTE recurrence rate off anticoagulation compared with recurrence rates below 5% for patients with a negative D-dimer [3]. Yet questions remain about its utility, especially for older patients, and whether characteristics of the test, such as when the D-dimer is measured or the specific cut point used to determine a positive versus negative result, might affect the relationship between D-dimer result and risk for recurrent VTE. Douketis et al conducted this meta-analysis, using patient-level data from 7 prior cohort studies, to clarify these issues.

In this study, a positive D-dimer was associated with a hazard ratio of 2.59 for recurrent VTE and an increased rate of VTE of 8.8 per 100 patient-years, compared with 3.7 per 100 patients-years for patients with a negative D-dimer (an absolute risk difference of 5.1 events per 100 patient-years). This association held regardless of age, timing of the D-dimer test after cessation of anticoagulation, and the cut point used to define a positive D-dimer (500 µg/L vs. 250 µg/L). Male sex independently predicted risk for recurrent VTE, and the occurrence of VTE in women taking hormones predicted a low risk for recurrent VTE. The results clarify several issues: (1) D-dimer testing is useful in older patients, whose higher baseline D-dimer levels had raised concerns about whether a positive D-dimer could be used to predict risk for recurrent VTE; (2) timing of D-dimer testing does not alter its ability to predict future VTE, reassuring clinicians that prior anticoagulation does not have a prolonged, meaningful effect on D-dimer after it is discontinued; and (3) the cut point defined by the manufacturer does not influence the usefulness of D-dimer.

This study had several important strengths. Most importantly, the study used a patient-level meta-analysis. Authors gathered all patient-level data from the 7 included studies, allowing for a determination of the patient-level factors that might be associated with risk for recurrent VTE or might confound the relationship between D-dimer level and risk for recurrent VTE. The number of patients included was large, providing high power to examine subgroups, and none of the studies dominated the pooled sample, with a range in sample size among the 7 studies of 110 to 497. Sensitivity analyses, which excluded patients with hormone-associated and thrombophilia-associated VTEs (which could be considered in a different category from unprovoked VTEs), did not alter the results, leading to more confidence in the conclusions of the study. All studies included in this meta-analysis were considered to be high-quality studies. The major limitations arose because of the availability of only 7 studies overall for this meta-analysis and the homogeneity of the pooled sample, with most subjects reported to be white. The authors actually failed to provide extensive demographic details about the pooled sample, which would have helped to determine how applicable these results are to broad populations.

The usefulness of D-dimer for predicting risk for recurrent VTE does not overcome the general recommendation that anticoagulation should be continued lifelong in patients with an unprovoked VTE who are at low risk for bleeding [2]. A future randomized controlled trial would be useful to clarify this issue; such a study could randomly assign patients with an unprovoked VTE and negative D-dimer after a period of anticoagulation to prolonged anticoagulation versus no anticoagulation. However, if patients with unprovoked VTE choose a trial off anticoagulation or have a high risk for bleeding, use of D-dimer will be useful for risk stratifying them. The timing of D-dimer testing appears to be flexible, compelling physicians to check D-dimer earlier rather than later, perhaps within the first month after completion of the anticoagulation course. This strategy could reduce the early recurrence risk in those patients found to have a high D-dimer.

Applications for Clinical Practice

D-Dimer is a useful test to help clarify risk of recurrent VTE in all patients after their first unprovoked VTE, regardless of age. The timing of D-dimer testing post-anticoagulation can be flexible, and the cut point for determining a positive test can be 500 µg/L or 250 µg/L.

—Review by Jason P. Block, MD, MPH

References

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