PERSPECTIVE

D-Dimer in Venous Thromboembolism

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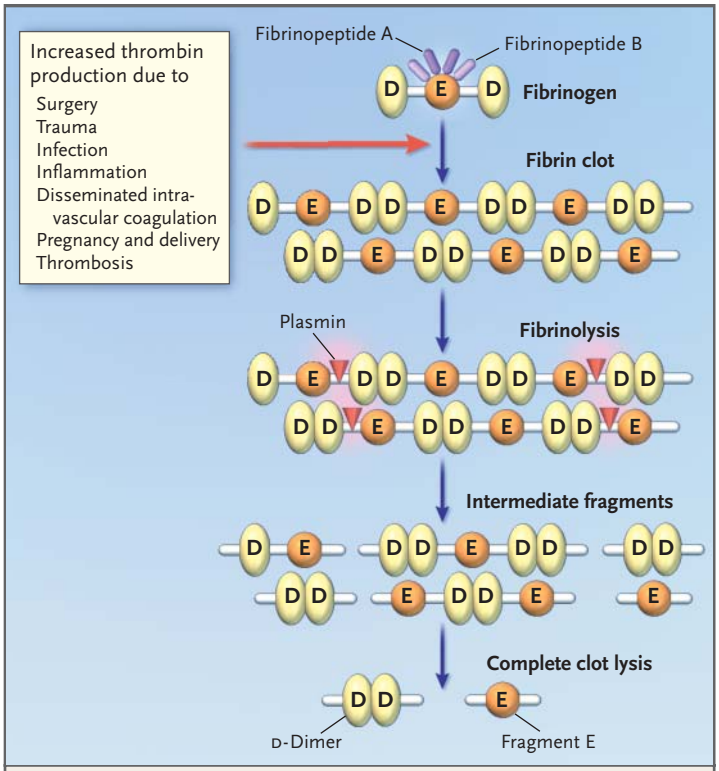
Venous thromboembolism is an important medical problem, with an estimated incidence in the United States of 100,000 to 300,000 cases per year. Of patients presenting with symptoms suggestive of deep venous thrombosis, only 30 percent actually have the disorder. In the emergency department, where medical decisions must be made rapidly, the ability to identify, safely and accurately, the 70 percent of patients with symptoms who do not have deep venous thrombosis and likewise to identify those who do have the disorder is critical. Recent studies of the clinical diagnosis of deep venous thrombosis have shown that when risk factors and possible alternative diagnoses are incorporated into a pretest clinical assessment, the predictive sensitivity of assessment increases to 75 percent.

The most sensitive and accurate test is the venogram. However, venography has limitations: it is associated with a 5 percent risk of allergic reactions, a need for considerable technical expertise, and a 1 to 2 percent risk of thrombophlebitis after the procedure. Of the noninvasive studies, real-time B-mode venous-compression ultrasonography has greater sensitivity and specificity (97 percent and 94 percent, respectively, for the identification of thrombosis in proximal leg veins) than other noninvasive techniques, such as venous Doppler ultrasonography, impedance plethysmography, and iodine-125–labeled fibrinogen scanning. The sensitivity of these techniques for calf-vein thrombosis is 73 percent at best, however, and ultrasonography is not accurate for detecting pelvic deep venous thrombosis. Twenty percent of patients who present with symptomatic deep venous thrombosis of the leg have isolated calf-vein thrombosis, and 30 percent of those patients will have subsequent extension of the clot into the proximal system.

Hence, serial ultrasound studies to detect extension of a distal clot into the proximal system are necessary. Using this approach, investigators have shown that the risk of pulmonary embolism from undetected calf-vein thrombosis with subsequent extension into the proximal venous system is less than 1 percent.[1] Sequential ultrasound analysis is expensive, however, and definitive diagnosis and treatment may be delayed. Wells et al.[2] showed that with the use of a pretest clinical-probability scoring system in which patients were divided into low-, intermediate-, and high-risk groups on the basis of clinical criteria, deep venous thrombosis could be safely ruled out on the basis of a single negative ultrasound result in patients who had a low clinical-probability score.

D-Dimer assays have been explored as tools for the diagnosis of deep venous thrombosis. D-Dimer fragments are produced during the degradation of thrombin-generated fibrin clots by plasmin. D-Dimer and fragment E are the final products of complete fibrinolysis (see Figure). Hence, the presence of D-dimer is a telltale clue that blood clotting has been initiated. The generation of monoclonal antibodies to the D-dimer fragment is the basis for the three main methods of D-dimer detection: the enzyme-linked immunosorbent assay (ELISA), the latex-agglutination assay, and whole-blood agglutination. ELISA is highly sensitive and provides quantitative results, but it is not specific for deep venous thrombosis, since it detects low levels of fibrin in a variety of conditions, such as infection, inflammation, vasculitis, pregnancy, trauma, and hemorrhage and after surgery, in association with incisions; moreover, ELISA is technically time-consuming.

Latex-agglutination assays are inexpensive and rapid but have a sensitivity of 80 percent, making them unsuitable for the diagnosis of deep venous thrombosis. Quantitative, automated latex assays, such as IL-Test D-Dimer, in which the degree of D-dimer–induced latex agglutination is measured by the decrease in light transmittance at 405 nm, are both sensitive and rapid, but they require spe-



Plasmin Degradation of a Fibrin Clot.

Fibrinogen is shown as a trinodular structure consisting of two D domains separated by a central E domain. Thrombin cleavage of fibrinopeptide A and fibrinopeptide B from fibrinogen results in the end-to-end association of D domains and the half-staggered lateral assembly of protofibrils, respectively, into fibrin clot. During fibrinolysis of fibrin, plasmin cleaves factor XIIIa–cross-linked fibrin into an array of intermediate forms. The D-dimer and E fragments are the result of terminal fibrin degradation.

cial equipment. Whole-blood agglutination assays, such as SimpliRED, are qualitative red-cell agglutination assays in which the monoclonal antibody specific for D-dimer is linked to a monoclonal antibody that binds to red cells. The results of whole-blood D-dimer assays have been criticized as being operator-dependent. An assay must approach 100 percent sensitivity to be the sole criterion for deciding whether a patient has deep venous thrombosis. However, D-dimer assays with a high negative predictive value for deep venous thrombosis may be useful for ruling out this disorder in patients with symptoms.

In a study reported in this issue of the *Journal* (pages 1227–1235), Wells et al. evaluated patients with symptoms of deep venous thrombosis by means of a clinical scoring system and then randomly assigned the patients to ultrasound imaging or to D-dimer testing with either the SimpliRED assay or the IL-Test, both of which have a high negative predictive value for deep venous thrombosis. They report that patients with a low clinical probability of deep venous thrombosis and a negative result on D-dimer testing could safely forgo further ultrasound testing. In patients in whom clinical scoring indicated that deep venous thrombosis was likely, serial ultrasound studies were required only in those who had a positive result on D-dimer testing.

A definitive diagnosis was made on the day of presentation in 82 percent of the patients who were randomly assigned to a D-dimer assay, as opposed to 65 percent of the patients assigned to ultrasonography. It is notable that in only 0.4 percent of the patients in whom deep venous thrombosis was ruled out did the disorder develop during follow-up. This study shows that the use of a D-dimer assay with a high negative predictive value for deep venous thrombosis, in conjunction with a pretest clinical scoring system, allows unnecessary ultrasound studies to be safely omitted in the evaluation of outpatients.

A strategy combining clinical assessment with D-dimer testing in the initial evaluation of outpatients with suspected deep venous thrombosis is a potentially powerful means to rule out the disorder rapidly and safely, without the need for ultrasonography. D-Dimer assays have not been standardized, however, and the results of the study by Wells et al. cannot necessarily be extrapolated to results obtained by other laboratories or with other D-dimer assay methods. Nevertheless, clinicians should strongly consider the D-dimer management strategy in the evaluation of outpatients with possible deep venous thrombosis. Before implementing the strategy, however, hospital laboratories should validate their D-dimer assay method and ensure that operators are proficient in the interpretation of assay results.

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1. Cogo A, Lensing AW, Koopman MM, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. Br Med J 1998;316:17-20.
2. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995;345:1326-30.