D-Dimer: A Warning for DVT

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Deep vein thrombosis (DVT) is a common medical condition that requires accurate diagnosis and prompt therapy to minimize the risk of pulmonary embolism (PE). It is inaccurate to diagnosis DVT by signs and symptoms alone.

When appropriate testing is performed, only 10% to 30% of patients referred with suggestive clinical findings have DVT. Objective testing involves compression ultrasonography of the proximal deep veins (if negative, repeat testing in one week to exclude proximal extension of isolated calf vein thrombosis) and occasional venography.

Despite advances, currently accepted testing strategies based on radiologic tests continue to have shortcomings. These shortcomings include the rare availability of radiologic tests at night or on weekends; the gold standard test (venography) is invasive, expensive and difficult to perform and interpret well; and strategies involving compression ultrasonography usually require serial studies.

D-dimer has the potential to simplify the evaluation of these patients because it is a relatively inexpensive, noninvasive screening test.

Chris' case

- Chris, 34, presents to the ED with a two day history of left calf pain and swelling.
- He has no personal or family history of deep vein thrombosis (DVT) or pulmonary embolism (PE).
- Chris does not recall injuring his leg and is otherwise healthy with no significant medical history.
- On examination, Chris' left calf appears slightly swollen and is 2 cm larger in circumference than the right, when measured 10 cm below the tibial tuberosity.
- There is 1+ pitting edema of the distal left leg and the calf and popliteal *fossa* are tender.
- The physician suspects Chris has a DVT and wonders if this diagnosis can be ruled out without calling the ultrasound technician.

The next step in diagnosing Chris is on page 75.

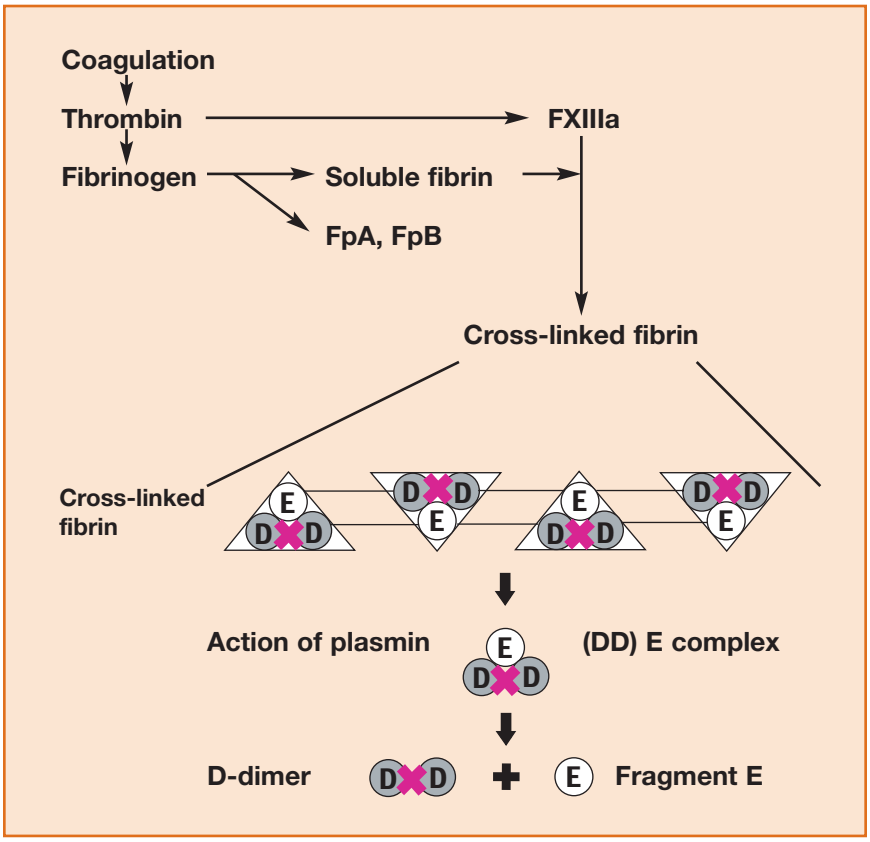

Figure 1. Formation of D-Dimer: Thrombin is formed during the clotting process. This enzyme cleaves fibrinopeptide A and fibrinopeptide B from fibrinogen, a protein made of three pairs of polypeptide chains connected by disulfide bonds to form three globular domains consisting of a central E domain connected to two D domains on either side. The resultant soluble fibrin monomers polymerize into an insoluble fibrin network and are further stabilized by covalent cross-links introduced by activated factor XIII. The cross-linking of fibrin generates unique antigenic determinants, one of which is the bond between the two D-domains of adjacent fibrin monomers. Thrombus formation is normally followed by a fibrinolytic response in which plasmin is generated and breaks down fibrinogen and fibrin. Plasmin is unable to break the covalent bonds between D-domains. Thus, when cross-linked fibrin is lysed, some of the degradation products contain D-dimer, the structure formed by cross-linked adjacent D-domains.

What is D-dimer?

D-dimer is a specific fragment of a cross-linked fibrin clot that is released into the blood when a clot is lysed by plasmin (Figure 1). D-dimer is an indirect marker of thrombotic activity.

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How is D-dimer measured?

The presence of D-dimer in plasma can be detected using monoclonal antibodies that recognize epitopes specific to the cross-linked D-dimer fragment. A variety of commercial D-dimer assays are available, which are based on the use of these monoclonal antibodies; however, there are generally three different assay formats (Figure 2).

#1 *Whole red blood cell agglutination assays:*

These tests use a bispecific antibody conjugate with binding sites for both D-dimer and a red cell antigen.

#2 *Enzyme-linked immunosorbent assays (ELISAs):*

The initial ELISAs were expensive, laborious and time consuming. A number of rapid variants suitable for clinical use have been developed.

#3 *Latex particle assays:*

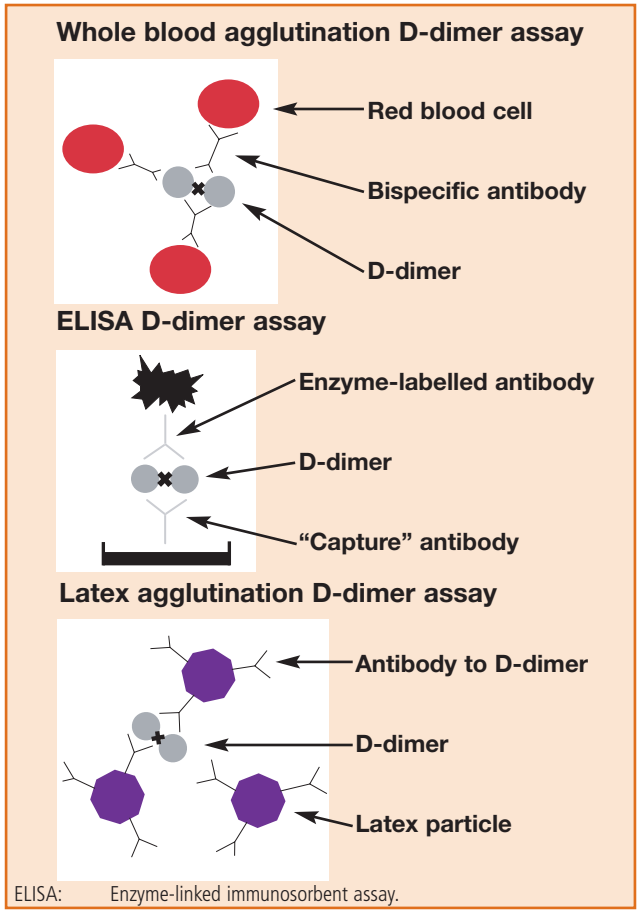
Earlier versions of these assays were qualitative or semiquantitative and were used to help confirm disseminated intravascular coagulation. These first-generation assays are unsuitable for evaluating patients with suspected DVT. Newer, automated quantitative versions (immunoturbidimetric assays) are performed on routine laboratory coagulometers.

It is important to recognize that results are incomparable between different assays, even those of similar formats. Reasons for this include:

- Distinct monoclonal antibodies with varying specificities for fibrinogen and fibrin breakdown products
- Dissimilar discriminant values used to determine positive and negative results
- Different commercial calibrants
- Variation in patient populations used to evaluate specific assays

How are D-dimer assays interpreted?

Levels of D-dimer are typically elevated with acute venous thromboembolism (DVT and PE). However,



ELISA: Enzyme-linked immunosorbent assay.

Figure 2. All assay formats utilize monoclonal antibodies that recognize epitopes specific to the D-dimer fragment. The whole blood agglutination assay uses a bispecific antibody conjugate with binding sites for both D-dimer and a red cell membrane antigen. In the presence of elevated D-dimer levels there is visible agglutination of the patient's red cells. Enzyme linked immunosorbent assays (ELISAs) are sandwich assays that rely on the use of two antibodies—a capture antibody and a tagging antibody. In latex agglutination assays, monoclonal antibodies specific for D-dimer are coated onto latex particles and particle agglutination is used to detect D-dimer.

More on Chris' case

- The ED physician applies the Wells model and determines that Chris' pretest probability of DVT is moderate (score of +2, with 1 point each for pitting edema and tenderness).
- The results of the D-dimer test are negative.
- The physician wonders if DVT has been excluded.

To learn if DVT has been excluded, turn to page 76.

Back to Chris' case

- The ED physician is told by the lab that the hospital uses a highly sensitive D-dimer that has been shown to rule out DVT in patients with a low or moderate likelihood of DVT.
- Chris is reassured after reviewing the test results and is comfortable making a follow-up appointment with his family physician regarding further management and investigation of his symptoms.
- Chris is instructed to return to the ED if his leg symptoms worsen or if he develops chest pain or shortness of breath.

levels are also increased in a variety of inflammatory and prothrombotic conditions associated with activation of coagulation, which includes:

- Recent surgery
- Recent trauma
- Infection
- Pregnancy and puerperium
- Disseminated intravascular coagulation
- Cancer
- Myocardial infarction
- Connective tissue disorder
- Advanced age

Certain types of assays may yield false-positive results, as seen with high levels of rheumatoid factor, lipemia, hyperbilirubinemia and hemolysis. In general, the specificity (proportion of patients without DVT who have a negative D-dimer result) of D-dimer tests for DVT is low and a positive

Table 1

D-Dimer outcome studies in patients with suspected DVT

	Strategy used to exclude DVT	Reference	False negatives (%)
Moderate sensitivity D-Dimer	Negative whole red blood cell agglutination assay (SimpliRED) plus negative ultrasound at presentation	3-Kraaijenhagen 4-Kearon	0.7 1.0
	Negative whole red blood cell agglutination assay (SimpliRED) plus low pretest probability	5-Kearon 6-Anderson 7-Wells	0.6 1.0 0.9
High sensitivity D-Dimer	Negative ELISA (VIDAS, < 500 ug/L,) plus negative ultrasound at presentation	8-Perrier	0
	Negative Instant IA, ≤ 0.5 ug/mL, plus negative ultrasound at presentation	9-Bernardi	0.2
	Negative immunoturbidometric assay (MDA, < 0.5 ug/mL), plus low or moderate pretest probability	10-Bates	0.4
	Negative Tinaquant, < 500 ug/L, plus low or moderate pretest probability	11-Schutgens	0.6

Table 2

Standardized model used to assess pretest probability of DVT[2]

Clinical features	Score
Active cancer (treatment ongoing or within previous six months or palliative)	+1
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for more than three days or major surgery, within four weeks	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	+1
Pitting edema (greater in the symptomatic leg)	+1
Collateral superficial veins (nonvaricose)	+1
Alternative diagnosis as likely or greater than that of DVT	-2
Score < or = 0: low probability Score 1 or 2: moderate probability Score > 2: high probability	-2 to 8

result can not be used to include the diagnosis (*i.e.,* these assays have a low positive predictive value [the proportion of patients with a positive test result who actually have DVT] for DVT). However, some D-dimer assays are sensitive (proportion of patients with DVT who have a positive test result) for DVT and the absence of elevated D-dimer levels makes the diagnosis of DVT less likely (*i.e.,* these assays have a high negative predictive value [proportion of patients with a negative test result who do not have DVT]). Thus, the potential value of D-dimer in suspected DVT is as an exclusionary tool.

What is the evidence for using D-dimer testing to rule out DVT?

Although each D-dimer assay has its own performance characteristics, the clinically useful D-dimer assays appear to be divisible into two main categories:

1. Assays with a very high sensitivity, but a rather low specificity
2. Assays with a moderate sensitivity, but a higher specificity

The first group typically includes the ELISA and certain immunoturbidimetric assays, while the second category includes the whole red blood cell agglutination assays. In order to safely rule out DVT, a D-dimer assay, used alone or in combination with other tests, should yield a false-negative result of 1% to 2% in clinical follow-up,[1] which is equivalent to the failure rate of venography or serial compression ultrasonography.

The results of clinical outcome studies that used D-dimer assays in the evaluation of patients with suspected DVT are summarized in Table 1. Most of these studies were conducted in outpatients and have used D-dimer testing in combination with either compression ultrasonography or clinical (pre-test probability) assessment. Although empiric assessment has been used, most of these studies incorporated the Wells model,[2] a validated structured clinical prediction guide (Table 2).

How are D-dimer assays used in patients with suspected DVT?

Although it has been suggested that highly sensitive D-dimer assays have the potential to be used as stand-alone tests to rule-out DVT, this has not been studied and is not recommended. A negative result with either category of D-dimer combined with a negative compression ultrasound at presentation appears to eliminate the need for serial ultrasounds. Although a negative result with a highly sensitive D-dimer assay has been used to exclude DVT in patients with a low or moderate pre-test probability of DVT, if a moderately sensitive D-dimer is used, a negative result only excludes DVT in those with a low pre-test probability. Dx

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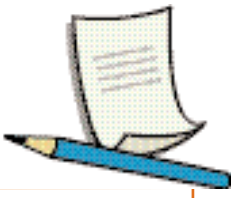
Take-home message



1. If D-dimer forms part of a diagnostic strategy, the details of the assay should be known, including type, operating characteristics (sensitivity and negative predictive value) and outcomes of clinical studies evaluating that particular assay. In general, an assay with proven sensitivity that has been validated in a patient population similar to that in which it will be used should be chosen. It has been suggested that institutions should audit ongoing performance of its D-dimer assay.
2. When DVT is suspected but access to diagnostic testing is likely to be delayed, it is common practice to administer empiric heparin before the diagnosis is confirmed. Several studies have shown a fall in D-dimer levels following anticoagulation with heparins, increasing the potential for a false-negative result. When possible, D-dimer assays should be performed on blood drawn prior to initiation of heparin therapy.
3. A negative D-dimer on its own does not rule out DVT.
4. A positive D-dimer does not diagnose DVT. If a patient's D-dimer result is positive, further radiologic testing (typically with compression ultrasonography) should be undertaken.