D-Dimer Assays in Diagnosis and Management of Thrombotic and Bleeding Disorders

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Abstract

D-dimer is a global indicator of coagulation activation and fibrinolysis and, therefore, an indirect marker of thrombotic activity. The utility of D-dimer measurement has been evaluated in several clinical situations including the exclusion of venous thromboembolism (VTE), prediction of future risk of VTE, and the diagnosis and monitoring of disseminated intravascular coagulation (DIC). Assay standardization remains problematic and clinicians need to be aware of variability in D-dimer assay performance and the characteristics of their institution's test when making clinical decisions. This article will review the available evidence for the utilization of D-dimer antigen measurement in the management of thrombotic and bleeding disorders.

Keywords
- D-dimer
- venous thromboembolism
- recurrence
- anticoagulant duration

D-dimer is a global indicator of coagulation activation and fibrinolysis and, therefore, an indirect marker of thrombotic activity. This specific cross-linked fibrin degradation product is formed through the sequential action thrombin, activated factor XIII (FXIIIa), and plasmin (►**Fig. 1**).[1–3] First, thrombin, generated when coagulation is activated, converts fibrinogen to fibrin and activates FXIII. Second, FXIIIa covalently cross-links D-domains in adjacent fibrin monomers. Third, plasmin (formed on the fibrin surface by plasminogen activation) cleaves substrate fibrin at specific sites, and when it cleaves fibrin cross-linked by FXIIIa, it generates D-dimer. D-dimer is cleared through the kidneys and the reticuloendothelial system and has a plasma half-life of approximately 8 hours.[4] Low levels of D-dimer can be found circulating under normal physiologic conditions, while pathologically elevated levels can be found in any condition associated with enhanced fibrin formation and fibrinolysis (►**Table 1**).[1–3] The utility of D-dimer measurement has been evaluated in several clinical situations; however, the D-dimer assays have been best validated for the exclusion of venous thromboembolism (VTE) and the diagnosis and monitoring of disseminated intravascular coagulation (DIC). This article will review the available evidence for the utilization of D-dimer antigen measurement in the management of thrombotic and bleeding disorders.

Measurement of D-Dimer

The presence of D-dimer in plasma can be detected using monoclonal antibodies that recognize an epitope present in FXIIIa-cross-linked fragment D-domain of fibrin but not in fibrinogen degradation products or noncross-linked fibrin degradation products. Many different D-dimer assays have been developed and marketed. All of these tests rely on the use of monoclonal antibodies to detect D-dimer molecules. In general, three techniques are available to assay D-dimer (►**Fig. 2**).[1–3] These are (1) enzyme-linked immunosorbent assays (ELISAs) that rely on antibody capture and labeling of D-dimer; (2) a whole-blood agglutination assay (SimpliRED, Siemens Healthcare Diagnostics, Newcastle, DE), that uses a bispecific antibody conjugate with binding sites for both D-dimer and a red cell antigen and is performed on whole blood; (3) latex agglutination assays that also use bispecific antibodies with specificity for the latex particle and D-dimer antigen. Earlier latex agglutination assays for D-dimer were qualitative or semiquantitative; however, newer automated, quantitative D-dimer assays (which are immunoturbidometric assays) are performed on routine, automated coagulation instruments. It is important to recognize that results are not comparable between different assays, even between those of similar formats. Potential reasons for the lack of comparable results are listed in ►**Table 2**. Numeric results of D-dimer

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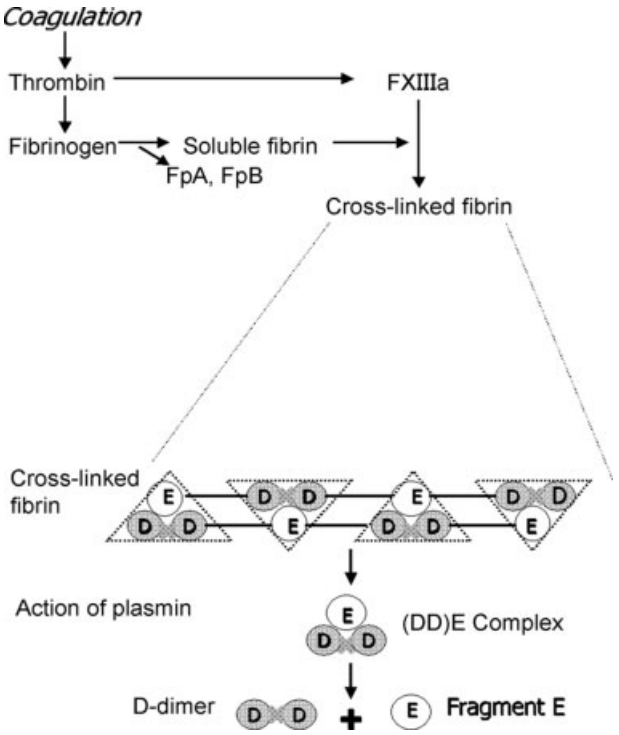

Fig. 1 Formation of D-dimer: During the process of clotting, thrombin is formed. This enzyme cleaves fibrinopeptide A (FpA) and fibrinopeptide (FpB) from fibrinogen, a protein made of three pairs of polypeptide chains connected by disulfide bonds to form three globular domains consisting of a central 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 (FXIIIa). The cross-linking of fibrin generates unique antigenic determinants, one of which is the bond between the two D-domains of adjacent fibrin monomers. Plasmin is generated during the fibrinolytic response and breaks down fibrinogen and fibrin; however, it is unable to break the covalent bonds between D-domains. Therefore, when cross-linked fibrin is lysed, some of the degradation products contain D-dimer, the structure formed by cross-linked adjacent D-domains. (Reproduced with permission from Bates SM. D-dimer: a warning for DVT. *Can J Diagnosis*. 2006;23:73–78).

measurements are reported as either a D-dimer concentration (for assays that use purified fibrin fragment D-dimer as the calibrator for their reference curves) or as fibrinogen equivalent units (FEUs, if the calibration material is obtained from controlled plasmin digestion of purified fibrinogen clotted in the presence of FXIIIa) depending on the material used to calibrate the assay-specific reference curve.[3] D-dimer concentrations can be approximately transformed to FEU by multiplying the result by two. Clinicians, therefore, should be aware of the specific assay used at their institution and its performance characteristics. It has been difficult to standardize D-dimer testing and, at present, the results of each assay should be considered method specific.[5,6]

Interpretation of D-Dimer Assay Results

Levels of D-dimer are typically elevated with acute VTE. However, elevated levels are also present in a wide variety of inflammatory and prothrombotic conditions (►**Table 1**). With certain types of assays, false-positive results may also be seen with high levels of rheumatoid factor, lipemia, hyperbilirubinemia, and hemolysis. The ideal D-dimer assay is easily performed, with rapid result availability, and characterized by high diagnostic sensitivity and a specificity that is high enough to be useful, along with good reproducibility around the cutoff value.[2] Clinicians should ensure that the assay they are using has been validated in patient management studies.

Table 1 Conditions associated with elevated D-dimer levels

• Venous thromboembolism (deep vein thrombosis and pulmonary embolism)
• Surgery
• Trauma
• Burns
• Infection
• Pregnancy and the puerperium
• Disseminated intravascular coagulation
• Cancer
• Myocardial infarction
• Stroke
• Atrial fibrillation
• Connective tissue disorders
• Inflammatory bowel disease
• Thrombolytic therapy
• Hemolysis
• Advanced age

Diagnostic Utility of D-Dimer in the Evaluation of Suspected Venous Thromboembolism

D-dimer tests have been used in the evaluation of suspected deep-vein thrombosis (DVT) and, subsequently, suspected pulmonary embolism (PE), for the past 20 years[1,3,7–10] and their incorporation into diagnostic algorithms has been refined over time. D-dimer levels are typically elevated in

Table 2 Reasons for differences between D-dimer assays

• Different monoclonal antibodies with varying specificities for fibrinogen and fibrin breakdown products
• Different assay formats
• Differences in instrumentation
• Different assay calibration standards
• Variation in discriminant values used to determine positive and negative results
• Differences in patient populations used to evaluate specific assays

patients with acute VTE.[1–3,7–10] However, because D-dimer levels may also be increased in a variety of nonthrombotic disorders, D-dimer is a sensitive but nonspecific marker for venous thrombosis. Consequently, although a positive result is not useful in confirming the diagnosis of DVT or PE, a negative result can aid in the exclusion of these conditions and limit the need for further investigation with expensive and invasive radiologic tests.[1,3,7–10] In hospitalized and other acutely ill patients commonly affected by the conditions listed in ►**Table 1**, D-dimer testing has less utility because of the high frequency of false-positive results.[7,11,12] Most of the data validating the use of D-dimer testing in suspected VTE come from evaluations of patients in the ambulatory setting (i.e., outpatient or emergency departments).[13] When VTE is suspected but access to diagnostic testing is likely to be delayed, it is common practice to administer empiric heparin or low molecular weight heparin before the diagnosis is confirmed or excluded. Studies have shown a fall in D-dimer levels following anticoagulation with heparins, increasing the potential for a false-negative result. Although the effect of short courses of heparin therapy and the time course of reductions in D-dimer levels is still a matter of debate, one review suggests that clinically significant decreases in D-dimer levels can be seen after 24 hours of therapy.[14] Therefore, when possible, D-dimer assays should be performed on blood drawn prior to initiation of heparin therapy.

Although each D-dimer assay has its own performance characteristics, the clinically useful D-dimer assays appear to be divisible into two main categories – those with a very high sensitivity but a rather low specificity and those with a moderate sensitivity but a higher specificity. In a meta-analysis of over 300 studies, ELISAs, enzyme-linked fluorescent assays (ELFAs), and quantitative latex or immunoturbidometric assays were more sensitive for VTE (sensitivity $> 90\%$) than were other assay types (►**Table 3**).[7] Based on these data, ELISAs and ELFAs, along with the latex immunoturbidometric assays, are generally termed "highly sensitive," while the whole-blood D-dimer assay is considered "moderately sensitive." The more sensitive assays displayed lower specificities for VTE than the less sensitive tests. To safely rule out VTE, a negative D-dimer assay result when used alone or with other tests, should yield equivalent failure rates in clinical follow-up as reference standard tests such as negative venography for DVT and negative pulmonary angiography or a normal ventilation–perfusion lung scan for PE (i.e., failure rates of 2% or less; negative predictive value of at least 98%).[3,7–13,15–17]

Multiple studies have investigated the use of D-dimer testing, either alone or in combination with noninvasive tests or clinical pretest probability assessment, to manage patients with suspected lower extremity DVT or PE.[3,9,10,13,18–42] Based on the results of these investigations, recent guidelines recommend the use of initial D-dimer testing when evaluating patients with either a low (with either a moderately or highly sensitive D-dimer assay) or moderate pretest probability (highly sensitive D-dimer only) of DVT.[13] If the D-dimer assay result is negative (below the threshold value), DVT is excluded and no further testing is necessary. However, a positive D-dimer result should be followed by venous ultrasonography of the affected leg. There have been no large management studies confirming the safety of excluding DVT solely on the basis of a negative D-dimer result in high pretest probability patients[13] and, therefore, initial testing with venous ultrasonography is recommended. However, a negative result using a highly sensitive D-dimer assay can obviate the need for serial ultrasound studies in this patient population.[13] If an initial pretest probability assessment is not undertaken, venous ultrasonography is the recommended first test. Again, a negative D-dimer result (using either a moderate or high-sensitivity assay in this case) eliminates the need for serial ultrasonography.[13]

Similar strategies can be used in patients with suspected PE. PE can be considered excluded in patients with a negative moderate sensitivity D-dimer test and low pretest probability[33–35] and in those with a negative highly sensitive D-dimer and a nonhigh pretest probability.[23,36–42]

Table 3 Accuracy indices of D-dimer assay methods in suspected venous thromboembolism[a]

	ELISAs[b]	ELFAs[c]	Latex agglutination			Whole-blood assay
			Immunoturbidometric	Semiquantitative	Qualitative	
Deep vein thrombosis						
Sensitivity, % (95% CI)	94 (86–97)	96 (89–98)	93 (89–95)	85 (68–93)	69 (27–93)	83 (67–93)
Specificity, % (95% CI)	53 (38–68)	46 (31–61)	53 (46–61)	68 (53–81)	99 (94–100)	71 (57–92)
Pulmonary embolism						
Sensitivity, % (95% CI)	95 (84–99)	97 (88–99)	95 (88–98)	88 (66–97)	75 (25–96)	87 (64–96)
Specificity, % (95% CI)	50 (29–71)	43 (23–65)	50 (36–64)	66 (43–83)	99 (94–100)	69 (48–84)

Abbreviation: CI, confidence interval.
[a]Data from Di Nisio et al.[7]
[b]ELISAs = enzyme-linked immunosorbent assays; data restricted to microplate assay format.
[c]ELFAs = enzyme-linked fluorescent assays.

Testing with either computerized tomographic (CT) pulmonary angiography or ventilation–perfusion lung scanning is recommended in patients with a positive D-dimer result and in all patients with a high pretest probability.

Few studies have evaluated diagnostic strategies for suspected upper extremity DVT and it is not clear that diagnostic research for lower extremity thrombosis can be extrapolated to upper extremity disease.[13] One study evaluated the accuracy of a rapid quantitative ELISA in 52 consecutive patients.[43] Although the sensitivity was 100% (95% confidence interval [CI], 78 to 100%), the specificity was only 14% (95% CI, 57 to 72%). Moreover, venous ultrasonography was used as the reference standard test rather than venography, making this accuracy determination potentially unreliable. No studies have evaluated the utility of D-dimer testing in the management of patients with suspected upper extremity DVT. Therefore, the role of D-dimer testing in this patient population remains uncertain.[13,44]

D-dimer assays have been less extensively evaluated in patients with suspected recurrent VTE than in those with a suspected first event.[13] D-dimer levels appear to return to normal values within 3 months of starting treatment for acute VTE in many patients[45] and generally remain within the normal range after anticoagulant therapy is withdrawn in the majority of patients.[46] Therefore, D-dimer testing should be useful in patients with suspected recurrence.

The high frequency of residual radiologic abnormalities after initial DVT makes the investigation of patients with suspected recurrence using standard radiologic tests difficult[13] and laboratory assays, like D-dimer, have the potential to be very useful in this setting. Five prospective cohort management studies have reported results for strategies involving D-dimer testing in patients with suspected recurrent DVT.[19,47–50] In a randomized trial of 1,096 outpatients with suspected DVT, of whom 102 had prior VTE,[19] the combination of an unlikely pretest probability (using the modified Wells model, which includes a history of previous VTE as one of the factors used to determine clinical probability) and negative D-dimer (either moderate or high sensitivity) had a frequency of VTE during 3-month follow-up of 0.9% (95% CI, 0.3 to 3.3%); however, results for the 102 patients with suspected recurrence were not presented separately. In two studies in which a negative sensitive D-dimer was used either in combination with an unlikely pretest probability using the modified Wells model[48] or a compression ultrasound at presentation that was either normal or showed an increase in residual diameter of less than 4 mm[49] to exclude recurrence, no patients experienced VTE during 3 months of follow-up. However, the first strategy may have limited utility as the combination of a negative D-dimer and unlikely pretest probability occurred in only 15% of patients.[48] Two larger prospective cohort studies suggest that negative results with highly sensitive assays exclude DVT in outpatients with suspected recurrent disease.[47,50]

D-Dimer Testing for Suspected Venous Thromboembolism during Pregnancy

Although D-dimer has assumed an increasingly prominent role in the exclusion of acute VTE in the nonpregnant population, it has not yet been rigorously evaluated in pregnant patients.[13] D-dimer levels increase with gestational age and during complicated pregnancies.[51–54] This reduces the test's specificity for VTE and by the third trimester, only a minority of healthy pregnant women will have a negative D-dimer results when highly sensitive assays and the same cutoff point as in the nonpregnant population are used.[54–57] An accuracy study of the whole-blood D-dimer assay in pregnant women with suspected DVT reported a sensitivity of 100% (95% CI, 77 to 100%) and a specificity of 60% (95% CI, 62 to 68%).[58] False-positive results were documented in only 51% of third-trimester patients, suggesting that this test warrants further investigation. The utility of this assay in pregnant women has not been evaluated in prospective management studies. The specificity of highly sensitive D-dimer assays for pregnancy-related DVT may be improved without sacrificing sensitivity by using higher D-dimer cut-point values[59]; however, validation in prospective management studies is required. D-dimer testing, therefore, is not recommended as a first line investigation in pregnant women with suspected DVT or PE.

D-Dimer Testing for Suspected Venous Thromboembolism in the Elderly

D-dimer testing is more likely to give a positive result in the elderly, limiting the usefulness of the test in these patients.[60,61] However, the combination of a low or unlikely pretest probability with a negative D-dimer result can still safely exclude DVT in a proportion of elderly patients.[62] An age-dependent D-dimer cutoff value, calculated by multiplying the age of the patient by 10 in those older than 50 years (e.g., the D-dimer cutoff value for a patient 65 years of age would be 650 µg FEU/L instead of the conventional 500 µg FEU/L), has been proposed for use in older patients with suspected VTE. This age-specific cut-point has been shown in retrospective analyses to substantially increase the proportion of elderly patients in whom the diagnosis of PE[63] and DVT[64] can be safely excluded. However, before this strategy is accepted into clinical practice, it is necessary to prospectively validate it in a diagnostic management study with patient's follow-up.

D-Dimer Testing for Suspected Venous Thromboembolism in Patients with Cancer

The utility of D-dimer testing in patients with cancer may be affected by both the high prevalence of VTE and the higher frequency of elevated baseline D-dimer levels in this group.[65] Although some studies have demonstrated that D-dimer testing has a lower negative predictive value in oncology patients,[65] other authors have reported that these assays have a comparable ability to exclude VTE in patients with cancer, as in those without an underlying malignancy.[66–68] A pooled analysis of databases from three prospective D-dimer diagnostic studies evaluating consecutive outpatients with suspected DVT that included a total of 2,696 patients, of whom 200 had cancer (83 or 41.5% with confirmed DVT) found that the negative predictive values of a negative D-dimer in combination with a low or unlikely pretest probability score

were 100% (95% CI, 69.8 to 100%) and 100% (95% CI, 82.8 to 96.6%), respectively, in those with cancer.[69] Although this combination of results appears similarly safe in oncology patients with suspected DVT as in those without cancer, it occurs relatively uncommonly in cancer patients (less than 15% of the time), limiting the clinical utility of this strategy in this population. Therefore, in general, cancer patients with suspected VTE should undergo diagnostic imaging, rather than D-dimer testing.

Using D-Dimer to Predict Venous Thromboembolism

D-dimer has also been evaluated in clinical settings associated with an increased likelihood of DVT and PE.[1,3] This section will briefly review the use of D-dimer to determine duration of anticoagulant therapy in patients with a history of unprovoked VTE and the need for primary prophylaxis in cancer patients.

D-Dimer Testing for Duration of Anticoagulant Therapy

Follow-up of patients for prolonged periods after an initial DVT or PE has revealed that VTE is a chronic illness requiring life-long prevention strategies. When anticoagulant therapy is stopped, there is a persistently elevated risk of recurrence that is highest soon after the acute episode and declines with time.[70] Several studies have examined the risk of recurrence after discontinuation of anticoagulation and available data suggests that this risk is largely determined by whether the acute episode has been effectively treated and by the patient's intrinsic risk of having a new episode of VTE (individual risk of recurrence).[70] The presence or absence of a reversible provoking risk factor at the time of the initial event and active cancer are among the most important factors influencing the risk of recurrent thrombosis after discontinuation of anticoagulant therapy.[70] The risk of recurrence following anticoagulant cessation is lower if the provoking factor was a recent surgery compared with a nonsurgical risk factor (e.g., airplane travel for 8 hours or more, pregnancy or estrogen therapy) at 1 versus 5% after 1 year and 3 versus 15% after 5 years. The risk of recurrence is 10% after 1 year and 30% after 5 years in patients who developed an unprovoked venous thromboembolic event and likely to be even higher in those with active cancer (perhaps 15% per year).[70]

The only way to prevent recurrent VTE is to continue anticoagulant therapy. Although ongoing anticoagulation is very effective for reducing the risk of recurrence, it is associated with risks of major bleeding. In general, decisions regarding duration of anticoagulant therapy after VTE should be individualized and based on balancing the risk of recurrence if anticoagulant therapy is stopped, with the risks of bleeding associated with ongoing anticoagulation. Anticoagulant therapy for VTE is generally continued until its benefits (reduction of recurrence) no longer clearly outweigh its risks (increase in bleeding) or it is patient's preference to stop treatment even if continuing treatment is expected to be of net benefit. Recent evidence-based clinical practice guidelines[70] give a strong recommendation for 3 months of anticoagulation for patients with VTE associated with a reversible provoking risk factor and for those with unprovoked VTE and a high bleeding risk. It is suggested that anticoagulant therapy be extended for patients diagnosed with unprovoked VTE who are judged not to be at high risk of bleeding. However, it would be helpful to know if there is a subset of these latter patients who are at lower risk of recurrence and are less likely to benefit from indefinite exposure to a potentially life-threatening and inconvenient intervention.

It has been suggested that laboratory evidence of activation of the coagulation system after withdrawal of anticoagulants may be related to the risk of recurrent VTE. Recent prospective studies have evaluated D-dimer to determine if this test can be used to help physicians better determine which patients may be considered at low enough risk to safely discontinue anticoagulation after a defined period of treatment. Two systematic reviews that examined the use of D-dimer measured after discontinuation of anticoagulants for unprovoked VTE reported approximately a doubling of the risk of recurrence for those with a positive D-dimer result compared with those with a negative D-dimer.[71,72]

In only one of the studies included in these meta-analyses was D-dimer measurement used to manage patients. The PROLONG study was a multicentre trial of 708 patients with a first unprovoked venous thromboembolic event who had received at least 3 months of oral anticoagulant therapy.[73] D-dimer testing was performed approximately 1 month after anticoagulant withdrawal, using a qualitative D-dimer (Simplify D-Dimer assay; Instrumentation Laboratory, Milan, Italy). Patients with a negative result did not resume anticoagulants, while those with a positive D-dimer were randomized to resume warfarin or remain off therapy. All patients were followed for recurrent VTE and suspected events were adjudicated blindly using an independent central committee. Patients with an abnormal D-dimer who remained off anticoagulant therapy appeared to be at higher risk of recurrence than those with a negative D-dimer (hazard ratio of 2.27; 95% CI, 1.15 to 4.46) and those with a positive result who remained on warfarin (hazard ratio of 4.26; 95% CI, 1.23 to 14.6) (►**Table 4**). Extended follow-up suggests that the recurrence risk in those with a negative D-dimer is 5% per year.[74] The variability in performance characteristics for different D-dimer assays suggests that validity of these findings should be confirmed for each assay, ideally with a prospective management study. Furthermore, it is not clear whether the annual risk of recurrence in those with a negative D-dimer (5 versus 2% for those with a positive D-dimer who remained on warfarin), is sufficiently low to convince patients (and physicians) to stop anticoagulant therapy.

Combinations of factors have the potential to be more important predictors of recurrence risk than single factors. Previous studies have shown that male sex is associated with a higher risk of recurrence, whereas females (especially those with thrombosis associated with hormonal therapy) are thought to be at lower risk.[70,75–78] In a post hoc analysis, the PROLONG investigators sought to investigate whether age and sex could be used to further stratify risk of recurrence associated with a negative D-dimer

Table 4 Risk of recurrent venous thromboembolism based on D-dimer levels drawn 1 month after discontinuation of anticoagulants for unprovoked venous thromboembolism[a]

	Recurrent venous thromboembolism	
	Events	%/Patient-year
Negative D-dimer[b] + no warfarin	24/385	4.4
Positive D-dimer[b] + no warfarin	18/120	10.9
Positive D-dimer[b] + warfarin	3/103	2.0

[a]Data from Palareti et al.[73]
[b]Simplify D-dimer (Simplify D-dimer assay; Instrumentation Laboratory, Milan, Italy).

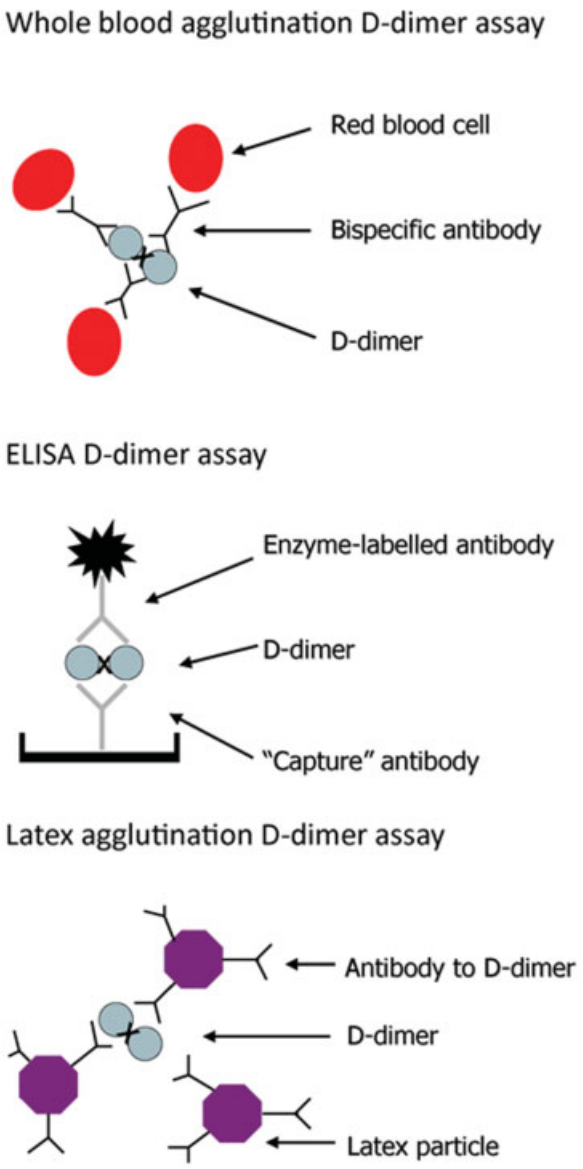

Fig. 2 D-dimer assay formats: All assay formats utilize monoclonal antibodies that recognize epitopes specific to the D-dimer fragment. The whole-blood agglutination assay uses a bispecific antibody conjugate with binding sites for both D-dimer and a red cell membrane antigen. In the presence of elevated 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. (Reproduced with permission from Bates SM. D-dimer: a warning for DVT. *Can J Diagnosis.* 2006;23:73–78).

1 month after anticoagulant withdrawal.[79] Using their long-term follow-up data, the investigators determined that among patients with a negative D-dimer and age less than 65 years, females had a low annual risk of recurrence (0.4% per patient-year). However, it should be noted that women with hormonally induced VTE were included in this study, potentially introducing a group of subjects with a very low risk of recurrent VTE.

Other investigators have sought to combine D-dimer with clinical risk factors. Rodger et al prospectively followed 600 patients with a first unprovoked venous thromboembolic event for a mean of 18 months following cessation of anticoagulant therapy.[80] The investigators used 69 potential predictors of recurrence documented before warfarin cessation to determine a rule that could identify patients with an annual risk of VTE of less than 3%. No combination of clinical predictors satisfied this criteria in men; however, women with one or fewer of leg hyperpigmentation, edema, redness; VIDAS D-dimer level of 250 µg FEU/L or greater while taking warfarin; body mass index of at least 30 kg/m^2 or age 65 years or greater had an annual risk of recurrence of 1.6% (95% CI, 0.3 to 4.6%). Data from a meta-analysis of individual patient data derived from 1,818 cases enrolled in seven prospective studies that included patients with a first unprovoked VTE who received conventional anticoagulant therapy and were followed for up to 5 years after treatment was stopped was used to develop another clinical prediction rule.[81] The main predictors of recurrence in this database were abnormal D-dimer after stopping anticoagulants, age less than 50 years, male sex and VTE not associated with hormonal therapy (in women) (DASH, D-dimer, age, sex, hormonal therapy). The annualized risk of recurrence was 3.1% (95% CI, 2.3 to 3.9%) for a score of 1 or less. Although both of these prediction rules may be useful in deciding whether anticoagulant therapy should be continued indefinitely or stopped after an initial treatment period of at least 3 months, prospective validation in independent populations is required.

D-Dimer Testing for Venous Thromboembolism Risk Stratification in Cancer Patients

Although the association of cancer with increased risk of thrombosis is well documented,[82–84] clinical studies have not consistently demonstrated benefit with thrombosis prophylaxis, likely secondary to low overall VTE event rates.[85] It is important, therefore, to identify subgroups of ambulatory

cancer patients for whom the risk of VTE and the benefits of thrombosis prophylaxis (improved morbidity, reduced mortality, more consistent delivery of cancer therapy, enhanced quality of life, and decreased use of health care resources) justify the risk, cost, and inconvenience of primary prophylaxis.

In a prospective observational cohort study of 821 patients with active cancer, elevated D-dimer levels ($\geq$75 percentile of the study population [1,440 µg FEU/L using the STA LIA test D-Di, Diagnostica Stago, Asnieres, France]) either alone (hazard ratio of 1.8; 95% CI, 1.0 to 3.2) or in combination with increased F1 + 2 (hazard ratio of 3.6; 95% CI, 1.4 to 9.5) were associated with an increased risk of VTE.[86] The cumulative probability of developing VTE after 6 months was 15.2% in those with elevated D-dimer and F1 + 2 and 5.0% in those with elevated D-dimer alone.

The addition of D-dimer (and soluble P-selectin) to a previous validated scoring system that incorporated sites of cancer, pre-chemotherapy platelet count, hemoglobin, and/or use of erythropoiesis stimulating agents, leukocyte count, and body mass index,[87] improved VTE risk prediction.[88] The risk of thromboembolism was increased from 9.6% in the highest risk patients using the original score to 35.0% with the expanded model, while the risk in the lowest scoring was 1.5 and 1.0% using the original and expanded models, respectively. However, the benefit of these models (i.e., the efficacy and safety of basing prophylaxis on model results) needs to be proven in interventional clinical trials.

D-Dimer in the Diagnosis and Monitoring of Disseminated Intravascular Coagulation

DIC is a syndrome characterized by generally uncontrolled activation of the coagulation system with excess thrombin generation, activation of the fibrinolytic system with excess plasmin generation, and consumptive coagulopathy.[2,89,90] Conditions commonly associated with DIC are listed in ►**Table 5**.[89] Clinical manifestations of DIC may vary from those associated with bleeding to those associated with thrombosis, depending on the cause and stage of the syndrome.

There is no single test that can definitively establish or exclude the diagnosis of DIC. Although normal D-dimer levels can reliably rule out DIC, elevated levels may or may not reflect the presence of this condition. Several scoring systems have been developed that incorporate measurement of platelet counts, fibrin-related markers, fibrinogen levels, and prothrombin time, along with various other tests.[89] The presence of elevated D-dimer levels has been incorporated into scoring systems proposed by the International Society on Thrombosis and Haemostasis Scientific Subcommittee[90] and the Korean Society on Thrombosis and Hemostasis[91] but not the Japanese Ministry of Health and Welfare[92] or Japanese Association for Acute Medicine[93] scoring systems, which incorporate measurement of fibrin-related markers (e.g., fibrin(ogen) degradation products). It has been suggested that these scoring systems can be used not only for the diagnosis of DIC but also to monitor its progression or resolution.[2]

Table 5 Conditions associated with disseminated intravascular coagulation

- Severe infection and sepsis
- Severe organ injury
  - Liver failure
  - Pancreatitis
- Massive trauma and burns
- Obstetric complications
  - Amniotic fluid embolism
  - Placenta previa
  - Retained products of conception
  - Placental abruption
- Toxins
  - Snakebites
- Immunologic reactions
  - Hemolytic transfusion reactions
  - Transplant rejection
- Vascular disorders
  - Kasabach-Merritt syndrome
- Malignancy

Conclusions

D-dimer is a quick, readily available, and reliable global indicator of coagulation activation and fibrinolysis and, therefore, thrombotic activity. It has been well validated for the exclusion of lower extremity DVT and PE and diagnosis of DIC. More work is required before D-dimer can be the recommended first line test in pregnant women with suspected VTE and in those with possible upper extremity DVT. The use of D-dimer in combination with clinical factors holds promise for determining which patients with a history of unprovoked VTE do not require indefinite anticoagulant therapy and determining subgroups of patients at high risk of first VTE who might benefit from primary thrombosis prophylaxis. This assay has the potential to be useful in a variety of other clinical settings. However, clinicians need to be aware of variability in D-dimer assay performance and the characteristics of their institution's test when making clinical decisions. Standardization of D-dimer assays would allow for more effective use of this test.

Conflict of Interest
Dr. Bates has received research support from Diagnostica Stago S.A.S. (manufacturer of D-dimer kits).

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