D-Dimer Testing in Laboratory Practice

Armando Tripodi

BACKGROUND: D-dimer is a reliable and sensitive index of fibrin deposition and stabilization. As such, its presence in plasma should be indicative of thrombus formation. There are many conditions unrelated to thrombosis in which D-dimer concentrations are high, however, making its positive predictive value rather poor.

CONTENT: Notwithstanding these limitations, D-dimer can be regarded as a most valuable laboratory tool to diagnose and manage a vast array of thrombosis-related clinical conditions, including (a) diagnosis of venous thromboembolism (VTE), (b) identification of individuals at increased risk of first thrombotic event (both arterial and venous), (c) identification of individuals at increased risk of recurrent VTE, (d) establishment of the optimal duration of secondary prophylaxis after a first episode of VTE, (e) pregnancy monitoring, and (f) diagnosis/monitoring of disseminated intravascular coagulation (DIC). This article is aimed at reviewing the merits and pitfalls of these applications.

SUMMARY: From my analysis of the literature, I draw the following conclusions. (a) D-dimer, as measured by a sensitive test, can be safely used to exclude VTE in symptomatic outpatients, provided that it is used in combination with the pretest clinical probability. (b) High concentrations of D-dimer are associated with an increased risk of recurrent VTE. (c) Patients who present with D-dimer above cutoff after stopping the regular course of oral anticoagulation benefit from extended prophylaxis. (d) Finally, D-dimer can be used as a fibrin-related degradation marker for the diagnosis/management of patients with DIC.

D-dimer is a specific product of the degradation of fibrin clots that results from the action of 3 enzymes: (a) thrombin, generated from the activation of the coagulation cascade that converts fibrinogen into fibrin clots; (b) activated factor XIII that cross-links fibrin clots by means of covalent bonds between fibrin monomers; and (c) plasmin, the ultimate enzyme of fibrinolysis that degrades cross-linked fibrin (1–3). Monoclonal antibodies (MoAbs)2 raised against specific epitopes on D-dimer react with cross-linked fibrin, but not with fibrinogen degradation products or non-cross-linked fibrin degradation products, thus ensuring high specificity of the D-dimer as a biomarker of fibrin formation and stabilization (4). Many types of D-dimer assays have been developed that can be broadly divided into 3 categories. (a) ELISAs, which are quantitative and highly sensitive, but time consuming; (b) latex-based immunoassays (5) performed manually with visual inspection that are semiquantitative and less sensitive than the ELISA (6), but more rapid; and (c) latex-based automated assays with immunoturbidimetric readings (7). The latter are quantitative, as sensitive as the ELISA, and very rapid and can be performed on a regular coagulometer. Latex particles coated with anti-D-dimer MoAbs are mixed with the test plasma. In the absence of D-dimer, particles remain in suspension as single entities for which the coagulometer signal gives high turbidimetric readings. Conversely, in the presence of D-dimer, the latex particles agglutinate and the suspension clarifies, and this translates into low turbidimetric readings. The difference between the 2 signals is proportional to the D-dimer concentration.

Many clinical conditions are characterized by increased D-dimer concentrations (Table 1). D-dimer testing can be potentially useful for the diagnosis and management of a variety of thrombosis-related clinical conditions, including disseminated intravascular coagulation (DIC), venous thromboembolism (VTE), ischemic cardiopathy, stroke, and thrombolytic therapy. On the other hand, the increased concentrations that are observed in many other nonthrombotic clinical conditions (Table 1) make D-dimer nonspecific for thrombosis. This limitation notwithstanding, various applications of D-dimer testing have been proposed over the years, including: (a) VTE diagnosis, (b) identification of individuals at increased risk of first thrombotic event

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(both arterial and venous), (c) identification of individuals at increased risk of recurrent VTE, (d) establishment of the optimal duration of secondary prophylaxis after a first episode of VTE, (e) pregnancy monitoring, and (f) DIC diagnosis/monitoring. This article is aimed at reviewing the merits and pitfalls of these applications.

VTE Diagnosis

Because the clinical diagnosis of deep vein thrombosis is unreliable, venous ultrasonography is the test of choice, owing to its high reliability in the diagnosis of proximal thrombosis (8–10). D-dimer testing emerged as a useful laboratory tool for the diagnosis of VTE over the last 20 years because it has high negative predictive value when used in combination with pretest clinical probability. The potential usefulness of D-dimer was first suggested for pulmonary embolism (PE) by Bounameaux et al. (11), who found that patients with PE had higher median concentrations of D-dimer than those without PE. The distributions of results for patients with and without PE were overlapping, however, making D-dimer testing of little value to confirm the diagnosis. These authors realized that if one considers a cutoff value (which in this case was 500 μg/L), very few (if any) patients with PE had D-dimer concentrations lower than the cutoff. This finding led them to postulate that D-dimer testing, although not useful to confirm PE, could be used reliably for the exclusion (11). This simple observation was soon extended to the diagnosis of deep vein thrombosis (12) and led to the new concept that D-dimer is a reliable index of fibrin deposition and, although not specific for VTE, has a high negative predictive value.

| Table 1. Conditions characterized by increased D-dimer concentrations. |
|-----------------------------|-----------------------------|
| Old age                     | Stroke                      |
| Neonatal period             | Peripheral arteriopathy     |
| Pregnancy                   | Aneurism                    |
| Hospitalization             | Congestive cardiac failure  |
| Disability                  | Hemolysis (falciform anemia)|
| Infection                   | Hemorrhage                  |
| Tumor                       | Acute respiratory distress syndrome |
| Recent surgery              | Liver or renal disease      |
| Trauma, burns               | Inflammatory bowel disease  |
| DIC                         | Thrombolytic therapy        |
| VTE                         | Aortic dissection           |
| Ischemic cardiopathy        |                             |

**DECISION THRESHOLDS**

Taking these observations into account, at least 2 D-dimer thresholds should be considered for decision making. The first, a conventional reference value, is calculated as the 95th percentile of the distribution of results from healthy individuals. This decision threshold should be employed to interpret results when D-dimer is used for evaluation of DIC and allied disorders. The second threshold is established in clinical studies of patients with suspected VTE, where the diagnosis of VTE is objectively confirmed by imaging. With use of concurrent D-dimer measurements, the optimal threshold is determined as the D-dimer concentration that gives the best diagnostic sensitivity (high negative predictive value) for VTE (see Fig. 1). Only the second cutoff value should be used for VTE diagnosis. Importantly, the D-dimer value corresponding to the 95th percentile of the distribution of results from healthy individuals and the cutoff value for VTE
The diagnosis may differ considerably within the same method.

**DIAGNOSTIC STRATEGIES**

There are many conditions in which D-dimer is high even in the absence of thrombosis, including recent surgery, malignancy, pregnancy, hospitalization, and others. The high results associated with such conditions should be considered as false-positive results. Conversely, there are situations in which D-dimer may be negative even in the presence of thrombosis. Such false-negative results can occur owing to poor test sensitivity, inaccurate cutoff calculation, hypofibrinolysis, symptoms of VTE longer than 7–10 days, and the initiation of antithrombotic therapy. Because of the relatively poor diagnostic specificity of D-dimer, different strategies have been developed over the years to improve the diagnostic efficacy for VTE exclusion (13). One such strategy is the determination of D-dimer to exclude VTE. Accordingly, only patients with D-dimer above cutoff are subjected to imaging tests. Such a strategy is not very safe, because some patients with VTE might go undetected and be denied antithrombotic treatment.

Another strategy is the determination of D-dimer after a negative imaging test. This approach is aimed at the follow-up of patients who present with isolated calf vein thromboses (undetectable by imaging, but with D-dimer above cutoff) that may subsequently evolve into proximal thromboses. Although this strategy might be used, it would require too many (unnecessary) imaging tests.

A third strategy is the determination of D-dimer combined with the pretest clinical probability (13). The clinical probability is defined using a scoring system that includes clinical signs, risk factors, and symptoms for deep vein thromboses or PE and alternative diagnoses (Table 2), where higher scores indicate higher likelihood of VTE (Table 2). This approach is the most widely used for the exclusion of deep vein thrombosis and PE in thrombosis centers worldwide; Fig. 2 illustrates how it works. The algorithm is applied to symptomatic outpatients in whom pretest clinical probability for deep vein thrombosis is calculated and D-dimer is measured. If D-dimer is negative (lower than

### Table 2. Pretest clinical probability score.a

<table>
<thead>
<tr>
<th>Deep vein thrombosis</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical signs or symptoms</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis or recent immobilization (plaster) of the lower limbs</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden (&gt;3 days) or recent major surgery</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness</td>
<td>1</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling</td>
<td>1</td>
</tr>
<tr>
<td>Edema (symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral veins</td>
<td>1</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis</td>
<td>–2</td>
</tr>
</tbody>
</table>

*a Modified from Wells (13).*

*b Probability of deep vein thrombosis: <1, low; 1–2, moderate; >2, high.*

*c Probability of pulmonary embolism: <2, low; 2–6, moderate; >6, high.*

A third strategy is the determination of D-dimer combined with the pretest clinical probability (13). The clinical probability is defined using a scoring system that includes clinical signs, risk factors, and symptoms for deep vein thromboses or PE and alternative diagnoses (Table 2), where higher scores indicate higher likelihood of VTE (Table 2). This approach is the most widely used for the exclusion of deep vein thrombosis and PE in thrombosis centers worldwide; Fig. 2 illustrates how it works. The algorithm is applied to symptomatic outpatients in whom pretest clinical probability for deep vein thrombosis is calculated and D-dimer is measured. If D-dimer is negative (lower than
the cutoff value) and the clinical probability is low, deep vein thrombosis can be excluded with a high degree of certainty. On the other hand, if D-dimer is negative, but the clinical probability for deep vein thrombosis is high, no decision can be made and further investigation with imaging procedures is required. Finally, if D-dimer is positive, further investigation with imaging is required regardless of the clinical probability. A similar algorithm with the appropriate pretest clinical probability can be used for PE. The above strategy has proved highly effective for ruling out VTE in management studies. Van Belle et al. (14) investigated more than 3000 symptomatic patients and found that the combination of a low pretest clinical probability in combination with low D-dimer effectively excluded PE, with only a 0.5% 3-month follow-up incidence of VTE.

D-dimer concentrations are usually increased in patients with cancer. Therefore, it is unclear whether D-dimer testing can be safely used to diagnose VTE in patients with cancer. In general, the diagnostic sensitivity appears to be good (15), and on this basis, the test can be used to safely exclude VTE. Its diagnostic specificity is poor, however, and therefore the use of D-dimer would imply that more imaging tests must be used anyway.

**CHOICE OF METHODS**

Many D-dimer test methods are available; the appropriate choice requires attention to the following considerations (Table 3). First, the method must have a cutoff value determined by clinical studies and validated by management studies. D-dimer tests available in the North American market for the exclusion of the VTE diagnosis are examined by the US Food and Drug Administration. This examination process requires the performance of clinical studies according to specific protocols before official approval. Different methods may display different cutoff values, and standardization across methods/laboratories is difficult to achieve (16–18). Second, the method should be diagnostically sensitive, but have acceptable diagnostic specificity to avoid too many imaging tests. Third, the method should be easily performed with rapid result availability. Fourth, the method should have good reproducibility, especially near the cutoff value. Finally, the method should give quantitative results. High D-dimer concentrations have been reported to be associated with the severity of PE and as predictors of adverse outcomes (19). Recently, Di Nisio et al. (20) conducted an excellent study in which they looked comparatively at the diagnostic sensitivities and specificities of different D-dimer methods. They found that ELISA (both microplate and fluorescence-based assays) and latex-based quantitative assays ranked highest in terms of diagnostic sensitivity compared with the semiquantitative latex-based assays, for both deep vein thrombosis and PE.

**TAKE-HOME MESSAGES**

D-dimer should not be used as a stand-alone test to exclude or confirm venous thromboembolism. Conversely, D-dimer, when measured by a sensitive test, can be safely used to exclude VTE in symptomatic outpatients, provided that it is used in combination with the pretest clinical probability. However, D-dimer cannot be safely used in the following patients because it can be falsely negative even in the presence of thrombosis (Table 4): (a) patients with symptoms of VTE for longer than 14 days (D-dimer may be falsely negative because aged thrombi are less amenable to plasmin digestion); (b) patients presenting with hypofibrinolysis; (c) patients with suspected VTE receiving therapeutic heparin or oral anticoagulants (these drugs may quench D-dimer generation). Finally, D-dimer combined with the pretest clinical probability should be used with caution in the elderly, hospitalized patients, or patients presenting with recurrent VTE (Table 4). In all the above conditions, low specificity should be expected and, although D-dimer can be used, its low specificity will lead to the associated expenses of a greater number of imaging tests.

**Table 3. Considerations in the choice of a D-dimer test.**

<table>
<thead>
<tr>
<th>Cutoff determined by clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>High diagnostic sensitivity (high negative predictive value)</td>
</tr>
<tr>
<td>Acceptable diagnostic specificity</td>
</tr>
<tr>
<td>Easily performed with rapid availability of results (within 30 min)</td>
</tr>
<tr>
<td>Good reproducibility around cutoff</td>
</tr>
<tr>
<td>Quantitative results</td>
</tr>
</tbody>
</table>

**Table 4. Limitations on the use of D-dimer for VTE diagnosis.**

<table>
<thead>
<tr>
<th>D-dimer cannot be used safely in the following situations:</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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</tr>
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<td>Patients with suspected VTE receiving therapeutic heparin or oral anticoagulants</td>
</tr>
<tr>
<td>D-dimer should be used with caution in the following situations:</td>
</tr>
<tr>
<td>Patients presenting with recurrent VTE</td>
</tr>
<tr>
<td>Elderly patients</td>
</tr>
<tr>
<td>Hospitalized patients</td>
</tr>
</tbody>
</table>
Identification of Individuals at Increased Risk for First Coronary Heart Disease

Many reports from long-term prospective studies have examined the associations of plasma markers with coronary heart diseases (reviewed in (21)). The results of these studies indicated that the highest relative risk was observed for fibrinogen (odds ratio 1.8), with D-dimer ranking as the second highest risk indicator (odds ratio 1.7). These estimates come from population-based studies, however, and it is unknown whether these relative risks can be applied to individual patients.

Identification of Individuals at Increased Risk for First VTE Event

The association of high plasma concentrations of coagulation markers with the risk of VTE has been reported in many case–control studies as reviewed by Lowe (21). The highest relative risk was observed for factor VIII (FVIII), with an odds ratio of 3.0. The relative risk of D-dimer is even higher, with an odds ratio of 3.8. Nevertheless, because these relative risks have been estimated in case–control studies, it is possible that prospective studies may give different results. Cushman et al. (22) addressed this issue by performing 2 prospective studies on the relationship of D-dimer with the risk of future VTE in nearly 22,000 healthy participants in the US. They found that D-dimer was strongly and positively related to the occurrence of future VTE, and that the relative risk of future VTE increased with increasing D-dimer concentration at enrollment to such an extent that patients belonging to the fifth quintile of the D-dimer distribution had an adjusted odds ratio of nearly 3.0 compared with those belonging to the first quintile.

Identification of Individuals at Increased Risk for Recurrent VTE

Palareti et al. (23) were among the first to investigate the risk of VTE recurrence by means of a prospective study on patients following an unprovoked VTE event; their results indicated that D-dimer measurement after anticoagulation was stopped had a high negative predictive value for recurrent VTE. The cumulative probability of recurrence during follow-up was significantly higher for patients with D-dimer above cutoff than those below cutoff. The resulting odds ratio was nearly 2.5, with a very tight confidence interval. Verhovsek et al. (24) reported results of a systematic review of studies of D-dimer when used to predict recurrent disease after stopping anticoagulant therapy for unprovoked VTE. Their review included nearly 2,000 patients, with a 2-year follow-up. The annual risk of recurrent VTE was 3.5% for patients with D-dimer below cutoff at enrollment and nearly 9% for those with D-dimer above cutoff. These studies have facilitated the use of D-dimer for determining the optimal duration of anticoagulation after a first episode of unprovoked VTE. This is a crucial issue for the management of patients with VTE, and until recently, the decision has been made solely on the basis of clinical criteria. Palareti et al. (25) reported on the use of D-dimer testing to determine the optimal duration of anticoagulant therapy. Their study enrolled patients with a first episode of unprovoked VTE, who received a regular course of oral anticoagulants for at least 3 months. D-dimer was measured 1 month after stopping oral anticoagulation. Patients with D-dimer below cutoff did not continue oral anticoagulation, whereas patients with D-dimer above cutoff were randomized either to stop or to resume oral anticoagulation. All patients were then followed for up to 1.5 years to assess for objectively confirmed recurrent VTE. The cumulative incidence of outcome was nearly 11 events per 100 person-years in those patients with D-dimer above cutoff who did not resume oral anticoagulation, and only 2.0 events per 100 person-years in those who had D-dimer above cutoff but resumed oral anticoagulation. This difference was statistically significant, corresponding to a hazard ratio of 4.3, with a relatively tight confidence interval.

Take-home Messages

High concentrations of D-dimer are associated with an increased risk of recurrent VTE. Furthermore, patients who, after stopping the regular course of oral anticoagulation, present with D-dimer above cutoff, benefit from extended prophylaxis.

Pregnancy

D-dimer concentrations increase in pregnant women compared with control women. Furthermore, the concentrations increase progressively throughout pregnancy (26, 27). In the postpartum period, they tend to decrease without reverting completely to normal for as long as 1 month after delivery (26, 27). This pattern is in line with the concept of a hypercoagulable state that is known to be associated with pregnancy and puerperium.

Take-home Messages

The practical implication of these findings is that D-dimer should not be used for VTE exclusion during pregnancy and puerperium, unless appropriate cutoff

Reviews

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Take-home Messages

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Pregnancy

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Take-home Messages

The practical implication of these findings is that D-dimer should not be used for VTE exclusion during pregnancy and puerperium, unless appropriate cutoff
values are known for these conditions. Such cutoffs are difficult to determine in practice, however. Furthermore, no pretest clinical probability assessment is available to be used in combination with d-dimer testing in these conditions. In general, it seems that d-dimer has acceptable diagnostic sensitivity for VTE exclusion (28) but, because of its poor specificity, it is not cost-effective (a relatively high number of imaging tests must be used thereafter). In theory at least, d-dimer testing could be used to predict the non-thrombotic outcomes of pregnancy, but the extent of its usefulness remains to be established.

**Diagnosis and Monitoring of DIC**

DIC is a complex syndrome, secondary to several underlying disorders that may lead to the activation of coagulation and fibrinolysis and subsequent consumptive coagulopathy (29). Although the proper management of DIC requires aggressive attempts to quell the underlying diseases, laboratory measurements may be helpful. In 2001, a subcommittee of the International Society on Thrombosis and Hemostasis (ISTH) issued clinical and laboratory criteria and a scoring system for DIC (30). The ISTH scoring system looks first to answer the question of whether the index patient has an underlying disorder known to be associated with DIC. If this is the case, then platelet counts, prothrombin time, fibrinogen, and fibrin-related degradation products (i.e., soluble fibrin monomers, fibrin degradation product, or d-dimer) should be ordered. Based on test results, a scoring system is calculated. According to the suggested scheme, the results of the fibrin-related degradation markers have a considerable impact in the score calculation as moderate or strong positivity score 2 or 3, respectively; low platelets are scored as 0–2 depending on the platelet count, prothrombin time scores as 0–2 depending on the prolongation above the upper reference limits, and fibrinogen scores as 1–2 depending on the extent of the observed decreased concentrations. According to this system, scores of 5 or more are compatible with overt DIC, and the calculation should be repeated daily to monitor the progression of the syndrome. Total scores <5 are suggestive (not affirmative) for nonovert DIC and the calculation should be repeated in the next 1–2 days. Another scoring system, which differs from the ISTH score in some aspects, has been proposed by the Japanese Ministry of Health (31). Laboratory testing is essentially the same in the 2 scoring systems, but in the Japanese system the occurrence of bleeding symptoms or organ failure has been added. Wada et al. (32) compared the 2 scoring systems for DIC. They took into consideration >1200 patients with suspected DIC. Agreement between the 2 systems was achieved in 67% of the patients (32).

**Take-home Messages**

Notwithstanding that both the ISTH and the Japanese score systems do not specifically mention d-dimer, this test is widely used as a fibrin-related degradation marker for DIC, essentially because it is readily available in most clinical laboratories and its assay is very simple and rapidly performed. Its precise role is not yet known, however, and future work is needed to assess its value in comparison with other fibrin-related degradation markers, such as fibrin degradation products or soluble fibrin monomers.

**Other Uses of D-Dimer**

Although increased d-dimer concentrations have been found in patients with abdominal aortic aneurism, whether such measurement is useful in the diagnosis and management of this condition is still debated. A relatively large metaanalysis showed that high d-dimer and fibrinogen are unlikely to replace the more resource-intensive ultrasonography as first-line diagnostic tool (33). Perhaps these laboratory tests could be used to monitor patients once the diagnosis has been established.

**Concluding Remarks**

D-dimer is a reliable and sensitive index of fibrin deposition and stabilization. As such, its presence in plasma should be indicative of thrombus formation. There are many conditions unrelated to thrombosis in which D-dimer is high, however, and thus its positive predictive value is rather poor. Notwithstanding these limitations, d-dimer can be regarded as one of the most valuable laboratory tools for the diagnosis and management of a vast array of thrombosis-related clinical conditions.

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