Clinical suspicion for venous thromboembolism (VTE) mandates objective testing to confirm or exclude the diagnosis. However, current imaging modalities are imperfect because of a small but important risk of complications with invasive techniques or limited sensitivity with noninvasive ones. A diagnostic tool for VTE is needed that is noninvasive and highly accurate, allowing immediate treatment decisions to be made in most cases. Plasma D-dimers (D-ds), specific cross-linked fibrin derivatives, partially fulfill these criteria in that they are sensitive markers for thrombosis but lack specificity. They therefore cannot be used to make a positive diagnosis of VTE; however, they generally have high negative predictive value and are useful as an exclusionary test, a potentially important role given that VTE is eventually ruled out in most patients investigated. Clinical management studies are clarifying the role of D-ds in the diagnostic paradigm of VTE: negative ultrasound and D-d findings obviate the need for serial imaging in suspected deep vein thrombosis, and anticoagulant therapy can be safely withheld in patients with non–high clinical suspicion for pulmonary embolism and non–high probability ventilation perfusion scan if D-d test results are negative. More recently, the combination of a negative SimpliRED (AGEN Biomedical Ltd, Brisbane, Australia) D-d result and low clinical suspicion derived using a formal scoring system has been shown to exclude deep vein thrombosis and pulmonary embolism and to obviate the need for imaging. Several different D-d assays are now available, and clinicians should be aware of the performance characteristics of the test used before incorporation into diagnostic algorithms as these will differ between assays, and the results of clinical management studies cannot necessarily be safely extrapolated to assays other than those specifically evaluated. If alternative assays are to be substituted, these should consistently have been shown to possess equivalent or greater sensitivity.

The incidence of venous thromboembolism (VTE) rises progressively with age, with a cumulative event rate greater than 10% by age 80 years, and is associated with substantial morbidity and mortality in the absence of treatment. The clinical signs and symptoms are not sufficiently specific to establish or exclude the diagnosis, and objective testing is required in the presence of clinical suspicion to aid management decisions, although all imaging techniques currently used have clinical or practical limitations.

Contrast venography (CV) and pulmonary angiography remain the gold standard diagnostic tests for deep vein thrombosis (DVT) and pulmonary embolism (PE), respectively, but they are invasive and are associated with a small but significant risk of complications. These tests are therefore no longer widely used as first-line investigations. Noninvasive diagnostic strategies have been developed, usually using ultrasound, the most accurate noninvasive test for suspected DVT, and ventilation-perfusion (VQ) scanning for suspected PE. However, VTE can only be
diagnosed or excluded with reasonable confidence using a 1-step process in a few patients. Three fourths or more of the patients with suspected DVT have negative ultrasound findings\(^8,9\) and require repeated imaging to identify the further 2% to 6% in whom occlusive proximal DVT becomes apparent in a week.\(^8,10\) In addition, 70% of patients with suspected PE have a non-diagnostic VQ scan\(^11\) (low or intermediate probability) and require further imaging using either pulmonary angiography or serial noninvasive imaging with ultrasonography to identify residual proximal DVT, a valid approach in patients with adequate cardiopulmonary reserve.\(^12,14\)

Given these shortcomings, a simple but reliable noninvasive test for VTE is highly desirable and should ideally have a sensitivity and negative predictive value of 100% as the consequences of nondiagnosis are potentially life threatening.\(^13\) Plasma D-dimers (D-ds) have proved to be the most useful blood markers of intravascular fibrinolysis\(^15\) and are of interest as an adjunctive exclusionary test in suspected VTE, potentially increasing the number of patients who can be satisfactorily treated without recourse to a second level of investigation.\(^16\) We review D-ds in relation to VTE and their incorporation into diagnostic strategies.

**WHAT ARE D-ds?**

Plasma D-ds are generated when the endogenous fibrinolytic system degrades fibrin, as in VTE, and they consist of 2 identical subunits derived from 2 fibrin molecules. Unlike fibrinogen degradation products, which are derived from fibrinogen and fibrin, D-ds are a specific cross-linked fibrin derivative.\(^17,18\) Because 2% to 3% of plasma fibrinogen is degraded to fibrin, small amounts are detectable in the plasma of healthy individuals. The half-life is approximately 8 hours, with plasma clearance via urinary excretion and the action of the reticuloendothelial system.\(^19\)

**RELATIONSHIP BETWEEN VTE AND D-d LEVELS**

D-dimer levels are increased by any condition in which fibrin is formed and degraded by plasmin\(^19\) and are the best currently available laboratory marker of activation of coagulation.\(^20\) D-dimer levels are elevated approximately 8-fold after VTE compared with controls, with levels falling to approximately one quarter of the initial value between weeks 1 and 2;\(^21\) they are significantly higher in patients with extensive proximal DVT than in those with below-the-knee DVT,\(^22\) with peak levels corresponding to the extent of thrombosis.\(^23\) D-dimer levels may be particularly useful in the diagnosis of recurrent DVT, a subgroup in which conventional imaging has important shortfalls.\(^18\) Using direct thrombus magnetic resonance imaging (MRI), Fraser et al\(^24\) recently showed that D-d levels correlate with clot volume and surface area. Clot surface area seemed to be the more important determinant, supporting the concept that D-d generation, release, or both occur primarily at the surface of the thrombus.

After a thrombotic event, D-d levels may normalize within 15 to 20 days\(^20,22\) and are probably most useful for diagnosis within 11 days of symptom onset.\(^21\) Although initiation of heparin calcium therapy causes a sharp decline in levels, absolute values remain increased compared with those of controls, and the test remains useful in patients awaiting investigation in whom treatment has already been started.\(^20,25,26\)

**OTHER CONDITIONS ASSOCIATED WITH RAISED D-d LEVELS**

Levels of D-ds are rarely elevated in healthy individuals\(^27\) but may be increased in any condition involving the formation and degradation of fibrin, such as infections, cancer, surgery, cardiac or renal failure, acute coronary syndromes, acute nonlunar stroke, pregnancy, and sickle cell crises.\(^19,27,30\) Furthermore, many of these conditions are also risk factors for VTE and may have initial symptoms or signs similar to PE.\(^20\) D-dimer levels are therefore less likely to be useful in patients with suspected VTE and 1 or more of these diagnoses because, for example, increased values occur in 80% to 90% of those with infections or malignancy.\(^31\)

**MEASUREMENT OF D-d LEVELS**

Measurement of D-d levels has been enabled by the development of monoclonal antibodies that bind to epitopes on D-d fragments that are absent on fibrin, fibrinogen, and non–cross-linked fragments of fibrin, with detection of resulting complexes by enzyme-linked immunosorbent assay (ELISA) or agglutination techniques.\(^29,32,33\) The classic microparticle ELISA technique is considered the gold standard,\(^34\) but it is not useful as a routine emergency test as it is suitable for batch analysis and is labor intensive. However, the recently developed VIDAS test (bioMérieux SA, Marcy-Étoile, France), which combines the ELISA method with a final detection in fluorescence,\(^35\) is fully automated and provides a result within 35 minutes and can therefore be used for single-sample testing.\(^36\) Two immunofiltration (membrane ELISA) techniques have also been introduced that have sensitivities similar to those of conventional ELISAs but higher specificities: the Instant IA D-d assay (Diagnostica Stago, Inc, Parsippany, NJ) gives a result in less than 8 minutes but is performed manually and is qualitative (positive or negative),\(^37\) and the NycoCard D-d assay (Nycomed Pharma AS, Asker, Norway) is semiquantitative and provides a result in less than 2 minutes.\(^37,38\)

Other techniques involve agglutination of latex beads or red blood cells and give a qualitative or semiquantitative result within a few minutes. For example, the SimpliRED test (AGEN Biomedical Ltd, Brisbane, Australia) is a red blood cell agglutination assay designed for use with fresh capillary or venous whole blood. It provides a result in less than 5 minutes and is therefore suitable for near-patient testing.\(^39\) More recently, immunoturbidimetric techniques have been developed that allow a quantitative estimation and represent a second generation in latex agglutination technology (eg, TinaQuant assay [Roche Diagnostics, F. Hoffmann-La Roche Ltd, Basel, Switzerland], Liat test assay [Diagnostica Stago, Inc], and MDA D-d [Organon Teknika B.V., Boxtel, the Netherlands]). Immunofiltration and
immunoturbidimetric techniques may therefore combine the advantageous properties of the ELISA with the speed and simplicity of the latex tests. The properties of the main D-d detection techniques are given in Table 1.

ACCURACY OF TECHNIQUES

Pooled data from 20 studies of more than 2000 outpatients with clinically suspected VTE using 3 different classic microplate ELISA assays (Dimertest [American Diagnostica Inc, Greenwich, Conn], Asserachrom Ddi [Diagnostica Stago, Inc], and Fibrinostika FbDP [Organon Teknika B.V.]) have shown a diagnostic sensitivity of 97% at a cutoff value of 500 ng/mL, with falsenegative rates presumably explained on the basis of a small thrombus mass (sensitivity may be lower in patients with isolated below-the-knee DVT), a long time lag between thrombus formation and D-d testing, and, possibly, an impaired pathophysiological fibrinolytic response in the occasional patient.

Specificity in these studies was approximately 35% to 45%, and D-d levels are currently regarded as useful only as exclusionary tests for VTE and are less useful in inpatient populations because of lower specificity consequent on comorbidity. More recent data also show high sensitivities for the 3 novel rapid ELISA-based assays; indeed, several studies evaluating the VIDAS assay have reported a sensitivity of 100%.

Whereas conventional latex agglutination assays are not regarded as sufficiently sensitive to be of clinical value, second-generation kits using either whole blood agglutination (SimpliRED) or immunoturbidimetric techniques (eg, TinaQuant, Liatest, and MDA D-d) have emerged with higher sensitivities and are clinically useful.

Van der Graaf et al recently assessed the diagnostic performance of 10 novel rapid tests based on ELISA or latex agglutination technology and 3 conventional ELISAs in 99 outpatients with suspected DVT who underwent CV (Table 2). Correlation between different assays is poor, and it is not currently possible to standardize D-d results from different assays, making it difficult to extrapolate results from one setting to another. Also, important interobserver variation may occur with semiquantitative tests. Studies have also shown that combining an additional variable, such as a clinical probability assessment, respiratory rate, arterial blood gas estimation, or measurement of alveolar dead space, augments the negative predictive value of a normal D-d value. For example, in a study of patients undergoing evaluation for suspected PE, the combination of a negative SimpliRED assay result and a PaO2 greater than 10.7 kPa had a negative predictive value of 100%.

The VIDAS and SimpliRED assays are the most extensively studied and widely used in the diagnosis of VTE. Pooled data indicate that although the VIDAS assay is the more sensitive of the two (90%-100% [generally 98%-100%]), specificity (5%-55% [generally, 40%]) is relatively poor so that a normal result has high negative predictive value but occurs in a small proportion of patients, limiting its diagnostic utility (only data from studies using a threshold of 500 ng/mL were included). By contrast, the SimpliRED assay is somewhat less sensitive (61%-100% [generally, 85%]) but more specific (20%-94% [generally, 70%]) so that the negative predictive value is lower but the test is likely to be diagnostically useful in a greater proportion of patients. The utility of these two tests in clinical management studies are reviewed herein. Note that specificity of assays vary depending on the population studied and will be highest in outpatient populations with a low prevalence of comorbidity.

D-d LEVELS IN THE ELDERLY

D-dimer levels increase linearly with age, particularly in the presence of coexisting functional impairment, because of a combination of factors, including reduced renal clearance, increased levels of plasma fibrinogen, and the presence of occult disease.

In one study of healthy individuals, average levels in the highest age quartile (71-90 years) were ap-

---

Table 1. Characteristics of the Different Classes of D-Dimer Detection Techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Examples</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microplate ELISA</td>
<td>Asserachrom Ddi, Enzygnost (Dade Behring Inc, Deerfield, Ill), and Fibrinostika FbDP</td>
<td>High</td>
<td>Low</td>
<td>Considered the gold standard; suitable for batch analysis and not useful in real time</td>
</tr>
<tr>
<td>VIDAS ELISA (bioMérieux SA, Marcy-Étoile, France)</td>
<td>Instant IA and NycoCard</td>
<td>High</td>
<td>Low</td>
<td>Similar sensitivity as classic microplate ELISAs; quantitative; suitable for real-time use</td>
</tr>
<tr>
<td>Membrane ELISA (immunofiltration)</td>
<td>D-DimerTest latex and D-DimerTest Whole blood agglutination</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Rapid, suitable for real-time use; comparable sensitivity to microplate ELISA; qualitative or semiquantitative</td>
</tr>
<tr>
<td>First-generation latex agglutination</td>
<td>Dimertest latex and D-DimerTest Whole blood agglutination</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Rapid, but insufficiently sensitive to be clinically useful</td>
</tr>
<tr>
<td>Second-generation latex agglutination (immunoturbidimetric)</td>
<td>TinaQuant and Liatest</td>
<td>High</td>
<td>Intermediate</td>
<td>Rapid and semiquantitative; comparable sensitivity to microplate ELISA</td>
</tr>
</tbody>
</table>

*ELISA indicates enzyme-linked immunosorbent assay.
†See the “Measurement of D-d Levels” and “Accuracy of Techniques” sections in the text for manufacturer names and locations.
approximately 4 times greater than those in the lowest quartile (11-30 years), hence specificity and there-fore diagnostic utility for VTE is lower in older patients (Table 3). In one study evaluating the optimal discriminatory threshold of the Vidas assay in elderly inpatients (average age, 86 years) with suspected DVT, specificity improved at a cutoff value of 750 ng/mL compared with 500 ng/mL without a decrease in sensitivity, but it was still poor at only 20%.

CAN D-d LEVELS EVER BE USED TO MAKE A POSITIVE DIAGNOSIS OF VTE?

The positive predictive value for VTE rises as D-d levels increase progressively above the diagnostic thresh- old, and in a study evaluating 671 outpatients with suspected PE, the specificity of D-d (Asserachrom Ddi ELISA) was 93% when levels exceeded 4000 ng/mL. This raises the possibility that, depending on the pre-test probability, in certain situations a high D-d level might be sufficient grounds to initiate treatment. However, this issue requires further study and, in the absence of further data, D-d levels should be used in an exclusionary capacity only at this stage.

MANAGEMENT STUDIES OF D-d IN SUSPECTED VTE

Data demonstrating the high sensitivity of certain D-d assays for the diagnosis of symptomatic VTE under the optimal conditions of performance studies suggest a putative role as an exclusionary test. However, outcome studies demonstrating that treatment can be safely withheld in suspected VTE using diagnostic approaches incorporating D-d assays under routine conditions are required, as similar performance cannot be assumed in the less predictable domain of clinical practice, and even a small margin of error may not be acceptable with a potentially lethal disease. For example, previous studies have demonstrated that outcome is excellent when treatment is withheld in suspected DVT on the basis of negative CV79 or serial ultrasound findings and in suspected PE with negative pulmonary angiographic findings or normal VQ scintigraphy results. Without similar data, routine clini-

<table>
<thead>
<tr>
<th>Table 2. Performance Characteristics of 13 D-Dimer (D-d) Assays in Suspected Deep Vein Thrombosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D-d Assay (Manufacturer)</strong></td>
</tr>
<tr>
<td>Qualitative Methods</td>
</tr>
<tr>
<td>Ministix§ (Bipool US Inc, Ventura, Calif)</td>
</tr>
<tr>
<td>SimpliRED§</td>
</tr>
<tr>
<td>Instant A§</td>
</tr>
<tr>
<td>Reference ELISAs</td>
</tr>
<tr>
<td>Asserachrom Ddi¶</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Enzygnost¶ (Dade Behring Inc, Deerfield, Ill)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Fibrinostika FbDP¶</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Semiquantitative Methods</td>
</tr>
<tr>
<td>NycoCard¶</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BC-DD§ (Dade Behring Inc)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Turbiquant§ (Dade Behring Inc)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IL-DD§ (Instrumentation Laboratory SpA, Milan, Italy)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>TinaQuant§</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vidas§</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Reprinted with permission from Van der Graaf et al. ELISA indicates enzyme-linked immunosorbent assay; ellipses, not applicable.
†See the “Measurement of D-d Levels” and “Accuracy of Techniques” sections in the text and Table 1 for manufacturer names and locations.
¶Three cutoff values are given for the quantitative assays. The first is the highest D-d level associated with sensitivity and negative predictive values of 100%; the second is the upper limit of the reference range; and the third is a D-d value twice the upper limit of the reference range.
§Latex agglutination assay.
‖Whole blood agglutination assay.
¶ELISA assay.
#Detection limit.

Table 3. Performance Characteristics of the Asserachrom Ddi ELISA (Diagnostica Stago, Inc, Persippany, NJ) in Different Age Strata at a Cutoff Value of 500 ng/mL in 671 Outpatients Investigated for Suspected Pulmonary Embolism*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>&lt;30</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>60</td>
<td>72</td>
<td>60</td>
<td>54</td>
<td>32</td>
<td>22</td>
<td>9</td>
</tr>
</tbody>
</table>

*Adapted from Perrier et al. ELISA indicates enzyme-linked immunosorbent assay.
cal use of D-d assays would be premature and could not be recommended.77

Several management studies have now evaluated D-ds in diagnostic algorithms for VTE incorporating noninvasive imaging53 and/or information from an a priori clinical probability assessment, the complimentary role of which in diagnosis has been previously demonstrated.82-85 Bernardi et al86 investigated 946 outpatients with suspected DVT. Treatment was withheld in 53 noninvasive workup was inconclusive. Treatment was withheld in 53 patients with nondiagnostic VQ scans and intermediate clinical probability of PE in whom D-d levels were less than 500 ng/mL, none of whom developed VTE during the following 6 months. An additional 363 patients were subsequently recruited, including another 74 with an intermediate clinical probability of PE, nondiagnostic VQ scans, and negative D-d test results. Again, no cases of VTE occurred in this subgroup during another 3 months of follow-up.74

Three trials have assessed the safety of obviating imaging in patients with suspected VTE on the basis of D-d level alone or in combination with a clinical probability assessment. Perrier et al80 evaluated a noninvasive diagnostic algorithm in 918 patients with suspected DVT or PE using D-d estimation (VIDAS assay) as the first step. Levels were less than 500 ng/mL in 159 patients (36%) with suspected PE. These patients were not investigated further, irrespective of clinical suspicion, and none developed VTE during the next 3 months. Patients with elevated D-d levels underwent VQ scanning or ultrasonography, whereas those with suspected DVT underwent US irrespective of D-d levels. By incorporating a clinical probability assessment, noninvasive diagnosis was possible in 94% of the entire cohort, and the risk of VTE at 3 months in those not given anticoagulants using this algorithm was 1.8%; only 2 of the 12 patients in this subgroup had normal D-d levels at presentation.

Kearon et al83 evaluated 445 outpatients with a suspected first episode of DVT who underwent a standardized assessment of clinical probability (Table 4) and D-d assay (SimpliRED); 40% had a low clinical probability for DVT and negative D-d findings, and this subgroup was not investigated further. This strategy was safe, with only 1 of 177 patients developing VTE during the subsequent 3 months, giving a negative predictive value for this combination of 99.4%. Finally, Wells et al82 evaluated a predominantly noninvasive diagnostic strategy in 930 outpatients with suspected PE in which the initial step comprised a standard assessment of pretest clinical probability93 (Table 5) and D-d assay (SimpliRED), as in the previous study. Those with low suspicion and negative D-d findings did not undergo further investigation, with all other patients undergoing VQ scanning. If the VQ scan was nondiagnostic, bilateral, lower-limb ultrasonography was performed, with further testing guided by the results of the clinical assessment, D-d assay, and VQ. Forty-seven percent of the entire group were considered not to have PE on the basis of low suspicion and negative D-d findings, and only 1 of these 437 patients developed VTE during the next 3 months, giving a negative predictive value of 99.5% for this combination. The overall frequency of VTE during follow-up in the cohort in whom PE was thought to have been initially excluded and in whom the

### Table 4. Clinical Probability Score Used in Patients With Suspected Deep Vein Thrombosis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (ongoing treatment or within past 6 mo or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for &gt;3 d or major surgery within 4 wk</td>
<td>1</td>
</tr>
<tr>
<td>Local tenderness</td>
<td>1</td>
</tr>
<tr>
<td>Thigh and calf swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm greater than asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema in symptomatic leg only</td>
<td>1</td>
</tr>
<tr>
<td>Dilated superficial veins (nonvaricose) in asymptomatic leg only</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as or more likely than deep vein thrombosis</td>
<td>−2</td>
</tr>
</tbody>
</table>

*Data from Wells et al83 and Kearon et al.89 This scoring system should not be used in patients with a history of venous thromboembolism.

†Low probability is ≤0; moderate probability, 1-2; and high probability, ≥3.
greater was the frequency of thromboses in the low-probability groups than in the high-probability group. However, 3 caveats should be borne in mind. First, these studies provide an evidence base for the use of D-d tests in noninvasive diagnostic algorithms for suspected VTE. In particular, the studies of Kearon et al.90 and Wells et al.92 demonstrate that imaging can safely be obviated in up to half of patients with suspected VTE using a formal clinical probability assessment in combination with a SimpliRED D-d test, and invasive testing is rarely required in the remainder. However, 3 caveats should be borne in mind. First, these results apply to a specific D-d test and method of clinical probability assessment. Substitution of an alternative assay would be safe only if its sensitivity equaled or exceeded that of SimpliRED, though diagnostic utility might be inferior if specificity was lower. Less sensitive assays should not be used. Second, the overall prevalences of VTE in these cohorts were less than 15% so that the frequency of thromboses in the low-probability groups was only 1% to 2%. The negative predictive value of a combined low probability and negative D-d finding will diminish as disease prevalence rises so that the safety of this approach cannot be assumed if a significantly higher prevalence of VTE is anticipated. Third, VTE was diagnosed in up to 20% of patients with a negative D-d result and high clinical suspicion, demonstrating that the SimpliRED assay cannot be used in isolation and reinforcing the need for a careful clinical assessment. In contradistinction, exclusion of PE on the basis of a negative VIDAS assay finding seemed safe in one study.99 Such an approach would not be acceptable unless sensitivity of the assay used was increased to at least 99%, although in the absence of further confirmatory data, it would seem prudent to exercise caution when the results of D-d testing using a highly sensitive assay and clinical suspicion are at odds.

### D-d as a Screening Test for Asymptomatic VTE

Screening studies on patients at high risk of DVT clearly demonstrate that only a few patients have local signs or symptoms. However, subclinical DVT is important as fatal PE may be its initial manifestation, and postthrombotic syndrome is an important sequela, particularly after proximal thrombosis. Although D-d testing alone would not allow positive diagnosis of DVT, the concept of its use as a screening tool in populations at high risk of VTE, potentially optimizing use of noninvasive imaging in a diminished subgroup, is theoretically attractive. The need for screening is debatable in general surgical and orthopedic patients as increasingly effective thromboprophylactic strategies are used. However, a strong case might exist in, for example, patients after stroke in whom prophylactic heparin use is no longer routinely recommended.

A few studies evaluating the role of D-d testing as a screening tool have been reported. Harvey et al.101 studied 105 nonambulatory stroke rehabilitation patients an average of 25 days after ictus. Patients were screened with bilateral lower-limb ultrasonography and D-d (Asserachrom Ddi ELISA) within the same 24 hours. Fourteen DVTs were identified, and a D-d threshold of 1092 ng/mL had a sensitivity of 100% and a specificity of 66%. Positive and negative predictive values were 31% and 100%, respectively. At this threshold, therefore, the D-d test excluded DVT with the same confidence as a negative ultrasound finding. Overall, this study demonstrated that DVT could be excluded in 57% of patients by D-d testing alone. These data cannot be extrapolated to patients in the acute phase of stroke because of potential confounding by the effect of stroke itself on D-d levels, and the evaluation of D-d as a screening tool in this context requires a separate study.

Bounameaux et al.102 performed D-d measurements (Asserachrom Ddi ELISA) and bilateral CV on postoperative day 8 in 185 patients who had undergone gastrointestinal tract surgery. Although D-d levels were increased substantially by surgery, a threshold of 3000 ng/mL had an 89% sensitivity and a 48% specificity (positive and negative predictive values, 35% and 93%, respectively) for the diagnosis of DVT.

Roussii et al.103 studied D-d (Asserachrom Ddi ELISA and Liatest) as a screening test for DVT with ultrasonography, CV, or both in 67 patients with spinal cord injuries and found that DVT could be excluded using a standard D-d threshold of 500 ng/mL (either technique) in 31%, obviating ultrasonography in these patients.

Studies evaluating the screening potential of D-d assays in the context of orthopedic surgery have yielded conflicting results. Crippa et al.104 screened 68 patients undergoing elective hip surgery with serial D-d measurements (LPIA D-d; Mitsubishi Kasei Corp, Tokyo, Japan; a quantitative automated immunoturbidimetric assay) and CV at day 10. At a cutoff value of 3500 ng/mL, the assay had a sensitivity of 100% and a specificity of 32% for DVT (positive and negative predictive values, 40% and 100%, respectively). Bonnard et al.105 evaluated 173 patients undergoing hip surgery (elective and emergency) using a D-d assay (Asserachrom Ddi ELISA) and ultrasonography on postoperative day 12. At a cutoff value of 2000 ng/mL, the sensitivity and specificity for proximal...
nal DVT were 79% and 36%, respectively. Whereas the negative predictive value at this threshold was 95%, the positive predictive value was only 9%, limiting its usefulness. A preoperative D-d threshold greater than 500 ng/mL had a sensitivity of 93% and a specificity of 23% for the subsequent development of proximal DVT (negative and positive predictive values, 96% and 36%, respectively), and preoperative D-d levels were also predictive of postoperative DVT in a study evaluating patients undergoing major abdominal surgery. Although this might support the concept that increased fibrin turnover identified patients with a preoperative hypercoagulable state at increased risk of subsequent DVT,107 preoperative D-d measurement did not predict postoperative DVT in the European Concerted Action on Thrombosis DVT study, the largest of its kind evaluating the relationship between preoperative hemostatic variables and subsequent thrombosis in patients undergoing hip arthroplasty.108 Last, Dunn et al measured D-d (Dimertest ELISA) in 90 patients after orthopedic surgery undergoing CV,109 demonstrating that D-d levels were also predictive of PE.34,112-118

**NEWER IMAGING MODALITIES FOR VTE**

Experience is increasing with spiral computed tomography and contrast-enhanced electron-beam computed tomography for the diagnosis of PE.34,112-118 Furthermore, MRI seems promising for the evaluation of DVT and PE,34,113,114,119 particularly direct thrombus MRI, which detects methemoglobin in maturing clots and provides a positive image of thrombi.120 A major advantage of MRI is that it allows evaluation of the lower limbs and thorax for clots at the same time, potentially facilitating a more titrated approach to treatment. For example, the presence or absence of residual proximal DVT in a patient with PE, the major factor determining the risk of PE recurrence in the absence of treatment,122-125 could affect decisions about the intensity and duration of treatment. Use of these techniques is likely to increase as technology advances, and invasive diagnosis of VTE may be completely obviated in the future. However, further data from prospective management studies in which anticoagulant treatment is withheld without further testing for VTE on the basis of negative imaging findings and large, multicenter studies are required to clarify the role of computed tomography and MRI in the diagnostic paradigm of VTE.7,112,125

**CONCLUSIONS**

During the past decade, D-d assays have evolved from a theoretically attractive exclusionary test in suspected VTE to one of practical value that seems to be safe and cost-effective when used within defined diagnostic strategies, obviating the need for imaging in a significant proportion of patients, minimizing the need for repeated or invasive investigations in the remainder, and allowing immediate treatment decisions to be made more frequently. However, many different assays are now commercially available, and clinicians should appreciate that these cannot necessarily be used interchangeably and should ensure that they are familiar with the diagnostic performance of the assay used in their own institution.

Ongoing studies will continue to define the role of D-ds in diagnosis. Further research is needed, for example, to evaluate the safety of using highly sensitive rapid assays, such as VIDAS, as stand-alone tests. In the absence of an assay that is highly sensitive and specific, studies evaluating a 2-step approach consisting of an initial clinical probability assessment and D-d assay using one of the more specific tests (eg, SimpliRED), followed by a highly sensitive assay in those with a negative result and non-low clinical suspicion, would be of interest as this approach would combine the merits of both classes of assay and potentially further reduce the need for imaging.

*Accepted for publication August 27, 2001.*

**Corresponding author and reprints:** James Kelly, BSc, MRCP, SpR in Elderly Care/GIM, Elderly Care Dept, c/o Alexandra Ward, North Wing, Ninth Floor, St Thomas’ Hospital, Lambeth Palace Road, Lambeth, London SE1 7EH, England (e-mail: jameskelly@northbrookfm.fsnet.co.uk).

**REFERENCES**


90. Crippa L, Ravasi F, D’Angelo S, et al. Diagnostic value of compression ultrasonography and fibrinogen-related parameters for the detection of...


