D-dimer for Exclusion of Venous Thromboembolism
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The vast majority (80% or more) of outpatients attending a hospital emergency department with clinical signs of venous thromboembolism (VTE; deep vein thrombosis and/or pulmonary embolism) will not have the disease.

- This illustrates the need for rapid, non-invasive and cost-effective diagnostic strategies for VTE exclusion.

The combination of risk stratification by clinical pre-test probability (PTP) assessment and D-dimer testing is recommended as the first step in the diagnostic pathway because it safely excludes VTE in about 1/3rd of suspected outpatients**.

- This has advantages for the health care system because it will greatly reduce the need for time-consuming and expensive imaging procedures and avoid unnecessary treatment with anticoagulants.

- D-dimer testing is not standardized and available assays vary widely in analytical, operational and clinical performance characteristics. Clinicians and laboratory managers should be aware of these aspects before selecting a D-dimer assay as part of a VTE diagnostic algorithm. Preference should be given to rapid, quantitative assays with the lowest coefficient of variation at the cut-off point and to those tests that have undergone proper clinical validation.


Experience with using D-dimer as a diagnostic help in suspected deep vein thrombosis (DVT) or pulmonary embolism (PE) has a history of almost twenty years (1). Its widespread use has been made possible with the development of rapid assays that allow result delivery within one hour or less after blood sampling. However, the heterogeneity of the assays has raised uncertainty among clinicians and called for rigorous evaluation of the various tests. Uncertainty further increased because the usefulness of the test was also found to be dependent upon the populations to which it was applied, due to variations in test specificity.

Depending on the particular assay used, D-dimer measurement is a moderate to highly sensitive diagnostic tool for the presence of DVT or PE (3). Particle agglutination assays such as classical plasma-based latex slide tests and direct whole blood tests, give quick answers but are generally less sensitive than ELISA methods. Rapid quantitative assays based on the ELISA technique or automated turbidimetric methods have been developed with an excellent sensitivity. Such tests are increasingly being incorporated in diagnostic algorithms for venous thromboembolism. Evidence has accumulated that DVT and PE can be safely ruled out in outpatients in the emergency room based on a negative D-dimer test alone. For safety reasons, however, this policy is restricted to non-high clinical probability patients. This implies that the D-dimer test must be used in conjunction with clinical probability assessment.

D-dimer testing for DVT/PE exclusion is particularly useful considering the prevalence of the disease among clinically suspected outpatients. This has been decreasing steadily over the past fifteen years with reported contemporary prevalence below 20% or even below 10% in some diagnostic centers in Canada and the US. Thus, the question is no longer to confirm but to exclude the disease, and to restrict further imaging modalities to those patients with a D-dimer level above the diagnostic cut-off. Other patient populations such as inpatients, postoperative patients, pregnant women, and elderly subjects have higher baseline D-dimer levels, thereby reducing the specificity for VTE. This limits the practical usefulness of the test in these populations in case of suspected venous thromboembolism.

The saga of D-dimer measurement has been exemplary. Diagnostic performance has been accurately determined with appropriate comparators (3). Usefulness has been assessed in large outcome studies (4). Finally, cost-effectiveness has also been established (5). However, the proportion of patients with positive D-dimer but without DVT or PE increases dramatically in daily clinical practice, probably in part because it is easier to order D-dimer testing than to question the pertinence of looking for DVT or PE in a given patient. Even a good test can be misused, and even a good test does not dispense from clinical reasoning.

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Venous thromboembolism (VTE) is a common medical condition with an annual incidence in the general population of about 0.2 percent (6). Clinical manifestations are deep vein thrombosis (DVT) and its major complication, pulmonary embolism (PE).

Deep vein thrombosis is caused by the formation of a blood clot (thrombus) within one of the main leg veins, and may lead to partially or completely blocked circulation.

The major risk associated with DVT is the development of PE, a severe respiratory complication, caused by a blood clot migrating into the pulmonary circulation. DVT and PE are strongly associated. Asymptomatic PE is detected in about 50% of patients with documented DVT and asymptomatic venous thrombosis is found in about 70% of patients with confirmed symptomatic PE (7).

Common symptoms of DVT are sudden pain in the calf, cramps and swelling of the affected leg. Common symptoms of PE are chest pain, dyspnea (shortness of breath) and/or syncope.

Mortality rates within one month of diagnosis are 6% and 12% in cases of DVT and PE, respectively (6). VTE causes considerable morbidity including post-thrombotic syndrome (PTS) in the case of DVT and chronic pulmonary hypertension in the case of PE (7). PTS is a chronic condition characterized by pain, swelling and skin ulceration of the leg.
VTE is a multi-factorial disease and often results from a combination of risk factors, including environmental and genetic sources (Table 1).

<table>
<thead>
<tr>
<th>Strong Risk Factors</th>
<th>Moderate Risk Factors</th>
<th>Weak Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fracture (hip or leg)</td>
<td>• Arthroscopic knee surgery</td>
<td>• Bed rest &gt; 3 days</td>
</tr>
<tr>
<td>• Hip or knee replacement</td>
<td>• Catheterisation (central venous lines)</td>
<td>• Minimal immobility (e.g. prolonged travel in car or plane)</td>
</tr>
<tr>
<td>• Major general surgery</td>
<td>• Chemotherapy</td>
<td>• Increasing age (&gt; 40 years)</td>
</tr>
<tr>
<td>• Major trauma</td>
<td>• Congestive heart or respiratory failure</td>
<td>• Laparoscopic surgery</td>
</tr>
<tr>
<td>• Spinal cord injury</td>
<td>• Hormone replacement therapy</td>
<td>• Obesity</td>
</tr>
<tr>
<td></td>
<td>• Cancer</td>
<td>• Pregnancy / ante-partum</td>
</tr>
<tr>
<td></td>
<td>• Oral contraceptives</td>
<td>• Varicose veins</td>
</tr>
<tr>
<td></td>
<td>• Paralytic stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pregnancy/post-partum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Previous VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Thrombophilia</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Risk factors for VTE.(8)

Prophylactic treatment with anticoagulant drugs is indicated in the presence of certain moderate or high risk factors. Patients with a first VTE event are at risk of having a second event. The annual recurrence rate is 3-10%.(7)

Once VTE is diagnosed, current practice is to provide an initial short treatment with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin, followed by an oral anticoagulant drug (e.g. warfarin) for several months to prevent embolization and recurrence.(9) The optimum dosage and duration of oral anticoagulant therapy after a first event, however, is largely dictated by underlying risk factors.(8,9)
How is VTE diagnosed?

VTE may or may not be associated with clinical symptoms such as pain and swelling of the affected leg (DVT) or dyspnea, chest pain and/or syncope (PE). This means that diagnosis of VTE is difficult and not reliable when based on clinical symptoms alone. Clinical suspicion of VTE must therefore be confirmed with objective tests.

Venography (phlebography) and pulmonary angiography are the gold standard methods to diagnose DVT and PE respectively – but they are invasive, costly and not universally available.

In recent years, these have been surpassed by alternative non-invasive techniques, such as compression ultrasonography (CUS) for suspected DVT and spiral computerized tomographic pulmonary angiography (CTPA) for suspected PE (Figure 1).

However, these modern imaging techniques also have limitations in terms of availability, cost and effectiveness. Furthermore, it is known that the prevalence of VTE among clinically suspected outpatients is relatively low (about 20%). This explains the need for an efficient non-invasive approach to safely exclude VTE, and to identify those patients in whom anticoagulant therapy can be safely withheld.

In recent years, clinical pre-test probability (PTP) assessment and D-dimer testing have been evaluated as additional tools to improve the effectiveness and cost-efficiency of non-invasive strategies to diagnose VTE.

Several outcome studies have now shown that the approach of combining PTP with a highly sensitive D-dimer assay can safely exclude disease in up to half of outpatients with suspected VTE, without the need for additional diagnostic investigations.
Fibrin, the main component of a thrombus, is formed by the activation of the coagulation system, whereas activation of the fibrinolytic system leads to the dissolution of the fibrin clot (Figure 2).

The resulting fibrin degradation products are a heterogeneous group of molecules characterized by the presence of multiple cross-linked D-domains (D-dimer). D-dimer is a direct biomarker of fibrinolysis (plasmin generation) and an indirect marker of coagulation (thrombin generation). The half-life is approximately eight hours.

D-dimer can be measured in plasma by immunoassays based on monoclonal antibodies reactive against D-dimer epitopes. Increased levels of D-dimer occur in a variety of conditions where the coagulation system is activated, including surgery, trauma, infection, inflammation, pregnancy, disseminated intravascular coagulation (DIC) and thrombosis.

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

Figure 2. D-dimer is a marker of fibrin clot formation and dissolution.
Why consider D-dimer in the diagnosis of VTE?

Due to the simultaneous activation of fibrinolysis, D-dimer levels are raised in the presence of large blood clots that obstruct the circulation in symptomatic patients with VTE. However, activation of coagulation and subsequent fibrinolysis also occurs in a variety of other disorders without giving rise to an occluding clot. Consequently, D-dimer is not a specific marker for VTE, since its level can also be increased due to co-morbid conditions such as cancer or recent surgery. D-dimer is also significantly elevated in the elderly and during pregnancy.

Therefore, a positive D-dimer assay alone will not confirm VTE. However, D-dimer levels are raised in almost all patients with acute VTE when assayed with a highly sensitive test. Consequently, a patient with a normal D-dimer plasma level (i.e. below a predefined cut-off value) is very unlikely to have DVT or PE.

The usefulness of this test, therefore lies in its ability to safely exclude the presence of VTE due to its high negative predictive value (NPV).

Prospective management studies have shown that D-dimer testing, combined with clinical probability assessment, allows rapid and safe exclusion of VTE in 30% to 50% of suspected outpatients (4).

D-dimer and clinical assessment are now highly recommended as the first step in the investigation of patients with suspected VTE (13-17).

This has two important advantages for the healthcare system:

- **Cost-savings for the hospital**
  - Avoids unnecessary imaging procedures and treatment.
  - Reduces length of hospital stay or need for transfer.

- **Improved patient comfort**
  - Avoids risk associated with invasive procedures.
  - Avoids bleeding complications associated with unnecessary anticoagulant treatment.
Choosing a D-dimer assay for VTE exclusion

Since D-dimer is not a standardized analyte and the results depend on the assay being used, clinicians should know the diagnostic performance of the test used in their own institution. D-dimer assays usually correlate, but results are not necessarily identical because of differences in antibody reactivity, analytical sensitivity, calibrator material and reporting units (12). This means that each D-dimer assay has its own typical normal range and VTE cut-off value and needs its own validation before it can be introduced into clinical practice for the exclusion of VTE (18).

Selection of the most appropriate D-dimer assay for VTE exclusion involves an assessment of analytical, operational and clinical performance criteria (Table 2). According to experts in the field, “…preference should be given to assays with the lowest coefficient of variation at the cut-off point and to those tests that have undergone proper validation of their sensitivity and specificity” (19).

The selection and validation of the most appropriate D-dimer assay is a 3-step process (10):

1. Technical and operational qualification of the test

Three main detection principles can be distinguished for the measurement of plasma D-dimer levels: ELISA, latex particle agglutination and whole-blood agglutination (12). Depending on the method, the result is qualitative, semi-quantitative or quantitative. Methods can be manual or automated and differ in turnaround time (TAT). For the management of outpatients

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### Table 2

Requirements of a D-dimer assay for VTE exclusion.

<table>
<thead>
<tr>
<th>Performance</th>
<th>Goal</th>
</tr>
</thead>
</table>
| **Analytical** | • Accurate test results around the cut-off:  
- Low inter-observer variability for qualitative assays  
- Low CV (<5%) for quantitative assays  
- No interference (e.g. hemolysis, lipiemia, bilirubin, rheumatoid factor) |
| **Operational** | • Easy to use  
- Availability 24 hours a day, 7 days a week  
- Rapid turnaround time (TAT)  
- Results available within one hour |
| **Clinical** | • High sensitivity and NPV (close to 100%)  
This is a determinant of safety (prevent false-negatives)  
• Reasonable specificity (>40%)  
This is a determinant of clinical usefulness (prevent too many false-positives)  
• Validated in appropriate clinical studies:  
  Accuracy study vs. reference method  
  - to determine optimal cut-off level  
  Prospective clinical outcome study  
  - to demonstrate safety of VTE exclusion; i.e. the 3-month thrombosis event rate in patients excluded on the basis of a normal D-dimer should not exceed 3% (upper limit of 95% confidence interval) |
with suspected VTE in the emergency department, preference is given to quantitative observer-independent systems with a short TAT and the lowest coefficient of variation (CV) at the cut-off point. A rapid, automated and quantitative ELISA such as VIDAS® D-Dimer Exclusion™ fits these requirements.

2. Selection of optimal cut-off point; accuracy study versus the reference method

The optimal discriminating D-dimer level for VTE exclusion (cut-off point) needs to be determined by a blinded prospective observational study in the target population (i.e. outpatients with suspected VTE). The presence or absence of VTE is confirmed by accepted reference methods such as serial CUS and multi-slice CTPA. The optimal cut-off point and the corresponding sensitivity (true positives) and specificity (true negatives) are then determined by standard statistical methods.

The sensitivity determines the safety of the D-dimer assay for VTE exclusion and should be close to 100% to minimize the number of false negatives (i.e. ensure a high NPV). The NPV, however, not only depends on the sensitivity of the assay but also on the prevalence of the disease: the higher the pre-test probability of VTE, the lower the NPV. Consequently, even a highly sensitive D-dimer assay may not safely rule out VTE in patients with a high clinical probability.

Therefore, D-dimer should not be used indiscriminately for VTE exclusion and needs to be combined with clinical PTP assessment.

The specificity determines the clinical usefulness of the assay; i.e. the proportion of patients in a suspected population that is below the cut-off point and can potentially be excluded, provided the PTP is low or moderate. In outpatients, the specificity of highly sensitive D-dimer assays is usually around 40% (i.e. 60% false positives). This means that in a typical outpatient population, with a VTE prevalence of 20%, about 1/3rd can be excluded with a high-sensitivity assay.

Because specificity is much lower in the elderly, pregnant women, patients with cancer and hospitalised patients, D-dimer has limited utility for VTE exclusion in these populations.

3. Prospective clinical management study (outcome study)

Once a D-dimer test has been selected based on its technical and operational merits (step 1) and accuracy criteria (step 2), its actual utility for VTE exclusion in terms of safety (thrombotic event rate on follow-up) and efficacy (reduced need for imaging) needs to be demonstrated in real life. This requires a prospective clinical outcome study in which further diagnostic imaging and anticoagulation are withheld in patients with suspected VTE who exhibit a low or moderate PTP and normal D-dimer test result. A systematic 3-month follow-up is required in excluded patients to allow detection of delayed thrombotic events and establish the true diagnostic performance of the test. The exclusion procedure is considered safe if the upper 95% confidence limit of the 3-month event rate does not exceed 3%.
Not all D-dimer assays are equal

To safely exclude VTE, assay sensitivity should approach 100%:

“For every 2% decrease in sensitivity, 1 per 1000 patients studied will die of recurrent PE as a result of inappropriately withholding anticoagulant therapy” (22).

D-dimer assays vary in sensitivity (3). Basically, a D-dimer assay with the highest sensitivity will provide the best safety (highest NPV). The ELISA D-dimer method is considered to be the ‘gold standard’ and dominates the comparative ranking among D-dimer assays for sensitivity and NPV:

“For excluding PE or DVT, a negative result on quantitative rapid ELISA is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding” (3).

VIDAS® D-Dimer Exclusion™, a rapid quantitative ELISA, offers an NPV > 99% at a cut-off of 500 ng/mL. This has been proven in more than 50 published peer-reviewed accuracy studies involving over 11,000 patients.

The actual safety and efficacy of VTE exclusion in suspected outpatients based on the combination of PTP scoring and VIDAS D-dimer has been validated in several published prospective clinical management studies, involving over 6,000 patients (Table 3). On average, the combination of a low or moderate PTP score with a normal VIDAS D-dimer value was observed in about 1/3rd of all patients who were excluded from further testing and did not receive anticoagulant treatment. This turned out to be very safe as demonstrated by the low overall thrombosis rate of only 0.2% upon 3-month follow-up (NPV 99.8%).

This makes VIDAS D-Dimer Exclusion the most extensively validated assay. On the basis of this evidence, VIDAS D-Dimer Exclusion has been cleared for VTE exclusion by regulatory authorities in the US and other countries.

<table>
<thead>
<tr>
<th>Study cohort (N)</th>
<th>VTE prevalence %</th>
<th>Exclusion by VIDAS D-dimer (low-moderate PTP)</th>
<th>Safety</th>
<th>Efficacy exclusion rate, %</th>
<th>Safety % VTE at 3-month follow up (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>474</td>
<td>23 (DVT)</td>
<td>27</td>
<td>1.6</td>
<td>(0.2-5.6)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>444</td>
<td>23 (PE)</td>
<td>36</td>
<td>0.0</td>
<td>(0.0-2.3)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>234</td>
<td>22 (PE)</td>
<td>26</td>
<td>0.0</td>
<td>(0.0-6.0)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>965</td>
<td>23 (PE)</td>
<td>29</td>
<td>0.0</td>
<td>(0.0-1.3)</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>1207</td>
<td>6 (PE)</td>
<td>39</td>
<td>0.2</td>
<td>(0.0-1.2)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>756</td>
<td>26 (PE)</td>
<td>31</td>
<td>0.0</td>
<td>(0.0-1.6)</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>1451</td>
<td>20 (PE)</td>
<td>29</td>
<td>0.0</td>
<td>(0.0-0.9)</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>876</td>
<td>12 (PE)</td>
<td>51</td>
<td>0.4</td>
<td>(0.1-1.6)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Total 6407</td>
<td>18</td>
<td>34</td>
<td>0.2</td>
<td>(0.1-0.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Effectiveness of VIDAS D-Dimer Exclusion: prospective management studies in outpatients with suspected VTE.
Utility of clinical assessment

The assessment of pre-test probability (PTP), with categorization into low-, moderate- and high-risk groups is an essential initial step in the current diagnostic management of patients with suspected VTE (29). The prevalence of VTE in these categories is <10%, 20-30% and 60-80%, respectively. The PTP of VTE can be assessed empirically or by using scoring systems based on a clinical decision rule (CDR) (29). The best-known examples of CDRs are the Wells’ scores for suspected DVT (Table 4) and PE (Table 5) and the Geneva score for suspected PE (Table 6).

Because the NPV is influenced by disease prevalence, the use of D-dimer is restricted to the low or moderate PTP groups due to the lower VTE rates in these categories. The majority of suspected outpatients (80-90%) present in these two PTP categories (29). A D-dimer assay with a high sensitivity allows safe exclusion in low and moderate PTP groups, whereas exclusion should be limited to the low PTP group with a less sensitive assay (3). D-dimer is not useful for exclusion in patients with high PTP (29).

**Clinical characteristic** | **Score**
--- | ---
Active cancer (treatment ongoing, within previous 6 months or palliative) | 1
Paralysis, paresis, or recent plaster immobilization of the lower extremities | 1
Recently bedridden ≥ 3 days or major surgery within previous 12 weeks requiring general or regional anesthesia | 1
Localized tenderness along the distribution of the deep venous system | 1
Entire leg swollen | 1
Calf swelling ≥ 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity) | 1
Pitting edema confined to the symptomatic leg | 1
Collateral superficial veins (non-varicose) | 1
Previously documented DVT | 1
Alternative diagnosis at least as likely as DVT | -2

In patients with symptoms in both legs, the more symptomatic leg is used. The total score is interpreted as follows (30):$

<table>
<thead>
<tr>
<th>Total score</th>
<th>PTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0</td>
<td>LOW</td>
</tr>
<tr>
<td>1 or 2</td>
<td>MODERATE</td>
</tr>
<tr>
<td>≥ 3</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

Alternatively, patients can be categorized into two risk groups (31): DVT unlikely (total score < 2) and DVT likely (≥ 2).
### Table 5. Wells’ model for predicting pre-test probability of PE (32, 33).

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment within 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Surgery or bedridden for 3 days during past 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>History of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt; 100 min-1</td>
<td>1.5</td>
</tr>
<tr>
<td>PE judged to be the most likely diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Clinical signs and symptoms compatible with DVT</td>
<td>3</td>
</tr>
</tbody>
</table>

The total score is interpreted as follows (33):

<table>
<thead>
<tr>
<th>Total score</th>
<th>PTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>LOW</td>
</tr>
<tr>
<td>4.5 - 6</td>
<td>MODERATE</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

Alternatively, patients can be categorized into two risk groups (32, 33):

PE unlikely (total score ≤ 4) and PE likely (> 4).

### Table 6. Geneva model for predicting pre-test probability of PE (34).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>60 – 79</td>
<td>1</td>
</tr>
<tr>
<td>≥ 80</td>
<td>2</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
<td>2</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100 min-1</td>
<td>1</td>
</tr>
<tr>
<td>PaCO₂ (kPa) &lt; 4.8</td>
<td>2</td>
</tr>
<tr>
<td>PaCO₂ (kPa) 4.8 – 5.19</td>
<td>1</td>
</tr>
<tr>
<td>PaO₂ (kPa) &lt; 6.5</td>
<td>4</td>
</tr>
<tr>
<td>PaO₂ (kPa) 6.5 – 7.99</td>
<td>3</td>
</tr>
<tr>
<td>PaO₂ (kPa) 8 – 9.49</td>
<td>2</td>
</tr>
<tr>
<td>PaO₂ (kPa) 9.5 – 10.99</td>
<td>1</td>
</tr>
<tr>
<td>Chest X-ray plate-like atelectasis</td>
<td>1</td>
</tr>
<tr>
<td>Elevated hemidiaphragm</td>
<td>1</td>
</tr>
</tbody>
</table>

The total score is interpreted as follows (34):

<table>
<thead>
<tr>
<th>Total score</th>
<th>PTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>LOW</td>
</tr>
<tr>
<td>5-8</td>
<td>MODERATE</td>
</tr>
<tr>
<td>≥ 9</td>
<td>HIGH</td>
</tr>
</tbody>
</table>
Decision protocols

Cost-effective diagnostic algorithms have been validated based on a rational sequential combination of several non-invasive tests (10). D-dimer testing combined with clinical probability assessment is generally recommended as the first step (13-17). It allows rapid and safe exclusion in about 1/3 of suspected outpatients (4).

Importantly, D-dimer assays cannot be used indiscriminately for VTE exclusion and the result should always be interpreted in the clinical context of the patient (35). D-dimer is not considered useful in patients with high PTP and a negative D-dimer in this category always requires further investigation. Long duration of symptoms and concomitant use of anticoagulants are other conditions that may potentially lead to false negative D-dimer results.

Diagnostic algorithm for DVT

Figure 3 shows an example of a diagnostic algorithm using clinical probability, D-dimer and ultrasound in patients with suspected DVT. A D-dimer assay with a high sensitivity, e.g. VIDAS® D-Dimer Exclusion™, is used in patients with low or moderate PTP. When negative, DVT is safely excluded. If DVT is not excluded, further investigation is required by CUS.

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**Diagnostic Approach to Suspected DVT**

**Clinical Decision Rule Pre-Test Probability of DVT**

- **LOW or MODERATE**
  - VIDAS® D-Dimer Exclusion™
    - Negative: NO Treatment
    - Positive: CUS
      - Positive Treatment
      - Negative Treatment

- **HIGH**
  - CUS
    - Negative: Venography
      - Positive Treatment
    - Positive: NO Treatment

CUS: compression ultrasound

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Bounameaux H and Perrier A. Hematol J 2003; 4: 97-103
Diagnostic algorithm for PE

Figure 4 shows the diagnostic pathways recommended by the PIOPED II Investigators in patients with suspected acute PE. Patients are first stratified according to an objective clinical assessment.

**Clinical Decision Rule**

1. **LOW or MODERATE**
   - VIDAS® D-Dimer Exclusion™
     - Negative NO Treatment
     - Positive CTA or CTA-CTV
       - Negative NO Treatment
       - Further Testing<sup>(1)</sup> if Moderate PTP & CTA alone
         - Positive Consider Location
           - (Sub)Segmental Further Testing<sup>(2)</sup>
             - Negative NO Treatment
             - Positive Treatment
           - Main/Lobar
             - Positive Treatment

**Diagnostic Approach**

- **CTA**: contrast-enhanced multidetector computed tomographic angiography
- **CTV**: venous-phase multidetector CT venography

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<sup>(1)</sup> Further analysis

<sup>(2)</sup> Treatment

<sup>(3)</sup> No treatment

**Figure 4. Diagnostic algorithm for patients with suspected PE**<sup>(17)</sup>.
In patients with low or moderate PTP, a rapid quantitative ELISA is recommended (e.g. VIDAS® D-Dimer Exclusion™). When negative, PE is safely excluded. If PE is not excluded, CT angiography in combination with venous phase imaging (CT venography) is recommended.

### TO SUSPECTED PE

#### Pre-Test Probability of PE

- **HIGH**
  - CTA or CTA-CTV

  **Negative Further Testing**
    - **Negative**
      - NO Treatment
    - **Positive**
      - Treatment

  **Positive Treatment**

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**Options for further testing (1):**
- Ultrasound or MRI venography

**Options for further testing (2):**
- Repeat CTA or CTA-CTV if poor quality
- Ultrasound or MRI venography in case of CTA alone
- Pulmonary scintigraphy (ventilation/perfusion lung scan)
- Digital subtraction angiography
- Serial ultrasound

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1. **Is it safe to exclude VTE in suspected patients based on a negative D-dimer result?**

Yes, VTE exclusion will be safe with a negative D-dimer. However, there are a number of restrictions that should be kept in mind. First, the recommended cut-off level that is used to interpret whether the D-dimer result is negative must have been properly validated \(18, 19\). Second, D-dimer has only been validated for VTE exclusion in suspected outpatients \(10\). In hospitalized patients, the diagnostic accuracy of D-dimer for VTE is questionable \(36\) and the diagnostic yield (proportion below the cut-off) will be too low \(37\). Finally, to avoid false negatives, it is of vital importance to interpret any negative D-dimer finding in the clinical context of the patient. This requires proper observation of the following patient-related factors \(38\):

- **Clinical pre-test probability (PTP)**
  D-dimer cannot be used as a stand-alone test for VTE exclusion and needs to be combined with an assessment of clinical PTP \(4, 13\). Depending on the sensitivity of the D-dimer assay, exclusion should be restricted to patients with low PTP or can be extended to patients with moderate PTP. D-dimer is not considered useful in patients with high PTP \(20\).

- **Duration of symptoms**
  The age of the clot is relevant when interpreting test results, because D-dimer decreases with the time elapsed from the onset of symptoms \(38\). The effect of the duration of symptoms has not been systematically investigated and, therefore, exact recommendations on when D-dimer will no longer be reliable for exclusion cannot be given. Lower sensitivities (false negatives) have been reported when D-dimer was measured 4 to 15 days after the onset of symptoms \(39-41\).

- **Prior use of anticoagulation**
  Because D-dimer and other objective tests are not always immediately available (e.g. at night), patients with suspected VTE are often given an initial dose of heparin. This practice can potentially cause false negative results because D-dimer decreases by about 25% within 24 hours after heparin injection \(42\). Therefore, the D-dimer result reported from blood obtained after starting heparin treatment should be interpreted with caution. D-dimer is also decreased by vitamin K antagonists \(43\).

The importance of the sensitivity of D-dimer to the location of the clot has been a matter of debate. D-dimer has a lower sensitivity for smaller clots in distal DVT \(44\) and subsegmental PE \(45\). Missing small distal clots, however, is considered to be of low concern because of uncertainty as to clinical significance and lack of data on the benefit of treatment \(46, 47\).
2. Does a positive D-dimer result indicate that my patient has a VTE?

No, D-dimer is not specific for VTE and can be elevated in many other circumstances, in particular:

- Old age
- Pregnancy
- Cancer
- Arterial disease (peripheral arthriopathy, coronary artery disease, stroke)
- Disseminated intravascular coagulation (DIC)
- Liver disease
- Infection
- Inflammation

Thus, a positive D-dimer result cannot be used to rule-in VTE and further objective imaging tests are needed to confirm the presence of a thrombus.

The implication of this diagnostic behavior is that the specificity of D-dimer for VTE (i.e. proportion of negative results in patients without VTE) does not reach 100%. The specificity of D-dimer for VTE depends on the method used and shows an inverse relationship with sensitivity. The specificity varies from 40-50% for high-sensitivity quantitative assays up to about 70% for low-sensitivity qualitative and semi-quantitative D-dimer assays (48).

The specificity is a determinant of the clinical usefulness of D-dimer for VTE exclusion (37). In a hypothetical outpatient population of 100 patients, with a typical 20% VTE prevalence, 32 patients can be excluded with a high-sensitivity D-dimer assay with a specificity of 40%. In other words, the number of patients that need to be tested (NNT) in the entire cohort to rule out one VTE would be three (NNT=3). If the specificity drops to 12%, the diagnostic yield will be much lower and then only 10 patients can be excluded (NNT=10).
3. Can D-dimer be used for VTE exclusion in subgroups of outpatients with conditions such as pregnancy, cancer, previous VTE and the elderly?

Yes, this is possible because there are no data that indicate that the sensitivity is affected by these clinical conditions. On the other hand, the specificity will drop at the usual cut-off that has been validated for the entire outpatient population (e.g. 500 ng/mL for VIDAS® D-Dimer Exclusion™). This affects the clinical usefulness in terms of the proportion of patients that can be excluded, which may be as low as 10% (NNT=10). Despite the lower diagnostic yield in various patient subgroups, it could nevertheless be worthwhile to perform a D-dimer test because it is rapid, inexpensive and may still prevent an imaging test in at least one out of every ten patients tested. This is particularly the case if the routine diagnostic strategy is based on upfront D-dimer in combination with a clinical decision rule. On the other hand, if the clinical setting is more imaging oriented and D-dimer results are not readily available, it might be more efficient to directly proceed to scanning procedures.

- **Pregnancy**

Normal pregnancy causes a progressive increase in circulating D-dimer, which peaks at delivery and gradually decreases to normal within 4 weeks after delivery (49-51). D-dimer increases with each trimester, so that only about 50% and 25% of women are below the usual cut-off in the 1st and 2nd trimester, respectively. D-dimer has no utility to rule out VTE in the 3rd trimester and the immediate post-partum period. Because of the limited potential utility and lack of proper validation studies, D-dimer testing is not part of recently published evidence-based recommendations on diagnostic testing of pregnant women with clinically suspected VTE (52).

- **Cancer**

Cancer is a common cause of VTE and has been shown to occur in 10-14% of outpatients with suspected VTE (53-55). In these studies, the prevalence of VTE in the cancer subgroups was on average 1.5-fold higher compared with non-cancer patients. The combination of D-dimer and clinical PTP assessment appears to be safe to rule out PE (53, 54) or DVT (55) in suspected outpatients with cancer. The exclusion rate, however, was 2 to 3-fold lower compared with non-cancer patients: NNT=10 vs. NNT=3 in suspected PE and NNT=4 vs. NNT=2 in suspected DVT.

- **Previous VTE (VTE recurrence)**

Patients with a first VTE event are at increased risk of having a second event (7). Studies in outpatients with suspected PE reported previous VTE episodes in 14% (53) and 18% (56) of the total cohort. D-dimer levels remain elevated in many patients after completion of the standard anticoagulant drug course for a first VTE episode (57). This may limit the clinical usefulness of D-dimer for exclusion of recurrent VTE. Subgroup analysis of large prospective outcome studies in patients with suspected PE have demonstrated that a negative D-dimer result allows safe exclusion of a recurrent event, albeit with a 2-fold lower exclusion rate (53, 56). A single-center management study has shown that D-dimer also allowed safe exclusion of suspected recurrent DVT, apparently without compromising the diagnostic yield (NNT=2) (56).
• **Elderly patients (>70 years)**

Both D-dimer and the prevalence of VTE increase with age and this may affect the clinical usefulness of the D-dimer test in the elderly. Subgroup analysis of studies in outpatients showed that the combination of PTP assessment and D-dimer allows safe exclusion in the elderly, albeit with a much lower efficacy (exclusion rate 10-14%; NNT=7-10).

4. **Can D-dimer be used to guide the duration of anticoagulation?**

No, not yet, despite promising data from prospective observational studies and a randomized trial. The optimal duration of oral anticoagulation is uncertain, particularly in patients with a first idiopathic VTE event. The risk of recurrence is greatest in the first 6-12 months but gradually diminishes thereafter. The benefit of an extended duration of anticoagulation may be offset by an increased risk of bleeding. It is therefore important to find those patients in whom extended anticoagulation may be warranted based on predictors of increased risk. D-dimer is emerging as a promising risk predictor for VTE recurrence, most notably to identify patients at low risk. However, further studies are needed before it can be introduced into routine clinical practice to gauge the duration of anticoagulation. Critical parameters include the time of measurement, the optimal cut-off and the effect of other risk predictors such as gender. Studies are ongoing to address these issues and define an optimal risk prediction rule to select low-risk patients in whom anticoagulation can be safely stopped after the standard 6-month course.

5. **Is there a potential future value for D-dimer in arterial thrombosis?**

Yes, arterial thrombosis can be considered as a disease area where D-dimer has potential to add valuable additional information for the treating physician. Heart attack and stroke, the most devastating consequences of atherosclerosis, are caused by acute thrombus formation resulting from plaque rupture. Epidemiological studies have demonstrated that D-dimer is an independent predictor for future coronary heart disease in the general population. However, it is unlikely that D-dimer will play a role in cardiovascular risk stratification in asymptomatic individuals. More promising is a role for D-dimer in optimizing risk stratification in acute settings such as patients presenting with chest pain due to acute coronary syndromes or patients with stroke. D-dimer may also have a prognostic role in atrial fibrillation and heart failure.


