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INTRODUCTION

Accurate, early diagnosis of VTE (DVT/PE) is critical to prevent complications and risk of death. Imaging techniques are required for a positive diagnosis, including compression ultrasound (CUS) and CT pulmonary angiography (CTPA) for diagnosis of DVT and PE, respectively (1).

However, the low prevalence of confirmed VTE in suspected outpatients (20% or less) underscores the importance of a first triage by a non-invasive exclusion test in order to avoid unnecessary imaging (2). Imaging is not only costly, but in the case of CTPA can also cause harm: cancer risk due to radiation exposure, contrast-induced nephropathy and excess bleeding risk associated with unnecessary use of anticoagulants in case of over-diagnosis (3).

Over the past 25 years, the clinical usefulness of D-dimer testing in the diagnosis of patients with suspected VTE has been extensively validated (4):

- Due to its high sensitivity for the presence of VTE, D-dimer allows its exclusion in suspected patients attending the emergency department (ED).
- For safety reasons, VTE exclusion by the D-dimer test should be restricted to patients with a non-high or an unlikely clinical probability for having VTE as assessed by validated clinical prediction rules.
- Due to its low specificity for the presence of VTE, D-dimer cannot be used as a rule-in test.

Consequently, the diagnostic management of DVT and PE is based on sequential use of tests, including clinical probability assessment, D-dimer and imaging techniques (1). These diagnostic algorithms have been extensively validated in outcome studies (5).

- Combined use of clinical prediction rules and D-dimer testing as first screen allows rapid identification of patients who do not require imaging and in whom anticoagulant treatment can be safely withheld.
- This is a cost-effective approach that avoids unnecessary imaging in about 1/3rd of outpatients with suspected VTE.

D-dimer assays are widely available, but vary considerably in their analytical, operational and clinical performance characteristics (4). Clinicians and laboratory managers should be aware of these aspects before selecting a D-dimer assay for VTE exclusion. Furthermore, clinicians should also understand the limitations of the D-dimer test for VTE exclusion within the clinical context of the patient (4, 6).

This booklet provides clinicians and laboratory managers with concise information on the pathophysiology and diagnosis of VTE, with special emphasis on the role of D-dimer, including criteria for its use as a valid exclusion test.

OUR SPECIAL THANKS GO TO

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for his expert advice in preparing this booklet.
VENOUS THROMBOEMBOLISM (VTE)
A ‘SILENT KILLER’ AND MAJOR CAUSE OF GLOBAL DISEASE BURDEN (7)

HIGH INCIDENCE (7)

- In the general Caucasian population, between 1 and 2 per 1000 develop VTE each year (about 2/3rd DVT and about 1/3rd PE), with a slightly higher incidence in men than women.
- Annual incidence rises with age to between 2 and 7 per 1000 after 70 years of age.
- Although the annual incidence is lower in Asians (< 0.5 per 1000) their disease burden is not low due to population aging.
- Up to 60% of VTE events occur during or after hospitalization, making it a leading preventable cause of hospital death.

CHRONIC RELAPSING DISEASE WITH HIGH MORBIDITY

- VTE has a high risk of recurrence: 11% within the first year, and 40% within 10 years (9).
- Long-term, VTE is associated with considerable disability (7).
- Approximately 10-20% of DVT patients develop severe post-thrombotic syndrome (PTS). This is a chronic disorder with decreased quality of life and reduced capacity to walk and to work, particularly due to development of venous ulcers.
- Up to 4% of PE patients develop chronic thromboembolic pulmonary hypertension (CTEPH), characterized by reduced cardiorespiratory capacity.

HIGH MORTALITY

- VTE is a medical emergency because PE can be life-threatening if not treated immediately. It has been estimated that of all VTE-related deaths, 34% are due to sudden fatal PE, 59% result from PE that remained undiagnosed and 7% of early deaths were correctly diagnosed with PE (8).
- In the USA and EU, more than 800,000 VTE-related deaths are estimated to occur each year, making VTE the third most frequent cause of cardiovascular mortality after heart attack and stroke (7).

HIGH ECONOMIC BURDEN

- VTE costs, the majority related to PE, have a large impact on the healthcare system (10). Including long-term morbidity (PTS, CTEPH), total annual VTE costs between 15 and 34 billion USD have been estimated for the US healthcare system.
- Total VTE-related healthcare costs of 640 million GBP have been reported in the UK (8).
Venous thromboembolism (VTE) results from the presence of a clot in the venous circulation (lower or upper extremity veins in particular) and/or by embolization of parts of the clot into the pulmonary circulation. Consequently, deep vein thrombosis (DVT) and pulmonary embolism (PE) are two clinical manifestations of the same disease. Asymptomatic PE is present in patients with proximal DVT, whereas asymptomatic DVT can also be detected in patients with PE.

Clot formation in the leg veins may occur at various sites. Venous thrombosis of the upper extremity, defined as a thrombus in the subclavian, axillary or brachial vein, accounts for 4-10% of all venous thromboses and is often asymptomatic.

The risk for PE becomes significant in the presence of a thrombus that extends into the popliteal veins or above (proximal DVT). Parts of the clot may break off from an actively propagating thrombus in the leg veins and embolize into the pulmonary circulation (transport through the superior vena cava, pass the right heart into the pulmonary arteries).

The nature and severity of symptoms depends on the size and location of the embolized thrombus.

### Figure 1: Types of acute DVT
1. **Ascending DVT** is the most common type of DVT. The clot originates in the calf muscle veins (distal DVT) and extends to reach the proximal femoral or iliac veins. Propagation into proximal veins may occur within days or even hours but can also take weeks.

2. **Transfacial thrombosis** originates in the superficial veins of the leg (greater or lesser saphenous vein). It can propagate proximally and may turn from superficial into deep vein thrombosis.

3. **Descending iliofemoral DVT** originates in the iliac veins, primarily the left iliac vein. Thrombotic obstruction of the iliac vein can develop within hours leading to massive leg swelling, pain and discoloration.

### Figure 2: Types of acute PE
1. **Peripheral, sub-segmental PE** is a mild form of PE characterized by pulmonary hemorrhagic infarction (local alterations of lung tissue with pleuritic pain or hemoptysis).

2. **Central, segmental or lobar PE** is a moderate form of PE characterized by isolated dyspnea (high probability V/Q lung scan in majority of cases).

3. **Central PE with massive pulmonary artery obstruction** is a severe form of PE associated with circulatory collapse (cardiac dysfunction).
VENOUS THROMBOEMBOLISM

Pathophysiology and risk factors

Pathophysiological mechanisms underlying venous thrombosis can be classified into three categories, known as Virchow’s triad, according to disturbances of (11):

- Blood flow (venous stasis, e.g. due to immobilization, obesity, heart failure).
- Blood vessel wall (e.g. due to surgery or trauma).
- Blood constituents (e.g. due to inheritable thrombophilia, drugs, pregnancy).

VTE is a multifactorial disease and in most cases more than one risk factor can be identified (14). The risk for VTE increases in proportion to the number of predisposing factors as well as the magnitude of the risk of each individual factor.

Currently recognized clinical VTE risk factors and the magnitude of their risk are listed in Table 1 (15). The most frequent risk factors include older age, obesity, history of VTE, cancer, long bed rest and major surgery (15). Considering temporal relationships, risk factors can be transient (e.g. trauma, surgery) or chronic (e.g. metastatic cancer, thrombophilia). Furthermore, risk factors can be genetic (heritable thrombophilia) or acquired.

Table 1: Risk factors for VTE (15)

**STRONG RISK FACTORS (ODDS RATIO > 10)**
- Fracture of lower limb
- Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
- Hip or knee replacement
- Major trauma
- Myocardial infarction (within previous 3 months)
- Previous venous thromboembolism
- Spinal cord injury

**MODERATE RISK FACTORS (ODDS RATIO 2-9)**
- Arthroscopic knee surgery
- Auto–immune diseases
- Blood transfusion
- Central venous lines
- Chemotherapy
- Congestive heart or respiratory failure
- Erythropoiesis-stimulating agents
- Hormone replacement therapy (depends on formulation)
- In vitro fertilization
- Infection (specifically pneumonia, urinary tract infection and HIV)
- Inflammatory bowel disease
- Cancer (highest risk in metastatic disease)
- Oral contraceptive therapy
- Paralytic stroke
- Postpartum period
- Superficial vein thrombosis
- Thrombophilia

**WEAK RISK FACTORS (ODDS RATIO < 2)**
- Bed rest >3 days
- Diabetes mellitus
- Hypertension
- Immobility due to sitting (e.g. prolonged car or air travel)
- Increasing age
- Laparoscopic surgery (e.g. cholecystectomy)
- Obesity
- Pregnancy
- Varicose veins

Knowledge of risk factors is important in the clinical management of VTE:

- **PREVENTION**
  To identify high-risk groups in whom prophylactic treatment is indicated (17).

- **DIAGNOSIS**
  To aid in clinical pre-test probability assessment (see clinical prediction rules), the first step to guide the optimal diagnostic strategy (1).

- **TREATMENT**
  To guide the optimal duration of anticoagulant therapy after a VTE event (18).

In 26-47% of cases, patients with a first episode of VTE do not have any identifiable precipitating cause or risk factor. These patients are referred to as having idiopathic or unprovoked VTE (16).
Signs and symptoms

Typical symptoms of DVT include swelling and/or pain in the affected leg as well as tenderness, increased warmth, erythema or distended superficial veins. DVT can also be asymptomatic. Because PE is a consequence of DVT, signs of DVT may also be present in patients with PE.

The suspicion of PE is particularly raised in patients presenting with dyspnea/tachypnea, pleuritic chest pain, syncope, hemoptysis or with sudden hemodynamic instability (shock or hypotension). In most clinical studies, suspected PE has been defined as “acute onset of new or worsening shortness of breath or chest pain without any other obvious cause” (29).

These signs and symptoms are neither sensitive nor specific for DVT or PE and many alternative diagnoses need to be considered (Table 2). The medical history and the presence of risk factors (see Table 1) are other important clues in judging the clinical probability of VTE.

The integration of multiple clinical factors into a clinical prediction rule (CPR) is a quick and easy way to discriminate suspected VTE patients into three categories of pretest probability (PTP): low, intermediate and high; or in two categories of pre-test clinical probability: unlikely and likely.

The clinical pretest probability guides the diagnostic work-up.

Table 2: Differential diagnosis

<table>
<thead>
<tr>
<th>SUSPECTED DVT</th>
<th>SUSPECTED PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strain or tear</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Arthritis of the knee or ankle including gout</td>
<td>Acute bronchitis</td>
</tr>
<tr>
<td>Ruptured Baker’s cyst</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Acute pulmonary edema</td>
</tr>
<tr>
<td>Calf muscle abscess</td>
<td>Pulmonary neoplasm</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Muscle strain</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Rib fracture</td>
</tr>
<tr>
<td>Varicose veins</td>
<td></td>
</tr>
<tr>
<td>Venous reflux</td>
<td></td>
</tr>
<tr>
<td>Vasomotor changes (e.g. in paralyzed leg)</td>
<td></td>
</tr>
<tr>
<td>Superficial venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

The most commonly used and best validated CPR’s are the Wells scores for DVT (Table 3) and PE (Table 4) and the revised Geneva score for PE (Table 5). All these scores also allow dichotomization into two categories: DVT/PE unlikely and DVT/PE likely. Simplified versions of the CPR’s for PE, with 1 point for each variable in the rule, have also been validated (15). The typical distribution of PTP categories and disease prevalence in each category is summarized in Table 6.

Table 3: Clinical prediction rule for DVT: the Wells score (20, 21)

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>• Active cancer (treatment ongoing, within previous 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>• Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>• Recently bedridden &gt;3 days or major surgery within previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>• Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td><strong>CLINICAL SIGNS, SYMPTOMS</strong></td>
<td></td>
</tr>
<tr>
<td>• Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>• Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>• Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>• Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>• Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td><strong>CLINICAL JUDGMENT</strong></td>
<td>-2</td>
</tr>
<tr>
<td>• Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
<tr>
<td><strong>CLINICAL PROBABILITY (3 LEVELS)</strong></td>
<td>TOTAL</td>
</tr>
<tr>
<td>• Low</td>
<td>&lt;0</td>
</tr>
<tr>
<td>• Intermediate</td>
<td>1 or 2</td>
</tr>
<tr>
<td>• High</td>
<td>≥3</td>
</tr>
<tr>
<td><strong>CLINICAL PROBABILITY (2 LEVELS)</strong></td>
<td>TOTAL</td>
</tr>
<tr>
<td>• DVT unlikely</td>
<td>&lt;2</td>
</tr>
<tr>
<td>• DVT likely</td>
<td>≥2</td>
</tr>
</tbody>
</table>

* In patients with symptoms in both legs, the more symptomatic leg is used.
Table 4: Clinical prediction rule for PE: the Wells score.

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RISK FACTORS</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>• Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>• Surgery or bedridden for 3 days during past 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>• Active cancer (treatment within 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>CLINICAL SIGNS, SYMPTOMS</td>
<td></td>
</tr>
<tr>
<td>• Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>• Heart rate &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>• Clinical signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>CLINICAL JUDGMENT</td>
<td></td>
</tr>
<tr>
<td>• Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

CLINICAL PROBABILITY (3 LEVELS)

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>2-6</td>
<td>≥ 7</td>
</tr>
</tbody>
</table>

CLINICAL PROBABILITY (2 LEVELS)

<table>
<thead>
<tr>
<th>PE unlikely</th>
<th>PE likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0-1</td>
</tr>
<tr>
<td>≥ 5</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

Table 5: Clinical prediction rule for PE: the revised Geneva score.

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RISK FACTORS</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>• Age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>• Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>• Surgery or fracture within 1 month</td>
<td>2</td>
</tr>
<tr>
<td>• Active malignancy</td>
<td>2</td>
</tr>
<tr>
<td>CLINICAL SIGNS, SYMPTOMS</td>
<td></td>
</tr>
<tr>
<td>• Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>• Hemoptysis</td>
<td>2</td>
</tr>
<tr>
<td>• Heart rate 75-94 beats/min</td>
<td>3</td>
</tr>
<tr>
<td>≥ 95 beats/min</td>
<td>5</td>
</tr>
<tr>
<td>• Pain on deep palpation of lower limb and unilateral edema</td>
<td>4</td>
</tr>
</tbody>
</table>

CLINICAL PROBABILITY (3 LEVELS)

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>4-10</td>
<td>≥ 11</td>
</tr>
</tbody>
</table>

CLINICAL PROBABILITY (2 LEVELS)

<table>
<thead>
<tr>
<th>PE unlikely</th>
<th>PE likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>0-2</td>
</tr>
<tr>
<td>≥ 6</td>
<td>≥ 3</td>
</tr>
</tbody>
</table>

Table 6: Pretest probability distribution and VTE prevalence.

<table>
<thead>
<tr>
<th>PTP category</th>
<th>Wells score DVT</th>
<th>Wells score PE</th>
<th>Revised Geneva score PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Total</td>
<td>DVT (%)</td>
<td>% of Total</td>
<td>PE (%)</td>
</tr>
<tr>
<td>3 LEVEL SCORE</td>
<td>(data from ref 25)</td>
<td>(data from ref 26)</td>
<td>(data from ref 26)</td>
</tr>
<tr>
<td>Low</td>
<td>44</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>High</td>
<td>20</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>2 LEVEL SCORE</td>
<td>(data from ref 21)</td>
<td>(data from ref 26)</td>
<td>(data from ref 24)</td>
</tr>
<tr>
<td>Unlikely</td>
<td>54</td>
<td>6</td>
<td>69</td>
</tr>
<tr>
<td>Likely</td>
<td>45</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

Diagnosis

NON-INVASIVE ALGORITHM

An accurate and rapid diagnosis of VTE in suspected patients is essential. Missing the diagnosis may result in a potentially fatal PE, whereas a false positive diagnosis may lead to unnecessary anticoagulant treatment that is associated with bleeding risk that can be fatal.

MISSING THE DIAGNOSIS

- Potentially fatal PE

FALSE-POSITIVE RESULT

- Unnecessary anticoagulants (risk of fatal bleeding)

Furthermore, as a result of the raised index of clinical suspicion, the prevalence of confirmed VTE among suspected outpatients has dramatically declined over recent years to values as low as 10% or less in certain populations. 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 withheld.
In the vast majority of patients, a non-invasive work-up is feasible. This consists of the sequential use of a CPR for clinical pretest probability assessment, D-dimer and imaging techniques (Figure 3) (1). Preferred imaging methodologies are compression ultrasound (CUS) for diagnosis of DVT and computerized tomographic pulmonary angiography (CTPA) for diagnosis of PE (Figure 4).

Although CTPA is the most reliable test for the diagnosis of PE, algorithms using V/Q scanning are equally safe and may be preferred in populations where radiation exposure is a concern (e.g. breast cancer risk in young women) (27).

Clinical assessment and D-dimer are recommended as the first step in the investigation of patients with suspected VTE (1, 4, 15). This strategy is cost-efficient (28) and safely excludes VTE in 30-50% of suspected outpatients (9).

In case of a high pretest probability or a positive D-dimer, objective confirmation is needed by CUS in case of suspected DVT or CTPA in case of suspected PE (1).

Given its high negative predictive value (NPV), D-dimer plays a key role in rapid exclusion of VTE. It is important to realize that the NPV will drop with increasing prevalence of VTE (pretest probability) and this rate of decline is determined by the sensitivity of the D-dimer assay (see Figure 6, page 18).

Highly sensitive D-dimer assays permit safe exclusion in patients with low and intermediate PTP, whereas a less sensitive D-dimer assay should be limited to patients with low or unlikely PTP (4).

D-dimer should NOT be used in patients with high PTP, because despite a normal D-dimer level, approximately 1 in 10 patients may still have PE (29).

In this algorithm, the D-dimer result refers to a highly sensitive assay. With less sensitive assays, exclusion is only possible in patients with a low (or unlikely) pretest probability.

In case of suspected PE, this algorithm is only valid when the patient is hemodynamically stable (15). With shock or hypotension, immediate CTPA or echocardiography (when CTPA is not available) is needed.
Adherence to above validated diagnostic strategy is crucial for diagnosing PE because of the 4-fold higher risk of recurrent PE and death when the diagnosis is missed. Furthermore, significantly fewer patients will receive an unnecessary radiation dose when the algorithm is correctly followed.

DVT is detected by compression ultrasonography (CUS, left) and PE by CT pulmonary angiography (CTPA, right). CUS directly visualizes the proximal veins in the leg which are subsequently assessed for their compressibility. Non-compressibility is diagnostic for acute proximal DVT with a sensitivity of 94% and specificity of 98%. A CTPA is performed after injection of intravenous contrast material. Multi-detector row CT scanners have a high sensitivity (96–100%) and specificity (97–98%) for acute PE.

**Table 7: Acute PE: risk stratification and management (ESC Guidelines)**

<table>
<thead>
<tr>
<th>EARLY MORTALITY RISK</th>
<th>RISK PARAMETERS</th>
<th>CLINICAL MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
<td>PESI Class III-V or sPESI ≥1</td>
</tr>
<tr>
<td>HIGH</td>
<td>Yes</td>
<td>Yes (*)</td>
</tr>
<tr>
<td>INTERMEDIATE-HIGH</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>INTERMEDIATE-LOW</td>
<td>No</td>
<td>No (**)</td>
</tr>
<tr>
<td>LOW</td>
<td>No</td>
<td>No (**)</td>
</tr>
</tbody>
</table>

PESI: Pulmonary Embolism Severity Index; sPESI: simplified Pulmonary Embolism Severity Index. PESI Class III to V indicates moderate (3-10%) to very high 30-day mortality risk (10-25%); sPESI ≥1 indicate high 30-day mortality risk (11%). Patients in PESI Class I or II or 0 points on sPESI are at low risk for 30-day mortality (<2%).

RVD: right ventricular dysfunction assessed on imaging (echocardiography or CTPA).

Cardiac biomarkers: markers of myocardial injury (cardiac troponin I or T) or markers of heart failure (B-type natriuretic peptides BNP or NT-proBNP).

* Assessment not necessary in patients with shock or hypotension
** PESI Class I or II; sPESI =0.
*** Assessment optional

Decisions on clinical management of PE in the acute phase are guided by the assessment of the patient’s early death risk (in-hospital or 30 days). Short-term mortality risk varies widely from 15% or more within hours after admission in hemodynamically unstable patients with shock or hypotension to less than 1% in normotensive patients without signs of right ventricular dysfunction (RVD).
D-DIMER

**Definition - Biochemistry**

D-dimer is a marker of activation of coagulation and fibrinolysis (Figure 5). Coagulation results in the formation of the fibrin clot, whereas subsequent degradation by the fibrinolytic system generates a heterogeneous mixture of fibrin degradation products characterized by the presence of multiple D-dimer epitopes.

**Small amounts of D-dimer are present in plasma from healthy individuals because of the continuous physiological turnover (fibrin formation and lysis) of 2-3% of plasma fibrinogen.**

**In VTE patients, the lysis of obstructing blood clots results in about 8-fold increased plasma D-dimer levels, which fall with the duration of symptoms and anticoagulant treatment (plasma half-life is approximately 8 hours)** (4).

Since D-dimer levels are raised in almost all patients with acute VTE when assayed with a highly sensitive test, a patient with a normal plasma level (i.e. below a predefined cut-off level) is very unlikely to have DVT or PE. Therefore, the usefulness of D-dimer lies in its ability to exclude the presence of VTE.

D-dimer is not specific for VTE and elevated levels are also observed in a variety of other conditions where activation of coagulation and fibrinolysis occurs (Table 8). This makes D-dimer less useful for VTE exclusion in hospitalized patients due to the high proportion of comorbid conditions with elevated D-dimer.

**Table 8: Elevated D-dimer in absence of VTE**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Inflammation (e.g. inflammatory bowel disease)</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Trauma, extensive burns</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Liver or renal disease</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Acute aortic dissection</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
</tr>
</tbody>
</table>
D-dimer assays

ACCURACY AND CRITERIA FOR A VALID EXCLUSION TEST

D-dimer levels can be measured by a variety of commercially available tests based on monoclonal antibodies reactive against D-dimer epitopes present on fibrin degradation products without cross-reactivity with fibrinogen (4, 35). Detection technology is based on sandwich-type ELISA, latex particle agglutination or direct whole blood agglutination.

D-dimer assays differ in their analytical, operational and clinical performance characteristics. They can be quantitative or qualitative, manual or fully automated, based on plasma or whole blood samples. The accuracy for VTE varies between assays with an inverse relationship between sensitivity and specificity. Quantitative automated assays have a high sensitivity (>95%) with a low specificity (40-50%), whereas manual whole blood agglutination assays have a lower sensitivity (~85%) but a higher specificity (~70%) (36). Quantitative enzyme-linked fluorescence assays (ELFA) offer the highest sensitivity (99%).

Because of the trade-off between sensitivity and specificity, clinicians should understand the diagnostic performance of the test used in their institution.

- 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 (NPV ≥ 98%) over a large pre-test probability range (Figure 6). Guidelines of the Clinical Laboratory Standards Institute (CLSI) recommend a minimum sensitivity of 97% in order for the NPV to reach a level of 98% or more in patients with low or intermediate PTP (37).

- The specificity determines the clinical usefulness (efficacy) of the assay in terms of the proportion of suspected VTE patients that can be excluded. The higher the specificity, the lower the number of positives that require further imaging to confirm the diagnosis.

- An optimal balance between sensitivity and specificity is required in order to safely exclude VTE (NPV ≥ 98%) and to avoid further imaging in a large enough proportion of suspected outpatients. This favors a high-sensitivity D-dimer assay because it can be used in both the low and intermediate PTP groups (Figure 6).

D-dimer assays lack standardization and the results depend on the assay being used (4). D-dimer assays usually correlate, but results are not identical because of differences in antibody reactivity, analytical sensitivity, calibrator material and reporting units. This means that each D-dimer assay has its own method-specific cut-off value for VTE exclusion that needs to be clinically validated.

The ultimate clinical validation is a prospective outcome study with a 3-month follow-up in excluded patients to detect delayed thrombotic events and establish the true diagnostic performance of the test. The exclusion procedure (i.e. combination of PTP and negative D-dimer) is considered safe if the upper 95% confidence limit of the 3-month thromboembolic failure rate does not exceed 3% (38).

Selection of the most appropriate D-dimer assay for VTE exclusion involves an assessment of analytical, operational and clinical performance characteristics (Table 9).

Preference should be given to assays that have undergone proper clinical validation and have a sufficiently low coefficient of variation at the cut-off point (4).

| Table 9: Requirements of a D-dimer assay for VTE exclusion (4, 35, 37) |
|-----------------------------|-----------------------------|
| PERFORMANCE | GOAL |
| ANALYTICAL | • Accurate test results around the cut-off  
- Qualitative assays: low inter-observer variability  
- Quantitative assays: low CV (<7.5%) |
| OPERATIONAL | • Easy to use: availability 24 hours, 7 days per week  
• Rapid turnaround time (TAT): <1 hour |
| CLINICAL | • High sensitivity (≥97%): safe exclusion in patients with low and intermediate PTP (NPV ≥98%)  
• Reasonable specificity (>40%): minimize the number of positives that require imaging to confirm the diagnosis  
• Validated in prospective outcome study: 3-month thromboembolic failure rate in excluded patients should not exceed 3% (upper limit 95% confidence interval) |
Simulation of the impact of assay sensitivity on the NPV in patients with low, intermediate or high PTP. Safe exclusion requires NPV of 98% or more. Examples include typical D-dimer tests such as a quantitative automated ELFA (Assay A; sensitivity 99%, specificity 40%), a quantitative automated latex-based assay (Assay B; sensitivity 95%, specificity 50%) and a whole-blood agglutination test (Assay C; sensitivity 88%, specificity 70%) (36).

No D-dimer assay can be used to safely exclude VTE in patients with high PTP. Highest confidence for safe exclusion in both low and intermediate PTP is offered by the D-dimer assay with the highest sensitivity (Assay A).

Is 500 µg/L a uniform cut-off for VTE exclusion?

There is no standardization of D-dimer assays and D-dimer results are either reported as D-dimer units or fibrinogen equivalent units (FEU; 1 µg D-dimer equals 2 µg FEU). Consequently, each method has its own cut-off value for VTE exclusion which needs to be clinically validated in outcome studies (4).

A cut-off value of 500 µg FEU/L has been used in one of the most extensively validated D-dimer assays (39). A combined analysis of 7 prospective outcome studies conducted with this D-dimer method showed that 40% of patients with low/intermediate or unlikely PTP were below this particular threshold with a 3-month thromboembolic failure rate of only 0.14% (NPV 99.86%) when left untreated.

Is it safe to exclude VTE based on a negative D-dimer result?

D-dimer should never be used as a stand-alone test for VTE exclusion and any negative result should be interpreted within the clinical context of the patient, including pretest probability.

Outcome studies combining clinical probability and D-dimer have clearly confirmed the safety of not treating suspected VTE patients with a non-high clinical probability and normal D-dimer (5, 39).

Under certain conditions lower than expected D-dimer results may occur giving rise to false negatives. This may include patients with a small thrombus burden such as distal DVT or subsegmental PE (4). However, the clinical relevance of small clots in these locations is debated (27). Moreover, despite the limited sensitivity for distal DVT or subsegmental PE, the safety of not treating suspected VTE patients with normal D-dimer and non-high clinical probability has been widely demonstrated (5, 39). The crucial point for clinicians is that patients with normal D-dimer levels have an uneventful 3-months follow-up.

Clinically relevant false negatives may occur in suspected VTE patients with high PTP, long duration of symptoms (more than one week) or receiving anticoagulants (4, 6, 29). Therefore, under these conditions it is not recommended to use D-dimer for VTE exclusion.
**FREQUENTLY ASKED QUESTIONS**

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**Does a positive D-dimer result indicate the patient has VTE?**

D-dimer is known to have moderate specificity for VTE and elevated D-dimer levels (i.e. above VTE rule-out cut-off) are observed in many clinical conditions (see Table 8). The likelihood for VTE rises with increasing D-dimer levels, which suggests the potential value of a separate rule-in cut-off (4). However, a reliable rule-in cut-off level has not been established.

Even if there is a cut-off above which D-dimer is specific enough to rule in the diagnosis, only very few patients will have a D-dimer above this level, limiting the usefulness of the test. Furthermore, clinicians would be reluctant to accept the diagnosis of DVT or PE based on a D-dimer test alone and would still request additional imaging (4).

Therefore, **D-dimer should only be used as an exclusion test.**

---

**Can D-dimer be used for VTE exclusion in special populations?**

D-dimer is elevated in the elderly, patients with cancer, the majority of hospitalized patients, patients with renal impairment and a large proportion of patients with previous VTE (4, 40). In combination with a clinical prediction rule, it is still safe to use D-dimer for exclusion in these patient populations (4, 6, 40). On the other hand, the clinical usefulness is lower due to the fact that a lower proportion of suspected VTE can be excluded.

The number needed to test (NNT) to exclude one VTE event is about 3 in unselected outpatients (i.e. the exclusion rate is 33%), but this figure is 2 to 10-fold higher in patients with previous VTE (NNT=6), cancer (NNT=9), elderly outpatients (NNT=20), renal impairment (NNT=9) and non-surgical inpatients (NNT=30) (4, 40).

Since D-dimer levels increase with age, their clinical utility for VTE exclusion is reduced in the elderly (28). To improve the efficiency of PE exclusion in older patients, while maintaining safety, a simple algorithm for an age-adjusted D-dimer cut-off has been derived (41).

In patients above 50 years of age the optimal cut-off is defined as patient’s age x 10.

*500 μg/L (conventional cut-off) \( \rightarrow \) age x 10 μg/L*

The utility of the age-adjusted cut-off for PE was validated in a large prospective outcome study (ADJUST-PE) (42). Compared with the conventional single cut-off, 12% more exclusions were obtained with the age-adjusted cut-off, with the most pronounced effect in elderly patients (5-fold higher exclusion rate in patients 75 years or older). Importantly, this increased diagnostic yield did not affect safety because the 3-month thromboembolic failure rate in patients with D-dimer ≥ 500 μg/L but below the age-adjusted cut-off was only 0.3% (95% CI 0.1-1.7%) with the upper limit of the 95% confidence interval well below the acceptable safety margin of 3%.

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**D-dimer is not recommended for VTE exclusion in pregnant women** (27). The main reason is its progressive increase with gestational age. Adapted D-dimer cut-offs have been proposed, but lack validation in prospective outcome studies (43). Furthermore, there are no CPR’s that have been properly validated for use in pregnant women with suspected VTE (27).

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**What is the difference between two- and three-level CPR’s?**

Since the NPV is influenced by disease prevalence, the purpose of a CPR is to assess whether a patient has a sufficiently low pretest probability to allow safe exclusion by D-dimer testing. To this end, validated CPR’s allow stratification in three categories (low, intermediate, high) or two categories (unlikely, likely): see Table 6. Both approaches have a similar accuracy, with a DVT/PE prevalence below 10% in low or unlikely categories. For clinical decision-making, it is also relevant to consider the proportion of patients classified in a given category, because this determines the proportion in which D-dimer can be applied. An example is shown in Figure 7 for the Wells PE score.

With a highly sensitive D-dimer assay, the three-level rule will be more efficient. Such an assay can be used in both low and intermediate PTP categories which account for 90% of all suspected patients as opposed to 70% for the unlikely category with the Wells PE score (Figure 7). Conversely, for a moderately sensitive D-dimer assay, the diagnostic yield can be improved by selecting the two-level score. In this case, the proportion of patients in which D-dimer can be safely applied for exclusion will be increased from 60% to 70% (Figure 7).

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Validation of the age-adjusted D-dimer cut-off in suspected DVT patients is in progress (ADJUST-DVT; ClinicalTrials.gov Identifier: NCT02384135).
Can D-dimer be used to guide the duration of anticoagulation therapy?

Following diagnosis of VTE, oral anticoagulant therapy (OAT) is necessary to prevent recurrence (18). Decisions on duration of OAT are guided by the risk of recurrent VTE after OAT discontinuation, the risk of major bleeding (1-3% per year when on OAT) as well as the case-fatality rates of both events which is 2-3-fold higher for major bleeding than for recurrent VTE (44).

In provoked VTE patients with a transient and reversible risk factor (e.g. surgery, trauma, prolonged immobilization), who have a low risk of recurrence, a short OAT duration (<3 months) is adequate because the risk of dying from major bleeding outweighs the risk of dying from recurrent VTE (18). In patients with a high risk of VTE recurrence (e.g. cancer), extended OAT duration is recommended because the risk of dying from recurrent VTE outweighs the risk of dying from bleeding (18).

Up to 50% of patients with a first VTE event are characterized as unprovoked VTE (i.e. without a known provoking cause). The optimal duration of OAT for unprovoked VTE is an important unanswered question in VTE management (45).

Compared to provoked VTE, these patients have about a 2-fold higher recurrence risk following OAT discontinuation (9). Consequently, extended or indefinite anticoagulation may be required (18). To justify this decision, the risk of fatal VTE should outweigh the risk of fatal bleeding in the long run. However, given the balanced risks of fatal VTE or fatal bleeding in unselected unprovoked VTE, clinicians do not have clear guidance on whether to continue or discontinue OAT after the standard period of 5-7 months.

The solution will be to focus on an individualized approach based on risk predictors that would identify unprovoked VTE patients with sufficiently low or high risk for recurrence to better justify the decision to discontinue or continue OAT. Single predictors such as D-dimer are not useful in isolation because they do not predict a low enough annual recurrence rate (<3%) to justify OAT discontinuation (45).

The REVERSE study derived a clinical decision rule, HERDOO2, which is simple to use and integrates D-dimer measurement with clinical and demographic predictors (Table 10). The rule identifies about 1 in 4 unprovoked VTE patients at low risk of VTE recurrence who may be able to safely discontinue anticoagulation.

The REVERSE study confirmed previously documented high annual recurrence risk in males (13.7%), but could not find any predictors to identify low risk men. In females, the rule identified high- and low-risk subgroups of about equal size with annual recurrence risk of 14.1% and 1.6%, respectively. The annual VTE risk in women with 0 or 1 risk factor appears sufficiently low (<3%) to justify safe discontinuation of OAT after 5-7 months. The safety and efficacy of this approach has been validated in the REVERSE II study, a large prospective outcome study involving over 3,000 patients (49).

Table 10: HERDOO2 clinical decision rule (49)

| Women with unprovoked VTE and 0 or 1 of the following features may be able to safely discontinue OAT after 5-7 months: |
| - Post-thrombotic signs: |
| Hyperpigmentation, Edema or Redness in either leg |
| - D-dimer ≥250 μg/L |
| - Obesity: BMI ≥30 kg/m² |
| - Older age: age ≥65 years |

NOTES:
- All predictors are assessed while the patient is still on OAT after 5-7 months.

Is there a place for D-dimer in other clinical scenarios?

In conjunction with other routinely available laboratory parameters, D-dimer is part of a scoring system to diagnose the presence of disseminated intravascular coagulation (DIC) (47). DIC is a serious complication of sepsis, cancer, and a variety of other disorders with systemic activation of blood coagulation.

The combined use of a clinical risk stratification score and D-dimer is a promising tool for the safe exclusion of acute aortic dissection (48).
REFERENCES


REFERENCES


LIST OF ABBREVIATIONS

- BNP: Brain (or B-type) natriuretic peptide
- CI: Confidence interval
- CPR: Clinical risk stratification rule
- CTEPH: Chronic thromboembolic pulmonary hypertension
- CTPA: Computerized tomographic pulmonary angiography
- D-dimer: Disseminated intravascular coagulation
- CV: Compression ultrasound
- CUS: Coefficient of variation
- DIC: Disseminated intravascular coagulation
- ED: Emergency department
- ELISA: Enzyme-linked immunosorbent assay
- ELFA: Enzyme-linked immunosorbent assay
- ESC: European Society of Cardiology
- FEU: Fibrinogen equivalent unit
- HERDOO2: Acronym for a clinical decision rule in women with unprovoked VTE based on post-thrombotic signs (e.g. NNT=3 if 33% of D-dimer test results are below the cut-off)
- NNT: Number needed to test to exclude one VTE event
- NPV: Negative predictive value
- NT-proBNP: N-terminal pro B-type natriuretic peptide
- OAT: Oral anticoagulant therapy
- PE: Pulmonary embolism
- PESI: Pulmonary Embolism Severity Index
- PPV: Positive predictive value
- PTP: Pre-test probability
- PTS: Post-thrombotic syndrome
- REVERSE: Acronym for a study on recurrent VTE: REcurrent VE Thromboembolism Risk Stratification Evaluation
- RVD: Right ventricular dysfunction
- sPESI: Simplified Pulmonary Embolism Severity Index
- VTE: Venous thromboembolism
- V/Q scan: Ventilation (V) and perfusion (Q) lung scintigraphy