EMPOWERING CLINICAL DECISIONS™

D-Dimer

for exclusion of VENOUS THROMBOEMBOLISM

The information in this booklet is given as a guideline only and is not intended to be exhaustive.
It in no way binds bioMérieux S.A. to the diagnosis established or the treatment prescribed by the physician.

bioMérieux S.A.
69280 Marcy l'Etoile
France
Tel. : 33 (0)4 78 87 20 00
Fax : 33 (0)4 78 87 20 90
www.biomerieux.com
www.biomerieux.com/d-dimer

BIOMÉRIEUX

BIOMÉRIEUX

VENOUS THROMBOEMBOLISM (VTE)

A 'SILENT KILLER' AND MAJOR PUBLIC HEALTH ISSUE

A COMMON CARDIOVASCULAR EMERGENCY

- With many of the known risk factors (age, immobility, surgery, obesity) increasing in society, VTE is an important and growing health problem [1].
- VTE occurs in all races, ethnicities and age groups, independent of gender.
- In the general Caucasian population, between 1 and 2/1,000 develop VTE each year [1-4]. This incidence rises with age, from less than 1/10,000 in children below 15 years to about 1/100 after 75 years of age.
- **Pulmonary embolism** (PE) is present in 1/3rd and **deep vein thrombosis** (DVT) in 2/3rd of cases [2]. Almost 2/3rd of VTE cases may be **hospital-acquired** [3, 4].

A POTENTIALLY FATAL BUT TREATABLE DISEASE

- Short-term (30-day) mortality is 6% after DVT and 12% after PE [2].
- In the USA and EU, the total annual number of VTE-related deaths may be as high as 840,000, making VTE the 2nd most frequent cause of cardiovascular mortality [3, 4].
- Hospital-acquired VTE events are responsible for about 2/3rd of VTE-related deaths, causing more preventable deaths than the more publicized hospital-acquired infection [3, 4].

A CHRONIC RELAPSING DISEASE WITH HIGH MORBIDITY

- 11% of VTE patients develop a recurrent event within one year, and 40% within 10 years [5].
- **Post-thrombotic syndrome** (PTS) occurs in 30-50% of DVT patients within 2 years [6]. PTS symptoms (pain, swelling and skin ulceration of the leg) are severe in about 10% of cases.
- Following an acute PE event, almost 50% of patients develop adverse events within 4 years [7].
- **Chronic thromboembolic pulmonary hypertension** (CTEPH) develops in less than 5% of PE patients within 2 years and may deteriorate into right heart failure [8].

A DISEASE WITH A HIGH ECONOMIC BURDEN

- $2-10 billion: estimated total annual healthcare costs of VTE-related incidents in the US [1].
- £640 million: total VTE-related healthcare cost reported in the UK [3].

For list of abbreviations, refer to page 31.

INTRODUCTION

Over the past 20 years, the diagnostic performance and clinical usefulness of D-dimer testing in the diagnosis of patients with suspected VTE have been extensively validated in numerous studies, including large outcome studies [9].

Due to its high sensitivity, D-dimer allows the exclusion of VTE in suspected patients. For safety reasons, **VTE exclusion by D-dimer should be restricted to patients with low or intermediate clinical probability** for having VTE. Due to its **poor specificity** for the presence of VTE, **D-dimer cannot be used for ruling in** and, therefore, is integrated into a **sequential diagnostic algorithm** that includes **clinical probability assessment** and imaging techniques [10, 11].

Rapid VTE exclusion by D-dimer has important advantages for the healthcare system:

- It is particularly useful in the ED because 20% or less of suspected outpatients will actually have VTE [12].
- It reduces the need for time-consuming and expensive imaging procedures by around 30% and avoids unnecessary treatment with anticoagulants.

D-dimer assays are **widely available, but vary considerably in their analytical, operational and clinical performance characteristics** [9]. 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 within the clinical context of the patient [9, 13].

This booklet provides the emergency physician and laboratory manager with up-to-date, comprehensive and yet concise information on the "do's and don'ts" of using D-dimer for VTE exclusion.

OUR SPECIAL THANKS GO TO

Prof. Arnaud Perrier, M.D., F.C.C.P. (Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland)
and
Prof. Grégoire le Gal, M.D., Ph.D. (Department of Internal Medicine and Chest Diseases, Brest University Hospital, Brest, France)
for their expert advice in preparing this booklet.

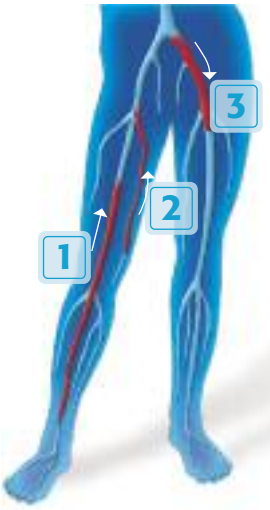
VENOUS THROMBOEMBOLISM

Definition and classification

- **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** [14].
- Consequently, **deep vein thrombosis** (DVT) and **pulmonary embolism** (PE) are two clinical manifestations of the same disease. Asymptomatic PE is present in about 50% of patients with proximal DVT, whereas asymptomatic DVT can be detected in 70% of patients with PE [15].
- Clot formation in the leg veins may occur at various sites (**Figure 1**). 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 [16].

Figure 1: Types of acute **DVT** [14]

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.

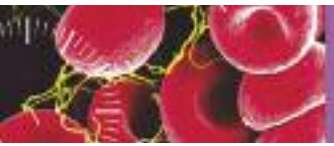


The risk for PE becomes significant in the presence of a thrombus that extends into the popliteal veins or above (**proximal DVT**). Parts of the clot may break off from an actively propagating thrombus in the leg veins, are then transported by the venous blood flow, pass the right heart and embolize into the pulmonary circulation.

Based on presenting syndromes, PE can be categorized as pulmonary hemorrhagic infarction (77% of cases), isolated dyspnea (20% of cases) or circulatory collapse (3% of cases) [17]. The nature and severity of symptoms depend on the size and location of the embolized thrombus (**Figure 2**).

Figure 2: Types of acute **PE** [14, 17]

1. **Peripheral, sub-segmental PE** with local alterations of lung and pleural tissue (hemorrhagic pulmonary infarction).
2. **Central, segmental** or **lobar PE** with functional impairment of respiration (perfusion/ventilation mismatch).
3. **Central PE** with **massive pulmonary artery obstruction**, associated with cardiac dysfunction (right heart failure).



Pathophysiology
Risk factors

Risk factors related to venous thrombosis can be classified into three categories, known as **Virchow's triad** [14]:

- Changes in blood flow (venous stasis).
- Changes in the blood vessel wall.
- Changes in blood composition.

VTE is a **multifactorial disease** and in most cases more than one risk factor can be identified [18]. 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 VTE risk factors and the magnitude of their risk are listed in **Table 1**. The most frequent risk factors include **older age, obesity, history of VTE, cancer, long bed rest and major surgery** [18]. 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**.

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** [2].

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

- **PREVENTION**
  To identify high-risk groups in whom **prophylactic treatment** is indicated [19].
- **DIAGNOSIS**
  To aid in **clinical pre-test probability assessment** (see clinical prediction rules), the first step to guide the optimal diagnostic strategy [10, 11].
- **TREATMENT**
  To guide the optimal **duration of anticoagulant therapy** after a VTE event [20].

Table 1: Risk factors for VTE [14, 18]

RISK FACTOR	STRENGTH
SURGERY	
Fracture (hip or leg)	STRONG
Hip or knee replacement	STRONG
Major general surgery	STRONG
Athroscopic knee surgery	MODERATE
Laparoscopic surgery	WEAK
TRAUMA	
Major trauma	STRONG
Spinal cord injury	STRONG
MEDICAL ILLNESS	
Malignancy	MODERATE
Congestive heart or respiratory failure	MODERATE
Paralytic stroke	MODERATE
Previous VTE	MODERATE
Bed rest > 3 days	WEAK
IATROGENIC FACTORS OTHER THAN SURGERY	
Central venous line	MODERATE
Chemotherapy	MODERATE
Oral contraceptives	MODERATE
Hormone replacement	MODERATE
NON-DISEASE RELATED CONDITIONS	
Pregnancy/post-partum/ante-partum	MODERATE
Advanced age	WEAK
Varicose veins	WEAK
Prolonged sitting (air or car travel)	WEAK
Obesity	WEAK
THROMBOPHILIA	
Antiphospholipid syndrome	STRONG
Severe antithrombin deficiency	STRONG
Severe protein C deficiency with family history	STRONG
Severe protein S deficiency with family history	STRONG
Factor V Leiden mutation, homozygous	STRONG
Factor V Leiden mutation, heterozygous	MODERATE
Prothrombin G20210A mutation	MODERATE
Elevated Factor VIII and IX levels	MODERATE
Hyperhomocysteinemia	MODERATE

STRONG: odds ratio >10
MODERATE: odds ratio 2-9
WEAK: odds ratio <2

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 general, suspected PE can be defined as **"acute onset of new or worsening shortness of breath or chest pain without any other obvious cause"** [21].

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 (prevalence <10%), intermediate (prevalence 10-30%) and high (prevalence > 40%).
- The clinical probability further **guides the diagnostic work-up**.

Table 2: Differential diagnosis

SUSPECTED DVT	SUSPECTED PE
Muscle strain or tear	Pneumonia
Arthritis of the knee or ankle including gout	Acute bronchitis
Ruptured Baker's cyst	Pneumothorax
Hematoma	Acute pulmonary edema
Lymphangitis	Pulmonary neoplasm
Lymphedema	Myocardial infarction
Cellulitis	Acute aortic dissection
Varicose veins	Muscle strain
Venous reflux	Rib fracture
Vasomotor changes (e.g. in paralyzed leg)	
Superficial venous thrombosis	
Post-thrombotic syndrome	

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**). The Wells scores also allow dichotomization into two categories: DVT/PE unlikely and DVT/PE likely. 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** [22, 23]

In patients with symptoms in both legs, the more symptomatic leg is used.

CLINICAL FEATURE	POINTS
RISK FACTORS	
• Active cancer (treatment ongoing, within previous 6 month 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
• Previously documented DVT	1
CLINICAL SIGNS, SYMPTOMS	
• 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
CLINICAL JUDGMENT	
• Alternative diagnosis at least as likely as DVT	-2
CLINICAL PROBABILITY (3 LEVELS)	TOTAL
● Low	≤0
● Intermediate	1 or 2
● High	≥3
CLINICAL PROBABILITY (2 LEVELS)	TOTAL
■ DVT unlikely	<2
■ DVT likely	≥2

Table 4: Clinical prediction rule for **PE: the Wells score** [24]

CLINICAL FEATURE	POINTS
RISK FACTORS	
• Previous DVT or PE	1.5
• Surgery or bedridden for 3 days during past 4 weeks	1.5
• Active cancer (treatment within 6 months or palliative)	1
CLINICAL SIGNS, SYMPTOMS	
• Hemoptysis	1
• Heart rate > 100 beats/min	1.5
• Clinical signs of DVT	3
CLINICAL JUDGMENT	
• Alternative diagnosis less likely than PE	3
CLINICAL PROBABILITY (3 LEVELS)	TOTAL
● Low	0-1
● Intermediate	2-6
● High	>6
CLINICAL PROBABILITY (2 LEVELS)	TOTAL
■ PE unlikely	≤4
■ PE likely	>4

Table 5: Clinical prediction rule for **PE: the revised Geneva score** [21]

CLINICAL FEATURE	POINTS
RISK FACTORS	
• Age > 65 years	1
• Previous DVT or PE	3
• Surgery or fracture within 1 month	2
• Active malignancy	2
CLINICAL SIGNS, SYMPTOMS	
• Unilateral lower limb pain	3
• Hemoptysis	2
• Heart rate	
75-94 beats/min	3
≥95 beats/min	5
• Pain on deep palpation of lower limb and unilateral edema	4
CLINICAL PROBABILITY (3 LEVELS)	TOTAL
● Low	0-3
● Intermediate	4-10
● High	≥11

Table 6: Pretest probability distribution and DVT/PE prevalence

PTP category	Wells score (data from ref 25)		Wells score (data from ref 26)		Revised Geneva score (data from ref 26)	
3 LEVEL SCORE	% of Total	DVT (%)	% of Total	PE (%)	% of Total	PE (%)
Low	44	5	59	6	36	9
Intermediate	36	17	35	23	59	26
High	20	53	6	49	5	76
TOTAL	100	19	100	12	100	22

2 LEVEL SCORE	(data from ref 23)		(data from ref 26)	
Unlikely	54	6	69	8
Likely	46	28	31	34
TOTAL	100	16	100	16

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 major or fatal bleeding.

Furthermore, as a result of the raised index of clinical suspicion, the **prevalence among suspected outpatients** has dramatically declined over recent years to values as **low as 10% or less** in certain populations [12]. 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 such as **compression ultrasound (CUS)** and **computerized tomographic pulmonary angiography (CTPA)** (Figure 3) [9-11]. Although CTPA is the most reliable test for the diagnosis of PE, algorithms using **V/Q scanning** are safe and may be preferred in populations where radiation exposure is a concern (e.g. breast cancer risk in young women).

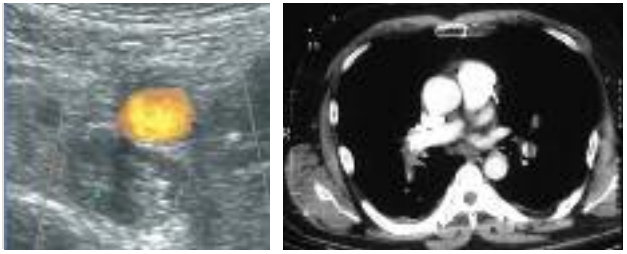
MISSING THE DIAGNOSIS
→ **potentially fatal PE**

FALSE-POSITIVE RESULT
→ **unnecessary anticoagulants**

- **Clinical assessment and D-dimer are recommended as the first step in the investigation of patients with suspected VTE** [27, 28]. This strategy is cost-efficient [29] and safely excludes VTE in 30-50% of suspected outpatients [30].
- In case of a **high pretest probability** or a **positive D-dimer**, objective **confirmation** is needed by **CUS** in case of suspected DVT [10] or **multi-detector CTPA** in case of suspected PE [11].

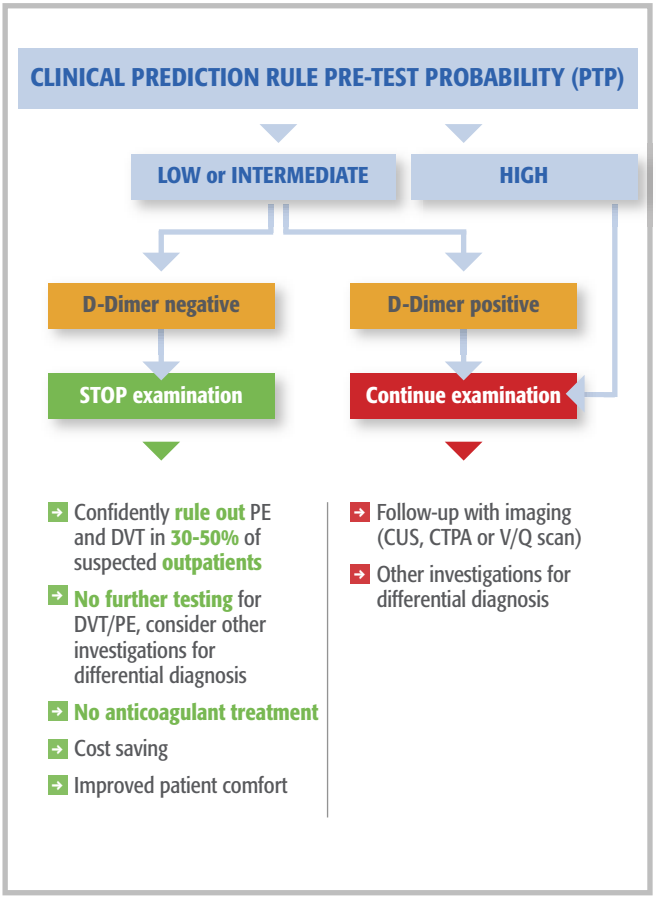
Given its **high negative predictive value** (NPV), **D-dimer plays a key role in rapid exclusion of VTE**. Because the NPV is not only influenced by the sensitivity of the assay but also by disease prevalence, the clinical probability level to which a D-dimer assay can be applied depends on its sensitivity.

- **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 PTP** [9] (see also **Table 10**).
- **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 [31].



Detection of DVT by compression ultrasonography (left panel) and PE by spiral CTPA (right panel).

Figure 3: Diagnostic algorithm for suspected **DVT** or **PE** in outpatients [9-11]



- In this algorithm, the D-dimer result **refers to a highly sensitive assay**. With less sensitive assays, exclusion is only possible in patients with low pretest probability.
- Adherence to a validated diagnostic strategy is crucial for PE exclusion because not following such strategy leads to 4-fold increased risk of subsequent PE and death [32].

Diagnosis • CLINICAL DECISION SUPPORT SYSTEM

Despite the availability of evidence-based guidelines, **the diagnosis of VTE remains a challenge for physicians** [32].

Computerized clinical decision support systems (CDSS) based on software algorithms that generate patient specific recommendations can contribute to assist the decision-making process.

- **SPEED** (Suspected Pulmonary Embolism in Emergency Department) is a CDSS software for suspected **pulmonary embolism** that has been developed by the University Hospital of Angers, France (available on www.thrombus.fr).
- **SPEED** runs on handheld computers and guides diagnostic decision-making step by step until the risk of error is low enough to rule-out or to rule-in pulmonary embolism with confidence.

The SPEED software algorithm guides the physician from initial entry of clinical data to final diagnostic decision-making.

- A multi-center randomized trial has demonstrated that SPEED leads to better diagnostic decision making than paper-based educational material [33].

PE prognosis • IMPACT ON PATIENT MANAGEMENT

PE is a potentially fatal disease, but the short-term mortality risk varies widely. In patients with shock or hemodynamic instability (massive or high-risk PE), mortality is 15-40% and death can occur within 1 hour after the onset of symptoms. In the 30% of patients with intermediate-risk (submassive PE) who are hemodynamically stable but exhibit signs of right ventricular dysfunction (RVD), mortality is 3-15%. In contrast, in the majority of patients who have normal right ventricular function, mortality is <1% [27].

Risk stratification is a useful tool in **guiding medical decision making** and this includes the assessment of clinical factors, RVD and myocardial injury (**Table 7**) [27, 34].

PE patients presenting with shock or hypotension have the highest risk of death and are candidates for aggressive intervention with thrombolysis or embolectomy [27].

There is a particular interest in identifying the large group of hemodynamically stable patients with low short-term mortality risk who may be referred for less costly outpatient care [34]. **Low-risk PE** patients may be identified by the **Pulmonary Embolism Severity Index** (PESI) [34], a clinical score based on 11 routinely available parameters. Measurement of cardiac marker **NT-proBNP** is emerging as another useful tool. A prospective management study showed that 45% of hemodynamically stable acute PE patients had low NT-proBNP levels and could be safely treated out of hospital [35].

Table 7: Risk stratification of **PE** (ESC Guidelines) [27]

PE-RELATED EARLY MORTALITY RISK	RISK MARKERS			POTENTIAL TREATMENT IMPLICATIONS
	Clinical (shock or hypotension)	RVD (*)	Myocardial injury (**)	
HIGH (>15%) 5-10% of cases	**Yes**	Pos (***)	Pos (***)	Thrombolysis or embolectomy
INTERMEDIATE (3-15%) Up to 30% of cases	**No**	Pos Pos Neg	Pos Neg Pos	Hospital admission
Low (<1%) Up to 60% of cases	**No**	Neg	Neg	Early discharge or home treatment

* RVD: right ventricular dysfunction, assessed by echocardiography and/or B-type natriuretic peptides (BNP, NT-proBNP).
** Myocardial injury is assessed by elevated cardiac troponins.
*** In the presence of shock or hypotension it is not necessary to confirm RVD/myocardial injury to classify high-risk.

D-DIMER

Definition - Biochemistry

D-dimer is a **marker** of activation of **coagulation** and **fibrinolysis** (**Figure 4**). 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**.

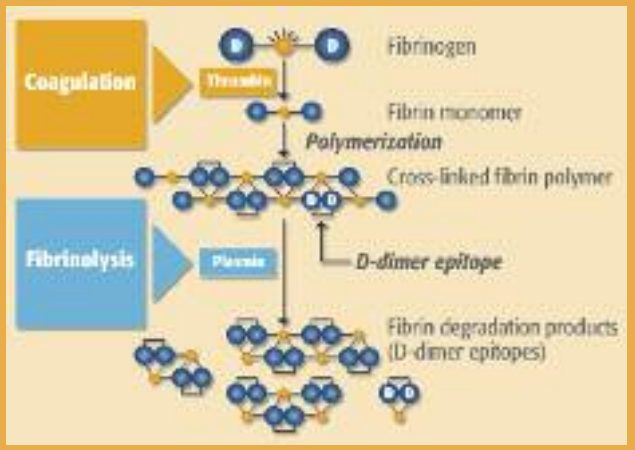


Figure 4: D-dimer is a marker of fibrin clot formation and dissolution [36].

Fibrinogen consists of two D-domains separated by a central E domain. The insoluble fibrin clot is formed by the polymerization of fibrin monomers that are generated by thrombin. Fibrin is stabilized by the formation of covalent crosslinks between two adjacent D-domains (this creates the D-dimer epitope). Lysis of fibrin by plasmin results in the generation of a mixture of soluble fibrin degradation products of variable size containing 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) [9].

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 [9, 36, 37]

Infection
Inflammation
Cancer
Surgery
Trauma, extensive burns
Disseminated intravascular coagulation (DIC)
Pregnancy
Older age
Impaired renal function
History of previous VTE
Cardio-/cerebro-vascular disorders • Acute coronary syndrome • Heart failure • Stroke • Atrial fibrillation • Cerebral venous thrombosis • Acute aortic dissection

Assays • 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 [9]. 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. 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%) [38].

Because of the trade-off between sensitivity and specificity, clinicians should understand the diagnostic performance of the test used in their institution (**Tables 10** and **11**; see pages 18-19).

- 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 over a large pre-test probability range. **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 [39].
- The **specificity** determines the **clinical usefulness** (efficacy) of the assay in terms of the proportion of suspected VTE patients that can be excluded. The lower the specificity, the higher the number of positives that require further imaging to confirm the diagnosis.

D-dimer assays **lack standardization** and the results depend on the assay being used [9]. 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% [40].

- 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** [9].

Table 9: Requirements of a D-dimer assay for VTE exclusion [9, 39]

REQUIREMENTS	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-hr - 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 diagnosis • **Validated in prospective outcome study:** 3-month thromboembolic failure rate in excluded patients should not exceed 3% (upper limit 95% confidence interval)

Diagnostic accuracy of D-dimer assays

Impact on **safety** and **efficacy** of VTE exclusion

The **safety** (negative predictive value, NPV) and **efficacy** (exclusion rate) of D-dimer are essential criteria to confidently rule out VTE in suspected outpatients; i.e. **reduce the need for further investigations** and **withhold anticoagulant treatment in a sufficiently high proportion**. These two criteria are determined by the prevalence of VTE (pre-test probability, PTP) and the diagnostic accuracy of the assay in terms of its sensitivity and specificity. This behavior is illustrated for two typical D-dimer assays. [38]

- **Assay A: high sensitivity** test (e.g. a quantitative ELISA-based assay); sensitivity **99%** and specificity **40%**.
- **Assay B: moderate sensitivity** test (e.g. a qualitative whole blood agglutination assay); sensitivity **88%** and specificity **70%**.

For both Assay A and Assay B, the **NPV** (**Table 10**) and the **exclusion rate** (**Table 11**) are calculated for a VTE prevalence of 10%, 30% and 70% as typically seen in patients with low, intermediate and high PTP, respectively. These calculations are made from standard 2x2 contingency tables given the sensitivity/specificity of the assay and the VTE prevalence.

Table 10: Impact of assay sensitivity on safety (negative predictive value) based on typical sensitivity values [38]

PTP GROUP (% of Total - typical values)	PREVALENCE OF VTE (%)	SAFETY ; NPV (%)	
		Assay A	Assay B
		Se 99%	Se 88%
LOW (30%)	10	99.7	98.1
INTERMEDIATE (60%)	30	98.7	93.2
HIGH (10%)	70	94.5	71.4

INTERPRETATION:
Safe exclusion requires NPV ≥98% (green area) [39].

- Assay A can be used for **safe exclusion** in both **low and intermediate PTP groups** (90% of total).
- Assay B only allows **safe exclusion** in the **low PTP group** (30% of total).

Table 11: Impact of assay specificity on efficacy (% of patients excluded) based on typical specificity values [38]

PTP GROUP (% of Total - typical values)	PREVALENCE OF VTE (%)	EFFICACY (% excluded)			
		Assay A		Assay B	
		Sp 40%		Sp 70%	
		% of PTP group	% of Total	% of PTP group	% of Total
LOW (30%)	10	36	11	64	19
INTERMEDIATE (60%)	30	28	17		
HIGH (10%)	70				
		TOTAL: 28		TOTAL: 19	

INTERPRETATION:

- **Assay A** safely excludes 36% and 28% in low and intermediate PTP groups, respectively. Taking into account the distribution of the PTP groups, this amounts to **exclusion of 28% of the total cohort** of suspected VTE patients.
- **Assay B** safely excludes 64% in the low PTP group (a higher proportion than Assay A due to the higher specificity of Assay B). However, due to the lower sensitivity of Assay B, this test **cannot be used to exclude** patients in the **intermediate PTP** group. Consequently, in the **total cohort** of suspected VTE patients, this assay will then **exclude a lower proportion of 19%**.

- The **diagnostic accuracy** of D-dimer assays has a clear impact on patient management.
- Test performance must achieve an **optimum balance between sensitivity** and specificity in order to safely exclude VTE (NPV ≥98%) and to avoid further imaging in a large enough proportion of suspected outpatients.
- As illustrated above, a **quantitative ELISA-based assay with a high sensitivity** can be used to exclude patients in both the **low and intermediate PTP groups**, and not just the low-risk group.

FREQUENTLY ASKED QUESTIONS

Is 500 ng/mL a uniform cut-off for VTE exclusion?

VIDAS® D-dimer Exclusion™, with a nominal cut-off value of **500 ng FEU/mL** is **the most extensively validated** D-dimer method for **exclusion of PE**. A combined analysis of 7 prospective outcome studies showed a VIDAS D-dimer result below this threshold in 40% of 5,622 patients with low/intermediate or unlikely PTP [41]. The 3-month thromboembolic failure rate in this cohort of 2,248 patients in which PE was excluded was only 0.14% (NPV 99.9%).

However, it is important to realize that there is **no standardization** of D-dimer assays and, consequently, each method has its own cut-off value for VTE exclusion which **needs to be clinically validated in outcome studies** [9]. Furthermore, D-dimer results are either reported as **D-dimer units or fibrinogen equivalent units** (FEU; 1 ng D-dimer equals 2 ng FEU).

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 pre-test probability and clinical context of the patient**.

Outcome studies combining clinical probability and D-dimer have clearly confirmed the **safety of not treating** patients with suspected VTE and **normal D-dimer** and non-high clinical probability [30, 41].

This may include some patients with **distal DVT** or **subsegmental PE**. However, the clinical relevance of small clots in these locations is debated. Moreover, the safety of not treating patients with normal D-dimer and non-high clinical probability has been widely demonstrated, irrespective of the presence of such small clots [30, 41].

Under certain conditions, however, lower than expected D-dimer results may occur giving rise to false-negatives.

Therefore, it is not safe to use D-dimer for VTE exclusion in patients with high PTP, long duration of symptoms (more than one week) or receiving anticoagulants [13, 31].

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, suggesting the potential value of a separate rule-in cut-off [9]. 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, very few patients will have a D-dimer above this level. 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.

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, most hospitalized patients** as well as a large proportion of **patients with previous VTE** [9]. Combined with a clinical prediction rule, it is **still safe to use D-dimer for exclusion in these patient populations** [9, 13]. However, the **clinical usefulness is lower** since 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, but this figure is 2 to 10-fold higher in patients with previous VTE (NNT=6), cancer (NNT=9), elderly outpatients (NNT=20) and non-surgical inpatients (NNT=30) [9].

Nevertheless, D-dimer remains cost-effective in **the elderly** even if only 5% have a negative result [29]. To improve specificity in older patients, without compromising safety, the use of **age-adjusted D-dimer cut-off** values has been retrospectively investigated in patients with suspected PE [42]. In patients > 50 years of age, the new cut-off (ng/mL, **VIDAS® D-dimer**) is defined as the **patient's age x 10**. Further external validation will be required before this can be introduced in clinical routine.

Pregnancy causes a progressive increase in D-dimer, which peaks at delivery and decreases to normal within 4 weeks after delivery [43, 44].

Due to the lack of proper validation studies, **D-dimer testing is not yet part of evidence-based recommendations** on diagnostic testing of pregnant women with clinically suspected VTE [45]. To improve specificity, without compromising sensitivity, **higher cut-off values** (1890 ng/mL for **VIDAS® D-dimer**) have been established for **DVT exclusion in suspected pregnant women** [46]. Further external validation will be required before this can be introduced in clinical routine.

What is the difference between the two-level and the three-level Wells CPR's?

Since the NPV is influenced by disease prevalence, the purpose of a CPR such as the Wells score is to find patients with a **sufficiently low pretest probability to allow safe exclusion by D-dimer testing**. To this end, the Wells scores for DVT and PE 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 < 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.

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 80-90% of all suspected patients as opposed to 50-70% for the unlikely category (Table 6). Conversely, for **a less sensitive D-dimer assay**, the diagnostic yield can be improved by selecting a **two-level Wells rule**. In this case, the proportion of patients in which D-dimer can be safely applied for exclusion will increase from around 50% to around 60% (Table 6).

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. This benefit, however, needs to be balanced against the risk for major bleeding during OAT. Based on underlying risk factors the **duration of OAT varies from 3 months, in the case of a transient provoking risk factor**, to **indefinite in the case of permanent risk factors such as cancer**, whereas a **minimum of 6 months is recommended in patients with unprovoked VTE** [20]. Evidence for the optimal duration of OAT in patients with unprovoked VTE is inconclusive and an ongoing topic of clinical research [47]. The aim of this research is to find **risk predictors** that would allow the **segregation of patients** into subgroups with low or high enough risk for recurrence to discontinue or continue OAT after the standard 6-month period.

Although **D-dimer** is a **strong predictor for recurrence in unprovoked VTE**, its sole use is not enough to guide the optimal duration of OAT [48].

Recently, the **REVERSE Study Group** has identified **additional clinical predictors and has integrated D-dimer** with these predictors in a simple **clinical decision rule** (Table 11) [47]. This rule is able to identify approximately 25% of patients with a first unprovoked VTE event with low enough annual risk of VTE recurrence (< 3%) to safely discontinue OAT after 5-7 months. The safety and efficacy of this rule is being validated in a **large prospective outcome study**.

Table 11: The 'Men and HERDOO2' clinical decision rule for OAT discontinuation in unprovoked VTE [47]

Women with **0** or **1** of the following features may be able to safely discontinue OAT:
• Post-thrombotic signs:
Hyperpigmentation
Edema or
Redness in either leg
• **D**-dimer ≥ 250 ng/mL (VIDAS® D-dimer)
• **O**besity: BMI ≥ 30 kg/m²
• **O**lder age: age ≥ 65 years

NOTES:
- D-dimer cut-off value of **250 ng/mL** is valid for **VIDAS D-dimer Exclusion**.
- All predictors are assessed while the **patient is still on OAT after 5-7 months**.
- The safety of this rule has not been established at this time.

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) [49]. DIC is a serious complication of sepsis, cancer, and a variety of other disorders with systemic activation of blood coagulation.

Emerging applications of D-dimer include **risk stratification of patients with community-acquired pneumonia** [50] **and exclusion of conditions such as acute aortic dissection** [51] or **cerebral vein thrombosis** [52]. D-dimer has also been reported as a global marker for VTE risk in the general population [53] and as a predictor of thromboembolic and cardiovascular events in atrial fibrillation [54].

D-dimer is **elevated in cancer where it has prognostic value** [55] and may serve as an indicator for occult malignancy in patients presenting with DVT [56].

REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(Suppl):S495-501.
2. White RH. The epidemiology of venous thromboembolism. Circulation. 2003; 107 (Suppl.1): I4-8.
3. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007; 98: 756-64.
4. Heit JA, Cohen AT, Anderson FA, VTE Impact Assessment Group. Venous thromboembolism (VTE) events in the US. Blood. 2005; 106: Abstract 910.
5. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica. 2007; 92: 199-205.
6. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol. 2009; 145: 286-95.
7. Klok FA, Zondag W, van Kralingen KW, van Dijk AP, Tamsma JT, Heyning FH, Vliegen HW, Huisman MV. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med. 2010;181:501-6.
8. Meyer G, Planquette B, Sanchez O. Long-term outcome of pulmonary embolism. Curr Opin Hematol. 2008;15:499-503.
9. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost. 2008; 6: 1059-71.
10. Tan M, van Rooden CJ, Westerbeek RE, Huisman MV. Diagnostic management of clinically suspected acute deep vein thrombosis. Br J Haematol. 2009;146:347-60.
11. Huisman MV, Klok FA. Diagnostic management of clinically suspected acute pulmonary embolism. J Thromb Haemost. 2009;7 (Suppl 1):312-7.
12. Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients. J Thromb Haemost. 2004; 2: 1244-6.
13. Bruinstroop E, van de Ree MA, Huisman MV. The use of D-dimer in specific clinical conditions: a narrative review. Eur J Intern Med. 2009;20:441-6.
14. Schellong SM, Bounameaux H, Büller HR. Venous thromboembolism. In: The ESC Textbook of Cardiovascular Medicine, 1st edition. Camm AJ, Lüscher TF, Serruys PW (eds), Blackwell Publishing, Oxford, UK, 2006.
15. Kearon C. Natural history of venous thromboembolism. Circulation. 2003; 107(Suppl. 1): I22-30.
16. Flinterman LE, Van Der Meer FJ, Rosendaal FR, Doggen CJ. Current perspective of venous thrombosis in the upper extremity. J Thromb Haemost. 2008; 6: 1262-6.
17. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest. 1997;112:974-9.
18. Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003; 107 (Suppl.1): I9-16.

19. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(Suppl): 381S-453S.
20. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(Suppl): 454S-545S.
21. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144:165-71.
22. Anderson DR, Kovacs MJ, Kovacs G, Stiell I, Mitchell M, Khoury V, Dryer J, Ward J, Wells PS. Combined use of clinical assessment and D-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). J Thromb Haemost. 2003;1:645-51.
23. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349:1227-35.
24. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-20.
25. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? JAMA. 2006 ;295:199-207.
26. Ceriani E, Combescure C, Le Gal G, Nendaz M, Perneger T, Bounameaux H, Perrier A, Righini M. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2010;8:957-70.
27. Torbicki A, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008; 29: 2276-315.
28. Keeling DM, Mackie IJ, Moody A, Watson HG; Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging. Br J Haematol. 2004;124:15-25.
29. Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. J Thromb Haemost. 2007;5:1869-77.
30. Ten Cate-Hoek AJ, Prins MH. Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism: a systematic review. J Thromb Haemost. 2005; 3: 2465-70.
31. Gibson NS, Sohne M, Gerdes VE, Nijkeuter M, Buller HR. The importance of clinical probability assessment in interpreting a normal D-dimer in patients with suspected pulmonary embolism. Chest. 2008;134:789-93.
32. Roy PM, Meyer G, Vielle B, Le Gall C, Verschuren F, Carpentier F, Leveau P, Furber A; EMDEPU Study Group. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. Ann Intern Med. 2006;144:157-64.
33. Roy PM, Durieux P, Gillaizeau F, Le Gall C, Armand-Perroux A, Martino L, Hachelaf M, Dubart AE, Schmidt J, Cristiano M, Chretien JM, Perrier A, Meyer G. A computerized handheld decision-support system to improve pulmonary embolism diagnosis: a randomized trial. Ann Intern Med. 2009;151:677-86.
34. Aujesky D, Hughes R, Jiménez D. Short-term prognosis of pulmonary embolism. J Thromb Haemost. 2009;7 (Suppl 1):318-21.
35. Agterof MJ, Schutgens RE, Snijder RJ, Epping G, Peltenburg HG, Posthuma EF, Hardeman JA, van der Griend R, Koster T, Prins MH, Biesma DH. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost. 2010;8:1235-41.
36. Bockenstedt P. D-dimer in venous thromboembolism. N Engl J Med. 2003;349:1203-4.

37. Karami-Djurabi R, Klok FA, Kooiman J, Velthuis SI, Nijkeuter M, Huisman MV. D-dimer testing in patients with suspected pulmonary embolism and impaired renal function. Am J Med. 2009 ;122:1050-3.

38. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;5:296-304.

39. CLSI. Quantitative D-dimer for the exclusion of venous thromboembolic disease; Approved Guideline. CLSI document H59-A. Clinical and Laboratory Standards Institute, Wayne, PA, USA, 2011.

40. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med. 2003;138:941-51.

41. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, Rodger M, Wuillemin WA, Le Gal G. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost. 2009;101:886-92.

42. Douma RA, le Gal G, Söhne M, Righini M, Kamphuisen PW, Perrier A, Kruip MJ, Bounameaux H, Büller HR, Roy PM. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. BMJ. 2010;340:c1475.

43. Chabloz P, Reber G, Boehlen F, Hohlfeld P, de Moerloose P. TAFI antigen and D-dimer levels during normal pregnancy and at delivery. Br J Haematol. 2001;115:150-2.

44. Epiney M, Boehlen F, Boulvain M, Reber G, Antonelli E, Morales M, Irion O, De Moerloose P. D-dimer levels during delivery and the postpartum. J Thromb Haemost. 2005;3:268-71.

45. Nijkeuter M, Ginsberg JS, Huisman MV. Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy: a systematic review. J Thromb Haemost. 2006;4:496-500.

46. Chan WS, Lee A, Spencer FA, Chunilal S, Crowther M, Wu W, Johnston M, Rodger M, Ginsberg JS.D-dimer testing in pregnant patients: towards determining the next "level" in the diagnosis of DVT. J Thromb Haemost. 2010;8:1004-11.

47. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, Vickars L, Ramsay T, Betancourt MT, Kovacs MJ. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ. 2008;179:417-26.

48. Bruinstroop E, Klok FA, Van De Ree MA, Oosterwijk FL, Huisman MV. Elevated D-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: a meta-analysis. J Thromb Haemost. 2009;7:611-8.

49. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med. 2004;32:2416-21.

50. Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. Ann Emerg Med. 2009;53:633-8.

51. Suzuki T, Distante A, Zizza A, Trimarchi S, Villani M, Salerno Uriarte JA, De Luca Tupputi Schinosa L, Renzulli A, Sabino F, Nowak R, Birkhahn R, Hollander JE, Counselman F, Vijayendran R, Bossone E, Eagle K; IRAD-Bio Investigators. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation. 2009;119:2702-7.

52. Cucchiara B, Messe S, Taylor R, Clarke J, Pollak E. Utility of D-dimer in the diagnosis of cerebral venous sinus thrombosis. J Thromb Haemost. 2005;3:387-9.

53. Cushman M, Folsom AR, Wang L, Aleksic N, Rosamond WD, Tracy RP, Heckbert SR.Fibrin fragment D-dimer and the risk of future venous thrombosis. Blood. 2003;101:1243-8.

54. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. J Am Coll Cardiol. 2010;55:2225-31.

55. Di Nisio M, Klerk CP, Meijers JC, Büller HR. The prognostic value of the D-dimer test in cancer patients treated with and without low-molecular-weight heparin. J Thromb Haemost. 2005;3:1531-3.

56. Schutgens RE, Beckers MM, Haas FJ, Biesma DH. The predictive value of D-dimer measurement for cancer in patients with deep vein thrombosis. Haematologica. 2005;90:214-9.

LIST OF ABBREVIATIONS

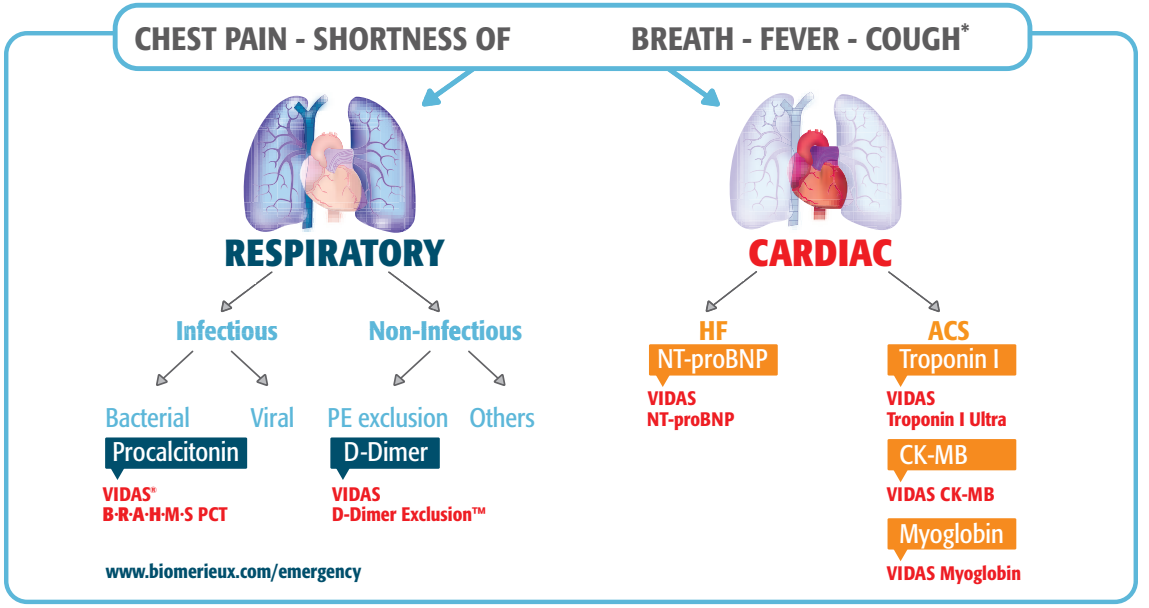
BNP	Brain (or B-type) natriuretic peptide
CDSS	Clinical decision support system
CPR	Clinical prediction rule
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computerized tomographic pulmonary angiography
CUS	Compression ultrasound
CV	Coefficient of variation
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
ED	Emergency department
ESC	European Society of Cardiology
FEU	Fibrinogen equivalent unit (500 ng FEU/mL = 250 ng D-dimer/mL)
HERDOO	Acronym for clinical prediction rule based on post-thrombotic signs (Hyperpigmentation, Edema, Redness), D-dimer, Obesity and Older age
NNT	Number needed to test to exclude one VTE event (e.g. NNT=3 if 33% of D-dimer test results are below the cut-off)
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 study on recurrent VTE: REcurrent VEnous thromboembolism Risk Stratification Evaluation
RVD	Right ventricular dysfunction
SPEED	Acronym for Suspected Pulmonary Embolism in Emergency Department, a computerized decision support system software to guide the diagnostic process in patients with suspected pulmonary embolism (available on www.thrombus.fr)
VTE	Venous thromboembolism
V/Q scan	Ventilation (V) and perfusion (Q) lung scintigraphy

VIDAS®

EMERGENCY DIAGNOSTICS SOLUTION

VIDAS mini VIDAS

Contribution of a Rapid Diagnostic Test Panel to Effective Triage of Emergency Department Patients presenting with Common Symptoms



* Four of the most frequent symptoms in patients presenting to Hospital ED.
Advance Data from Vital and Health Statistics; no 372. Hyattsville, MD: National Center for Health Statistics. 2006.

HF: Heart Failure - ACS: Acute Coronary Syndrome - PE: Pulmonary Embolism

VIDAS® D-dimer Exclusion™ is widely considered to be the **reference ELISA test** for **exclusion of VTE in low- and moderate-risk patients**.

- **FDA-cleared and CE-marked** for exclusion of PE and DVT when used in conjunction with a pre-test probability model at a cut-off of 500 ng/mL.
- **High sensitivity** for maximum safety: **NPV > 99%**.
- **Most extensively validated D-dimer test**: 7 prospective outcome studies with > 8,000 patients with suspected PE [41].

LARGE EMERGENCY TESTING PANEL*

CARDIAC	VIDAS Troponin I Ultra	Ref. 30 448
	VIDAS CK-MB	Ref. 30 421
	VIDAS Myoglobin	Ref. 30 446
	VIDAS NT-proBNP	Ref. 30 449
THROMBOSIS	VIDAS D-Dimer Exclusion™	Ref. 30 442
	VIDAS D-Dimer Exclusion™II	Ref. 30 445
INFECTIONS	VIDAS B.R.A.H.M.S PCT	Ref. 30 450
OTHERS	VIDAS Digoxin	Ref. 30 603
	VIDAS hCG	Ref. 30 405

* Some of these reagents have not yet obtained regulatory clearance in some countries.
Please contact your local bioMérieux representative for further information and product availability.