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Editor's Choice-How to use D-dimer in acute cardiovascular care

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Abstract

D-dimer testing is important to aid in the exclusion of venous thromboembolic events (VTEs), including deep venous thrombosis and pulmonary embolism, and it may be used to evaluate suspected aortic dissection. D-dimer is produced upon activation of the coagulation system with the generation and subsequent degradation of cross-linked fibrin by plasmin. Many different assays for D-dimer testing are currently used in routine care. However, these tests are neither standardized nor harmonized. Consequently, only clinically validated assays and assay specific decision limits should be used for routine testing. For the exclusion of pulmonary embolism/deep vein thrombosis, age-adjusted cut-offs are recommend. Clinicians must be aware of the validated use of their hospital`s D-dimer assay to avoid inappropriate use of this biomarker in routine care.

Keywords

D-dimer, acute cardiovascular care, pulmonary embolism, thrombosis

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Introduction

Physiological haemostasis can be considered as a protective response to prevent excessive bleeding after vascular injury or trauma. Thrombosis indicates an imbalanced haemostasis leading to thrombus formation in the arterial or venous system.[1,2] After thrombin cleaves fibrinogen into fibrin monomers the monomers can align and are allowed for cross-linking by means of covalent bonds in response to activated factor XIII, calcium and platelets.[3,4] Plasmin degrades the cross-linked fibrin to fibrin degradation products including D-dimers (see Figure 1). The latter, can be measured using monoclonal antibodies and serves as a diagnostic test for ruling out thromboembolic diseases in specific patient populations, or for monitoring of disseminated intravascular coagulation (DIC). This review aims to provide information for clinicians on how to use and interpret D-dimer testing, in acute cardiovascular care.

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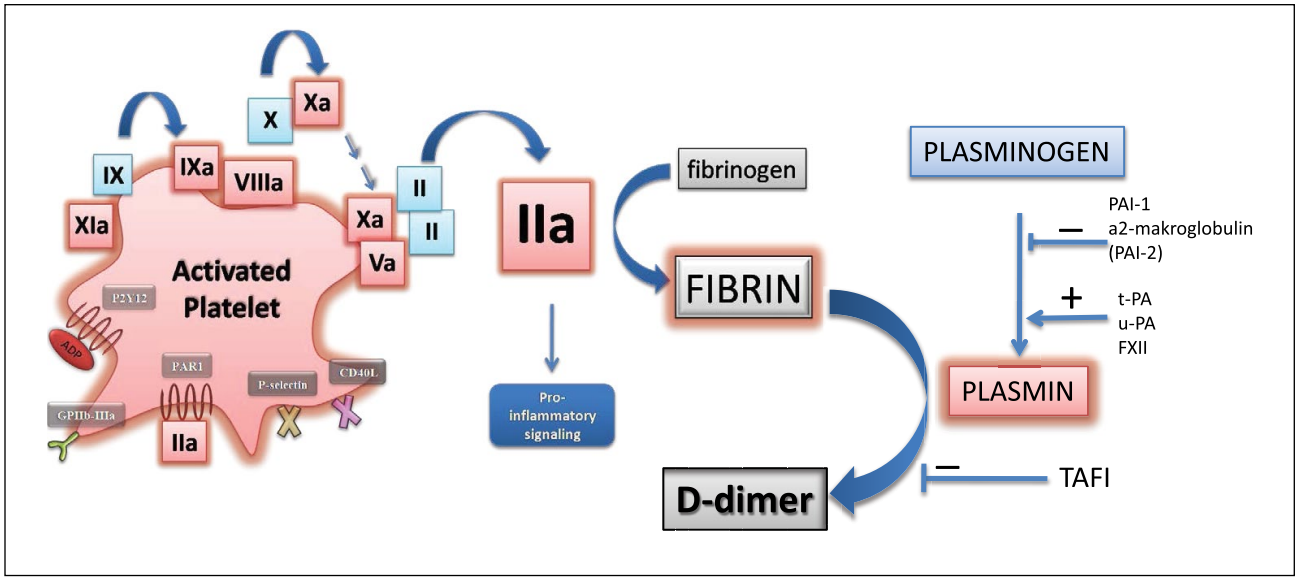

Figure 1. Pathophysiology of D-dimer formation.
The prothrombinase complex FXa+FVa generates large amounts of thrombin on the activated platelet surface during the propagation phase of coagulation. Thrombin then cleaves fibrinogen to fibrin and together with FXIII a stabilising fibrin network is formed. The proteolytic degradation of fibrin is performed by plasmin. Tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) play essential roles in the conversion of plasminogen to plasmin. Plasminogen activator inhibitor (PAI)-1, a serine protease inhibitor, is an important inhibitor of the fibrinolytic system and rapidly forms complexes with tPA and uPA. PAI-1 is an acute phase protein and has large intraindividual variation. PAI-2 is only formed in the placenta during pregnancy. Thrombin activatable fibrinolysis inhibitor (TAFI) regulates fibrinolysis and is activated by thrombin and plasmin. Plasmin-driven TAFI activation ensures that TAFI is formed in close proximity to fibrin.

Pathophysiology

The D-dimer molecule consists of two cross-linked D fragments from fibrinogen. Although D-dimer is generated during fibrinolysis, it is a marker of thrombin activity and fibrin turnover and thus reflects both haemostasis and fibrinolysis. D-dimer has a half-life of approximately 8 h and becomes detectable in blood approximately 2 h after index thrombus formation.[5] However, D-dimer is not a specific marker for coagulation activity which limits its usefulness. This is because of the close relationship between coagulation and inflammation and the fact that several 'actors' in the coagulation cascade are involved in both of these systems. Elevated levels may be seen in conditions in which fibrin is formed and then broken down, such as recent surgery, arrhythmias, pregnancy, trauma, infection, heart attack, and some cancers or conditions in which fibrin is not cleared normally, such as liver cirrhosis (Table 1). D-dimer levels increase with age and are higher in women compared to men,[6,7] and also appears to be associated with the atherosclerotic burden.[8]

Table 1. Diseases with elevated D-dimer.

- Acute myocardial infarction
- Peripheral arteriopathy
- Acute upper gastrointestinal haemorrhage, other haemorrhage
- Aortic dissection/aneurysm
- Acute respiratory distress syndrome
- Arterial or venous thromboembolism
- Fibrinolytic therapy
- Atrial fibrillation
- Consumptive coagulopathy – DIC
- Infection
- Malignancy
- Pregnancy
- Pre-eclampsia
- Sickle cell disease/haemolysis
- Stroke
- Superficial thrombophlebitis
- Trauma, burns
- Hospitalisation
- Old age
- Neonatal period
- Disability

DIC: disseminated intravascular coagulation.

Assays for D-dimer measurement

D-dimer assays detect plasmin-mediated fibrinogen degradation products (FDPs) that contain cross-linked D fragments. Monoclonal antibodies in most assays are directed against specific epitopes of the D-dimer fragment but not to epitopes on fibrin, fibrinogen, or non-cross-linked fibrin fragments.[9] Depending on the degree of lysis of cross-linked fragments a heterogeneous mixture of FDPs of different molecular weight all containing the D-dimer epitope

Table 2. Features of an ideal D-dimer assay.

1. Quantitative assay.
2. Large measuring range, including both low range values, as observed in patients with anticoagulant therapy, and high levels, as observed in patients with disseminated intravascular coagulation.
3. No influence of fibrinogen degradation products on assay results.
4. No influence of variations in fibrinogen concentration on assay results.
5. Rapid turnaround time (<15 min).
6. Appropriately validated decision limits in large clinical studies for the intended use.

Adapted from reference 78.

Table 3. Reasons for lack of D-dimer assay standardisation and harmonisation.

- >20 Different monoclonal antibodies used by >30 different assays.
- Antibodies have different analytical sensitivities and specificities.
- D-dimer molecular structure is not homogeneous.
- Antibodies show different cross-reactivity with fibrin degradations products of varying molecular weight.
- There is no internationally certified D-dimer calibrator.

Adapted from reference 10.

may be formed. Because of the unique reactivity of different D-dimer, antibodies to these different molecular weight species vary, there may be variable results if different assays are used within the same patient.[10] In addition, some antibodies have significant cross-reactivity with non-cross-linked degradation products of fibrin or fibrinogen when the assay antibodies are not specific for the D dimer fragment.[11] The features of an ideal D-dimer assay and reasons for lack of assay standardisation and harmonisation are listed in Tables 2 and 3.

Several assays and instruments are available for D-dimer measurements including enzyme-linked immunofluorescence assays (ELFAs), enzyme-linked immuno-sorbent assays (ELISAs), and latex–enhanced immuno-turbidimetric or nephelometric assays (see Table 4). The latter display the best diagnostic sensitivities for deep venous thrombosis (DVT) and pulmonary embolism (PE).[12,13] In a recent meta-analysis of 217 DVT studies and 111 PE studies,[13] the sensitivities of the D-dimer ELFA (DVT 96%; PE 97%), microplate ELISA (DVT 94%; PE 95%), and latex-enhanced quantitative assay (DVT 93%; PE 95%) were superior to those of the less sensitive whole-blood D-dimer assay (DVT 83%; PE 87%), latex semi-quantitative assay (DVT 85%; PE 88%) and latex qualitative assay (DVT 69%; PE 75%). The latex qualitative and whole-blood D-dimer assays had the highest sensitivities and specificities (DVT 99%, 71%; PE 99%, 69%). Based on these data, ELISAs and ELFAs,[12] along with the latex immune-turbidimetric assays,[13] are generally termed 'highly sensitive', whereas the whole blood D-dimer assay is considered 'moderately sensitive'.[12] In patients with suspected PE, assays with a moderate sensitivity should only be used when there is low PE pretest probability whereas highly sensitive assays can also be used in patients with an intermediate pretest probability. However, in patients with a high pretest probability, D-dimer testing alone should not be used for ruling-out of PE, not even using a high sensitive D-dimer assay.

Point-of-care vs central laboratory D-dimer testing

Routine laboratory testing is usually performed in central laboratories of hospitals on automated analysers. Based on consensus among experts, 60 min are considered to be an appropriate turnaround time (TAT) for D-dimer testing.[14] When this criterion cannot be fulfilled, the implementation of rapid quantitative point-of-care (POC) testing may be considered.

A number of POC D-dimer assays with appropriate diagnostic accuracy and user-friendliness are available.[15] These tests including membrane-based immune-assays with reflectometric quantitative detection, membrane-based manual immune-assays, or whole blood agglutination tests that usually yield results within 10–15 min.

Not all D-dimer assays are appropriate to be used for exclusion of DVT or PE. It is important to know whether the Food and Drug Administration (FDA) has cleared the assay for exclusion of DVT and/or PE or whether the assay has only been approved as an aid in diagnosis, which means that additional tests (usually objective imaging tests) are required to rule-out a venous thromboembolic event (VTE) reliably. In addition, D-dimer results have to be interpreted at well-established clinical cut-off values, which are different from reference values.

Commercially available D-dimer assays with FDA approval differ largely with respect to assay type, intended use, clinical performance, reference values and clinical cut-offs, (see Table 4). In particular, the decision cut-off has to be established from clinical studies, and therefore is assay

Table 4. Assay type, intended use, clinical performance, reference values and clinical cut-offs.

Proprietary and established names	Company	Assay type	Type of test	Intended use A=exclude B=aid	Reference range	Cut-off	Sens %	Spec %	NPV %	Clinical studies	Source FDA 510(k) number	Year
Clearview Simplify D-Dimer	Agen Biomedical Ltd	Rapid immunochromatography test	Qual	DVT B DIC	NA	80 ng/ml	100	52.9	100	Yes	K993276	14.12.1999
Clearview Simplify D-Dimer	Agen Biomedical Ltd	Rapid immunochromatography test	Qual	PE B DIC	NA	80 ng/ml	100	47.9	100	Yes	K993276	14.12.1999
VIDAS 0-Dimer Exclusion 11Assay	bioMerieux, Inc.	Enzyme-linked fluorescent assay	Quant	VTE A	90% less than 500 ng/ml	500 ng/ml	NA	NA	NA	NA	K112818	31.07.2012
Stratus CS Acute Care	Siemens Healthcare Diagnostics	Solid phase radial partition immunoassay	Quant	VTE A		450 ng/ml FEU	98.9	42.5	99.6	Yes	K110303	16.05.2011
Innovance	Siemens Healthcare Diagnostics	Turbidometric assay	Quant	VTE A		500 ng/ml FEU	98.9	39.6	99.6	Yes	K091916	29.10.2009
HemosIL	Instrumentation Laboratory Inc	Latex enhanced immunoassay	Quant	VTE A	NA	500 ng/ml	100	42.3	100	Yes	K090264	05.02.2010
MDA	Organon Teknika Corporation	Latex particle based immunoassay	Quant	VTE DIC	NA	NA	NA	NA	NA	NA	K000492	07.06.2000
Stratus CS D-Dimer (DDMR) Assay	Dade Behring	Solid phase radial partition immune assay	Quant	VTE B	NA	450 ng/ml	94	52	96	Yes	K051597	17.08.2005
Tinaquant	Roche	Immunoturbidimetric assay	Quant	VTE A	NA	<0.5 µg/ml FEU	NA	NA	NA	NA	K062203	14.03.2007
Triage	Biosite, Inc. Now Alere?	Fluorescence immunoassay	Quant	VTE B	90th % = 400 ng/ml; 95th % = 600 ng/ml	NA	NA	NA	NA	NA	K042890	29.11.2004
Advance	Dade Behring	Latex-enhanced turbidimetric test	Quant	VTE B	90% interval 0.54–2.09 mg/l	BCS System: 1.6 mg/l, Sysmex CA-1500: 1.0 mg/l	NA	NA	NA	Yes	K041438	11.08.2004
Sta-Liatest-D-Di	Diagnostica Stago	Immuno-turbidimetric assay	Quant	VTE A	NA	<0.50 µg/ml (FEU)	97	75.5	99.7	Yes	K141144 CLSIH59A	03.09.2014
Cardiac D-Dimer	Roche	Turbidometric latex assay	Quant	VTE	0.50 mg/l	NA	NA	NA	NA	NA	K033491	01.09.2004
SimpliRed	Sekisui Diagnostics	Autologous red cell agglutination assay	Qual	NA	NA	NA	93.8	67.1	NA	Yes	Package insert	09/2007
Pathfast	Mitsubishi Kagaku Iatron, Inc.	Chemiluminescent enzyme immunoassay	Quant	VTE	0.686 µg/ml FEU 95th percentile	0.686 µg/ml FEU	NA	NA	NA	NA	K072288	06.05.2009

DIC: disseminated intravascular coagulation; DVT: deep venous thrombosis; FEU: fibringogen equivalent units; NA: not available; NPV: negative predictive value; PE: pulmonary embolism; VTE: venous thromboembolic event.

specific and not always 500 ng/ml. Several assays have been approved by the FDA for exclusion of VTE. However, currently only one POC D-dimer assay[15] meets the performance characteristics recommended by Clinical and Laboratory Standards Institute (CLSI) 59 guideline,[16] i.e. NPV⩾98% (lower limit of confidence interval (CI)>95%) and sensitivity ⩾97% (with the 95% lower limit of the one-sided CI of the sensitivity >90%) and has been FDA approved for exclusion of DVT and/or PE (Table 4).

Because many POC D-dimer tests show good diagnostic accuracy to aid in the exclusion of DVT, the decision of which test to use will likely depend on their user-friendliness. Reading test results for the quantitative tests was judged to be easier than for the qualitative test.[15] Consistently, a meta-analysis of 23 studies in 13,959 patients[17] confirmed the usefulness of the quantitative assays and favoured quantitative over qualitative POC assays for excluding venous thromboembolism, particularly among patient with low pre-test probability of VTE.[17]

Pre-analytical, analytical and post-analytical limitations of D-dimer assays

D-dimer can be measured in whole blood, heparinised or citrated plasma (3.2% buffered sodium citrate). The latter represents the specimen of choice.[18]

Quantitative assays should be preferred over semi-quantitative or qualitative assays for several reasons: firstly, variations in the clarity of the qualitative result (inadequate sample loading, streaking or staining of the chromatography paper, very faint second line), secondly, quantitative D-dimer assays rely on optical measurement of light absorbance and therefore may be less vulnerable to inter-observer differences; thirdly, sensitivity of quantitative D-dimer assays (both enzyme-linked and turbidimetric) is significantly higher, but with a lower specificity.[12] The measuring range and linearity of the assay should be as wide as possible, preferably between 50 and 5,000 µg/l in order to avoid time delays related to sample dilution.[10,19] As with any other biomarker that is used to rule-out a disease, the D-dimer test needs to have high precision for results at, or close to, the cut-off value for accurate exclusion of VTE. Therefore, we recommend that D-dimer immunoassays ideally should measure concentrations at the cut-off with an inter-assay coefficient of variation (CV) of less than 10%.

There are several confounders that have to be considered when interpreting test results which are summarised in Tables 1, 5, and 6. Analytically true positive D-dimer levels may occur in a variety of conditions which may impair the clinical diagnostic performance of the test and should therefore be carefully considered by the emergency physician when requesting D-dimer and interpreting results (Table 1). True false positive D dimer results are infrequent and most commonly related to analytical errors (see Table 6).[19]

Table 5. Reasons for clinically false negative D-dimer test results.

- Patient started on anticoagulant therapy 24 h before D-dimer tested
- Oral anticoagulant therapy
- Small (often distal) thrombosis and insufficient clot size
- Upper extremity DVT
- Old clots
- Children
- False positive result from radiology
- Deficient fibrinolytic system (tPA deficiency or high PAI level)

DVT: deep venous thrombosis; PAI: plasminogen activator inhibitor; tPA: tissue plasminogen activator.
Adapted from reference 77.

Table 6. Analytically false positive or false negative D-dimer results.

- Identification errors
- Calibration bias
- Reagent deterioration
- Analyser malfunction
- Instrumental carryover or sample contamination
- Interference
- In-vitro haemolysis
- Hyperbilirubinaemia
- Turbidity
- Heterophile or auto antibodies
- Clotted samples

Adapted from reference 19.

Assay formats and instrumentation for D-dimer testing differ largely. Therefore, D-dimer test results obtained with different methods can neither be directly compared nor used interchangeably. The most frequently used medical decision limit is 500 µg/l, but reference intervals and clinical cut-off values cannot be extrapolated between methods because of lack of assay standardisation (see Table 3).

Laboratory issues – critical clinical concepts

D-dimer is a marker of thrombosis with subsequent fibrinolysis but not specific for thromboembolic diseases.

1. Only assays that have been appropriately validated in clinical studies should be used for routine testing and only for the clinical indication the assay has been approved for (i.e. whether the assay has a clearance to exclude venous thrombosis or whether it should be only used as an aid to diagnose venous thrombosis.[18]

2. Assay specific optimal medical decision limits have to be used in clinical practice.
3. Quantitative assays are preferred over semi-quantitative or qualitative assays as they allow exclusion of venous thromboembolism in patients with intermediate pretest probability as well.

Indications for D-dimer testing in acute cardiovascular care

After initial reports on the role of low D-dimer for exclusion of PE[20] followed by confirmative studies for ruling-out of DVT,[21] D-dimer measurement is currently considered the biochemical gold standard for the laboratory exclusion of clinically suspected VTE. Since D-dimer levels return to normal values within three months after an acute lower limb DVT,[22] low D-dimer level can also be used as predictors of low probability of a recurrent VTE.[23,24] In addition, D-dimer has an established indication for the diagnosis and monitoring of coagulation activation in DIC.[25] The role of D-dimer for other indications, such as diagnosis and risk stratification of coronary artery disease (CAD), early diagnosis of acute coronary syndrome (ACS), or atrial fibrillation, is less well explored.

Clinical approach to a patient with suspected VTE

Measurement of D-dimer is not recommended as a standalone test for ruling out or diagnosing VTE at emergency department (ED) admission,[10,12,19,26–30] since without appropriate clinical pre-selection the D-dimer results may be false negative.[31] Therefore, D-dimer testing should be incorporated into a diagnostic algorithm (for DVT see Figure 2(a), for PE see Figure 2(b)) that considers pretest probability.[32–34] Its predominant use is for the evaluation of outpatients with possible VTE. The sensitivity and specificity of the measurement is markedly reduced in hospitalised patients because so many have comorbidities and thus they are also often high risk patients. Wells et al. introduced a clinical decision rule, initially with three levels (low, moderate and high),[35] later simplified to two levels (unlikely and likely, Figure 3).[21] Other established and validated clinical scores include the Geneva[36,37] and simplified Geneva scores.[38] Clinical decision rules have also been adopted to primary care.[39,40] Much less is known about the use of physician *gestalt* assessment of clinical probability ('*gestalt*' is defined as a physician's unstructured clinical probability estimate after collecting routine data from patient history, physical examination with or without basic laboratory tests, electrocardiography, or chest radiography).[41] A recent meta-analysis of 52 studies including 55,268 patients demonstrated that combining a decision rule or a physician's unstructured estimate (*gestalt*) with D-dimer testing seemed safe for all strategies, except when the less-sensitive Wells rule (cut-off value $\leqslant 4$) was combined with less-sensitive qualitative D-dimer test.[41] It is important to note that the validated clinical scores cannot be used in isolation to make accurate diagnostic decisions in VTE.[42] For example, DVT was still detected in 5% of cases with a low pre-test probability according to the Wells score.[42] Therefore, national guidelines on the clinical use of D-dimer testing in patients with suspected VTE recommend assessment of clinical probability based on validated algorithms followed by D-dimer measurement (Table 7).[16,43–45] Such a strategy of selected testing of D-dimers proved at least as safe as and even more efficient than systematic assessment of D-dimer for diagnosing a first episode of suspected DVT.[46] Such an approach may reduce the need for costly further evaluation.[47]

For PE, similar to DVT, a combination of a low clinical probability and a negative D-dimer test has been shown to effectively rule-out PE, with a three-month follow-up incidence of VTE of only 0.5%.[32] Recommendations in National guidelines for the use of D-dimer in suspected VTE[43,44] (Table 4) or PE[45] and their implementation to a clinical probability score are very similar.

Medical decision limits are assay specific and must be derived from appropriate clinical studies; and may therefore be different than the frequently quoted 500 ng/ml (see Table 4). If decision limits are not provided in the package insert or FDA summary information, institutional cut-offs must be established.

There is a need for specific recommendations in the two distinct settings with divergent pre-test probability and D-dimer level. In the first setting with high pre-test probability normal D-dimer should be ignored. For the second setting with low pretest probability and very high D-dimer level, recommendations are less clear. However, there is some evidence that very high D-dimer levels increase the likelihood of PE even in patients with low pretest probability for PE. The Christopher Study[48] on 1515 patients showed that patients with D-dimer levels higher than 2000 ng/ml and an unlikely clinical decision rule had a pulmonary embolism prevalence of 36%. Whether this finding should translate into more intensive diagnostic and therapeutic measures in patients with very high D-dimer levels irrespective of clinical decision rule remains to be studied in prospective trials.

Limitations of computed tomography (CT) pulmonary angiography in diagnosis of thromboembolic diseases

Patients exhibiting a higher pretest probability for PE, and those with suspected distal DVT should always be sent for further diagnostic imaging tests.[16] Because the reported false-negative rate of CT pulmonary angiogram alone in high-risk patients ranges from 5.3%[49] to 40%.[50] it is therefore recommended that high-risk patients with a negative CT angiogram undergo additional diagnostic testing prior to ruling out VTE.[16,43–45] Hence, for patients

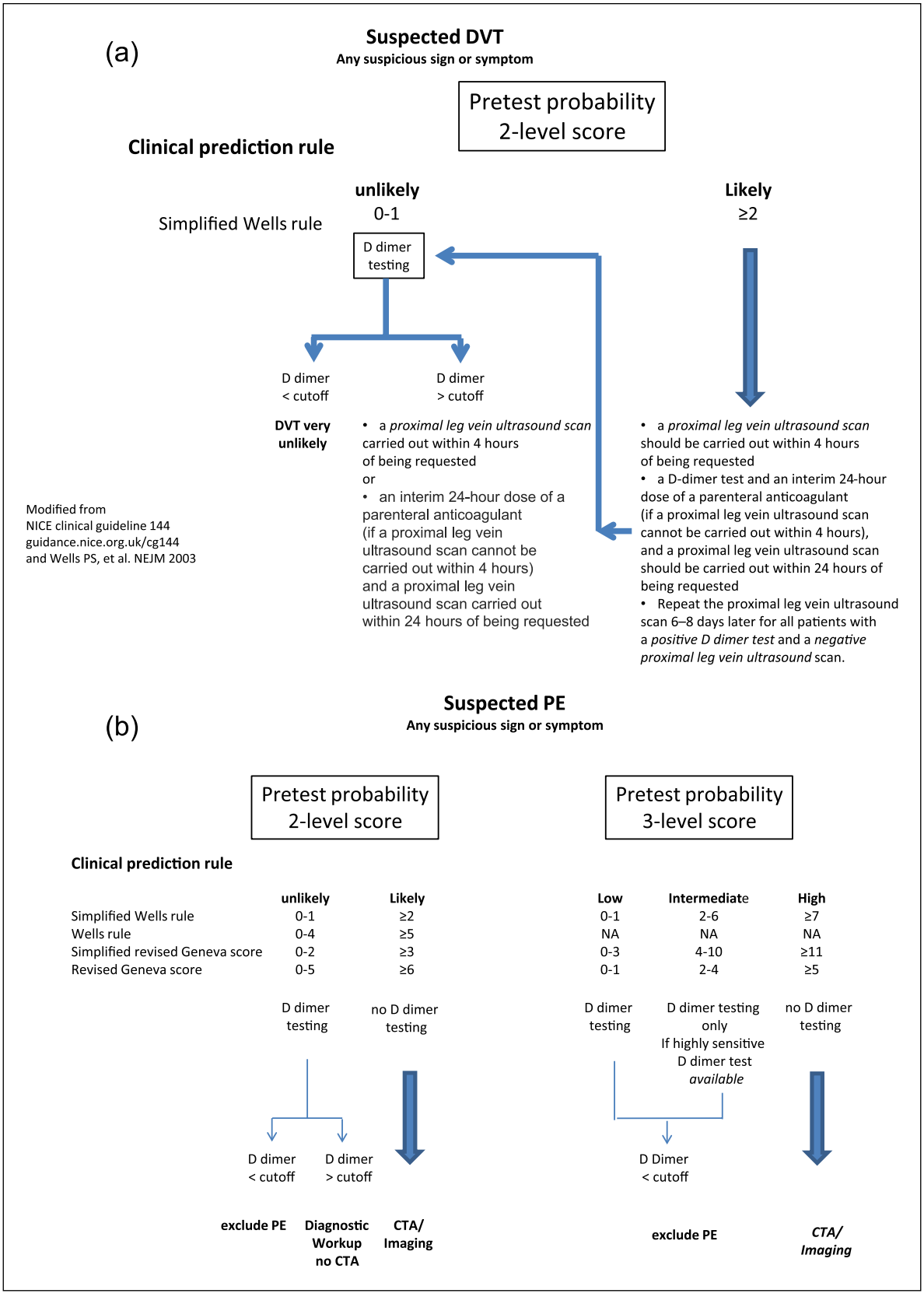

Figure 2. (a) Suspected deep venous thrombosis (DVT): any suspicious sign or symptom; (b) suspected pulmonary embolism (PE): any suspicious sign or symptom.

with a high pretest probability for PE and a negative CT angiogram result, additional diagnostic testing such as D-dimer, lower-extremity imaging, ventilation perfusion scintigraphy, traditional pulmonary arteriography should be done prior to exclusion of VTE disease. A negative, highly sensitive, quantitative D-dimer result in combination with a negative multi-detector CT pulmonary angiogram result provides a post-test probability of VTE disease less than 1%.

The intended use of each D-dimer assay has to be considered

The intended use of the assay and the specified cut-off for the intended use must be considered.[16] As mentioned above a product may be cleared by the FDA for the exclusion of venous thrombosis or as an aid in the diagnosis of DVT and/or PE (Table 4).

When the assay is used for the exclusion of venous thrombosis, the assay must meet certain characteristics. CLSI H59[16] recommends the following assay characteristics:

- Negative predictive value (NPV)⩾98%
- Sensitivity⩾97%
- Sufficient sensitivity to provide discrimination
- Good reproducibility at the level of the threshold for exclusion of VTE
- Well established diagnostic threshold

Notably, exclusion criteria apply to lower extremity DVT and PE only and cannot be used to exclude upper extremity DVT, arterial thrombosis, and are not recommended in a paediatric population. In addition, D-dimer testing for exclusion of VTE is confined to primary care and in the ED in patients with unlikely PE or low DVT probability. Its use in elderly, pregnant women, heart failure or cancer patients is not in the label.[45]

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	−2
Clinical probability simplified score	
DVT *likely*	2 points or more
DVT *unlikely*	1 point or less

Figure 3. Clinical decision rule for deep venous thrombosis (DVT).

Special settings – off-label use of D-dimer testing

The diagnostic yield of D-dimer relies on its specificity, which varies according to patient characteristics. The specificity of D-dimer in suspected PE decreases steadily with age and may reach <10% in patients above 80 years.[51] D-dimer is also more frequently elevated in patients with cancer,[52,53] in hospitalised patients,[54] and during pregnancy[55,56] and in patients with heart failure. Therefore, the number needed to test in order to exclude one PE varies between three in the emergency department to ⩾10 in the specific situations listed above.[45]

D-dimer and age. Due to comorbidities, activation of the coagulation system or inflammation, D-dimer concentrations increase with age, and the D-dimer assay is more likely to give a positive result in patients over 50 years,[57] limiting the usefulness of the test. However, if the D-dimer is negative it can still be used to rule out VTE in elderly patients with low pre-test probability. In contrast, the prevalence of normal D-dimer values decreases with age, which means that more radiological investigations are necessary to exclude VTE. Implementation of higher cut-offs in the elderly bear the potential of false-negatives and have therefore been regarded as unsafe. However, a recent retrospective study by Douma et al.[58] suggested that higher cut-offs might be safely used in patients over 55

Table 7. Recommendations for D-dimer testing in European Society of Cardiology (ESC) guidelines.

- In non-high risk suspected PE
  In non-high-risk PE, basing the diagnostic strategy on clinical probability assessed either implicitly or using a validated prediction rule is recommended (LOE IC)
  Plasma D-dimer measurement is recommended in emergency department patients to reduce the need for unnecessary imaging and irradiation, preferably using a highly sensitive assay (LOE IC)
- Low clinical probability
  Normal D-dimer level using either a highly or moderately sensitive assay excludes PE (LOE IA)
- Intermediate clinical probability
  Normal D-dimer level using a highly sensitive assay excludes PE (LOE IA)
  Further testing should be considered if D-dimer level is normal when using a less sensitive assay (LOE IIaB)

LOE: level of evidence; PE: pulmonary embolism.
Adapted from reference 45.

years of age, and are reliable. A formula for calculating age-adjusted D-dimer cut-off values in patients aged 50 years or older is provided:

$$\text{Age-adjusted cut-off} = (\text{age, years}) \times 10\ \mu g/l$$

A recent meta-analysis[59] evaluating 13 cohorts including 12,497 patients with a non-high clinical probability for suspected VTE demonstrated that the use of an age-adjusted D-dimer cut-off value in patients over 50 years increased the specificity of D-dimer in all age categories with only a small insignificant decrease in sensitivity, which remained above 97% in all patients.[59] Findings on VTE were consistently confirmed for suspected PE in a multi-centre, multinational, prospective management outcome study in 19 centres on 3346 patients. In addition, it was demonstrated that age-adjusted cut-offs remained accurate even among the 766 patients aged >75 years.[60]

D-dimer in pregnancy. The D-dimer test result is more likely to be positive in pregnant women. Concentrations increase progressively throughout pregnancy,[61,62] and the D-dimer result is nearly always positive in the third trimester.

A normal D-dimer value has the same exclusion value for PE in pregnant women as in other patients with suspected PE. Given the paucity of studies, measurement of D-dimers is an option, especially in early pregnancy in order to avoid unnecessary exposure of the foetus to diagnostic radiation, even though the probability of a negative result is lower than in other patients with suspected PE. An elevated D-dimer result should be followed by lower limb compression ultrasound since a positive result warrants anticoagulation treatment and makes thoracic imaging unnecessary. If ultrasonography is negative, and PE is a concern, the diagnosis should be pursued.

D-dimer in cancer patients. In patients with a known malignancy, the need to rule out DVT is paramount as the prevalence of DVT is twice that in patients without cancer.[63] Unfortunately, D-dimer levels may be elevated in cancer patients even in the absence of a thrombosis, and none of the diagnostic algorithms have been validated in cancer patients. Furthermore, due to the higher prevalence of DVT in cancer patients, the NPV of D-dimers in this population is lower than in patients without cancer.[64] In a meta-analysis of 13 studies in 10,002 patients the prevalence of the combination of a low score on the Wells rule and a negative D-dimer test among cancer patients result was only 9%.[42] Moreover, in these low risk patients deep vein thrombosis was still present in 2.2%.[42] Carrier et al.[63] reported that 88–94% of cancer patients required additional diagnostic testing beyond D-dimers, thus diminishing the value of D-dimer testing in this population.[63] Taken together, measurement of D-dimer is seemingly not an aid to diagnose DVT in cancer patients.

Novel, less-well established indications for D-dimer testing in acute care

Acute aortic dissection (AAD). Another application of D-dimer is in the diagnosis or exclusion of aortic dissection. In a recently published meta-analysis it was suggested that plasma D-dimer <500 μg/l is a useful screening tool to identify patients who do not have aortic dissection.[65] Two other meta-analyses[66,67] conferred supporting evidence that D-dimer represents a highly sensitive biomarker for the exclusion of AAD, with 100 % sensitivity at a cut-off of 100 μg/l and 99% at a cut-off level of 500 μg/l.[66] In contrast, a positive D-dimer lacks specificity for AAD, thus limiting its clinical role for this indication.

Acute myocardial infarction (AMI). Increased D-dimer levels in AMI are associated with increased risk of new cardiovascular event or death even though troponin or NT-proBNP in multimarker risk stratification analysis provided more information to traditional clinical risk scores for prognosis.[68,69] The early change of D-dimer after AMI also identifies a cohort at reduced risk of new cardiovascular event. Those with increased or unchanged D-dimer early after the AMI had an increased risk of new cardiovascular events.[70] However, practice guidelines still do not recommend D dimers for risk assessment in AMI as there is still not enough evidence for the independent prognostic relevance of D dimer in contemporary cohorts of AMI patients.

In atrial fibrillation. Atrial fibrillation is accompanied with increased risk of thromboembolism where the pathophysiological environment is more similar to the situation in venous thromboembolism with reduced flow particularly in the left atrial appendage. Today clinical risk scores, such as the CHA_2DS_2-VASC score, are used for estimation of the risk of stroke in patients with atrial fibrillation. A number of studies have, however, clearly demonstrated that D-dimer is increased in atrial fibrillation and the degree of elevation is related to the thrombus formation.[71–74] Higher D-dimer levels in atrial fibrillation both in patients with and without anticoagulant treatment are associated with increased risk of stroke and death.[75] Future studies are needed for evaluation of the utility of D-dimer and other biomarkers for the decision of anticoagulant treatment in atrial fibrillation.[76]

Summary: Critical clinical concepts on indications for D-dimer testing in acute cardiovascular care

1. D-dimer is a reliable biomarker for the exclusion of thromboembolic disorders in combination with the Geneva or Wells score.
2. Assay specific cut-offs must be used.

3. In the above 50-year-old population age-adjusted decision limits improve diagnostic accuracy and should be used.
4. In pregnancy, malignancy, infections, post-surgery or trauma (<4 weeks) or liver cirrhosis the use of D-dimer is not recommended.
5. D-dimer is currently not recommended for the diagnosis and risk stratification of acute coronary syndrome.
6. There is increasing data on the use of D-dimer testing for exclusion of AAD and D-dimer testing is recommended for this indication.

Conflict of interests

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