Doppler ultrasound and D-dimer
Friend or foe?

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Summary
The diagnosis of venous thromboembolism has evolved considerably with the development of standardized diagnostic algorithms that include clinical probability assessment, D-dimer measurement and the use of non-invasive imaging modalities such as compression ultrasonography and computed tomography angiography. The implementation of these strategies aims to improve resource allocation and patient outcome. The judicious use of these diagnostic tools requires a thorough knowledge of the appropriate clinical setting in which every test and strategy is efficient and can be used safely. For this purpose, D-dimer measurement and compression ultrasonography are complementary: the former is mainly used to exclude VTE in selected patients, while the latter is used to confirm the presence of an underlying DVT.

This review provides an appraisal of the features and use of D-dimer and compression ultrasonography in the context of suspected venous thromboembolism.

Keywords
D-dimer, ultrasonography, clinical probability, deep vein thrombosis

DD assays
The activation of the coagulation cascade leads to the production of thrombin, which in turn cleaves fibrinogen to produce fibrin monomers that subsequently crosslink and stabilize. To ensure regulation of the coagulation cascade, the endogenous fibrinolytic system is simultaneously activated. Plasma-induced degradation of cross-linked fibrin thereby generates several fragments including DD. DD production is highly specific of fibrin degradation. However, several conditions other than thrombosis also enhance fibrin production and subsequent degradation. In other words,

- DD blood concentration increases in the presence of VTE,
- but DD production does not necessarily reflect an underlying thrombosis.

Over the last two decades, the diagnostic approach to deep vein thrombosis (DVT) and pulmonary embolism (PE) has evolved considerably. The index of suspicion for venous thromboembolism (VTE) has increased progressively among clinicians, leading to an increase in the number of diagnostic tests performed at the expense of greater resource utilization and radiation exposure.
by the development of monoclonal antibodies that recognize DD antigens and then form immunocomplexes. Each commercially available assay has different performance characteristics as each recognizes various DD epitopes and employs diverse methods for immunocomplex detection. These disparities between assays lead to a significant variation in sensitivity and specificity for the presence of thrombosis, depending on which DD test is used. Clinicians should be aware of these particularities as proper interpretation of the results requires knowledge of the clinical setting and the test characteristics.

DD measurements using quantitative enzyme-linked immunosorbent assays (ELISA) are highly sensitive (over 95%) for acute VTE (2, 3). However, ELISA assays are time consuming, which restricts their use in an emergency room setting. Combining the ELISA technique with the detection of immunocomplexes by fluorescence (ELFA, enzyme-linked fluorescence assay) has been shown to improve test rapidity while maintaining equivalent sensitivity (e.g., Vidas D-dimer Exclusion® test) (3, 4).

Semi-quantitative and qualitative latex-based techniques are less sensitive for VTE detection and prone to high inter-observer variability, which explains their low rate of use in clinical practice at least in Europe. The recently developed automated quantitative latex agglutination test, which uses the turbidimetric detection method (e.g., Tinaquant® test), has improved the performances of this type of test, with characteristics very similar to the ELISA method (3, 5).

The manual whole-blood agglutination test (e.g., SimpliRED® assay) can be performed rapidly at the bedside and does not require complex instrumentation or equipment. In a recent meta-analysis, the reported sensitivity for DVT and PE was 83% and 87%, respectively (3). This intermediate sensitivity limits the clinical use of whole-blood assays to patients with a low clinical probability. Moreover, the result is highly dependent on observer interpretation (visual reading) (6).

The main utility of DD assays is to safely exclude a diagnosis of VTE in appropriately selected patients. This explains the clinical interest in highly sensitive DD assays, such as ELISA, ELFA and quantitative turbidimetric methods. Even when using highly sensitive assays, a negative DD result alone does not rule out a diagnosis of VTE. Indeed, DD testing should be fully integrated in a sequential diagnostic strategy that includes an assessment of the clinical probability of having VTE as the initial step.

Clinical probability

With respect to DD testing, the actual post-test probability depends on the prevalence of the disease (VTE) in the study population (based on Bayes’ theorem). Hence, a DD test combined with the pre-test clinical probability determines the post-test probability of VTE, identifying which patients can have the diagnosis ruled out on the basis of a negative DD result. In addition, the assessment of probability is intended to identify patients for whom the introduction of anticoagulant treatment should be considered while awaiting a definitive diagnostic confirmation.

The pre-test clinical probability can be estimated either by using standardized clinical decision rules (CDR) or more intuitively, based on the physician’s clinical gestalt impression. Both have been shown to be reasonably accurate for estimating clinical probability, although higher inter-observer reliability was reported with the CDR (kappa = 0.62 vs. 0.33 for intuitive assessment) (7, 8).

In cases of clinically suspected DVT, the Wells score (Tab. 1) is the most widely used and categorizes patients into three probability groups (9): low, intermediate or high probability.

The prevalence of DVT is less than 5% in patients with a low clinical probability, while it is approximately 15% and 70% in patients with an intermediate and a high clinical probability, respectively.

With regard to PE, two CDR have been proposed and externally validated: the PE Wells score and the Geneva score (10–12). With both scores, patients are accurately classified into three risk categories corresponding to a prevalence of the disease of
- 5 to 10% (low clinical probability),
- 20 to 30% (intermediate clinical probability),
- 60 to 80% (high clinical probability).

The Wells score has been criticized for the inclusion of a subjective criterion (whether an alternative diagnosis is more likely than PE). On the other hand, the original Geneva score requires an arterial blood gas analysis, which is not always available. Accordingly, the Geneva score has been revised to facilitate clinical implementation (13–15). This so-called revised Geneva score is entirely based on available clinical features and objective parameters, obviating the need for blood gas analysis. Likewise, the Wells score has also been modified to reflect a dichotomous two-level scheme (PE unlikely or likely) instead of the traditional three levels of probability (low, intermediate or high) (16, 17) (Tab. 1).

Although these CDR have shown similar accuracy in establishing the probability of PE, they are not totally equivalent with respect to the clinical setting. The practical choice of one CDR over another should be based on the local prevalence of PE, the sensitivity of the available DD assay and the patient’s characteristics (inpatient or outpatient) (18). When the prevalence of PE is above 20%, the Wells score seems less reliable and the revised Geneva score should be preferred. This is easily understandable, for the Geneva score was derived and validated in a similar population. Moreover, when using a highly sensitive DD assay, the three-level classification scheme excludes a PE diagnosis in a higher number of patients. Conversely, the performance of a less sensitive DD assay is better (more patients can have the diagnosis ruled out) when used with the modified two-level Wells score. Indeed, this two-level classification assigns more patients to the unlikely probability group than are assigned to the low probability group when using the three levels of probability. Finally, in hospitalized patients, the Wells score should be preferred as all other rules were validated exclusively in an outpatient setting.
Clinical probability in combination with DD measurement

A diagnosis of VTE can be ruled out in the presence of a non-high (low/intermediate) clinical probability combined with a negative DD result. Hence, the diagnosis can be excluded without further investigation in approximately 30% of outpatients. In this context, two DD assays have been largely validated. In patients with a non-high clinical probability, a negative DD Vidas assay was associated with a 3-month thromboembolic risk of 0.14% (95% CI 0.05 to 0.41%) in untreated patients (19). These results confirm what has been demonstrated previously in outcomes studies (15, 17, 20, 21). Similarly, the Tina-quant test, a turbidimetric assay, has also been well validated, with a low 3-month thromboembolic risk in patients with a low (or unlikely for the modified Wells score) PE probability (17, 22).

To summarize, a diagnosis of VTE can be safely ruled out when a negative highly sensitive DD assay result is combined with a low/intermediate or unlikely clinical probability (Fig. 1). Nevertheless, it must be emphasized that when using a less sensitive DD assay, a diagnosis of VTE can be excluded only in patients with a low or unlikely probability.

In cases of high clinical probability, the post-test probability of VTE remains elevated (> 3%) even with a negative DD result. Consequently, DD measurement has no role in this setting and the investigation should proceed directly to CUS or thoracic computed tomography based on the clinical features.

DD measurement in special clinical situations

Some clinical situations lead to an increase in DD blood concentration without the presence of thrombosis (e. g., infections, cancer, inflammation, recent surgery). In addition, these situations are frequently associated with an increased risk of VTE, lowering the yield of DD testing.

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**Tab. 1** Main clinical decision rules for probability assessment of clinically suspected deep veins thrombosis (DVT) or pulmonary embolism (PE)

<table>
<thead>
<tr>
<th>score</th>
<th>items</th>
<th>points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wells’ score</strong></td>
<td>deep veins thrombosis (DVT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>active malignancy (within 6 months)</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>immobilization (paralysis or cast)</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>bed rest &gt; 3 days or surgery &lt; 4 weeks</td>
<td>+1</td>
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<tr>
<td></td>
<td>pain on palpation of deep veins</td>
<td>+1</td>
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<tr>
<td></td>
<td>swelling of entire leg</td>
<td>+1</td>
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<tr>
<td></td>
<td>calf swelling (&gt; 3cm difference)</td>
<td>+1</td>
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<tr>
<td></td>
<td>pitting oedema (affected side only)</td>
<td>+1</td>
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<tr>
<td></td>
<td>collateral superficial veins (non-varicose)</td>
<td>+1</td>
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<tr>
<td></td>
<td>alternative diagnosis at least as likely as DVT</td>
<td>−2</td>
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<tr>
<td></td>
<td>clinical probability</td>
<td></td>
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<tr>
<td></td>
<td>low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>intermediate</td>
<td>1−2</td>
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<tr>
<td></td>
<td>high</td>
<td>≥3</td>
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<tr>
<td></td>
<td>pulmonary embolism (PE)</td>
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<tr>
<td></td>
<td>previous PE or VTE</td>
<td>+1.5</td>
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<tr>
<td></td>
<td>heart rate &gt; 100/min</td>
<td>+1.5</td>
</tr>
<tr>
<td></td>
<td>recent surgery or immobilization</td>
<td>+1.5</td>
</tr>
<tr>
<td></td>
<td>clinical signs of DVT</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>alternative diagnosis less likely than PE</td>
<td>+3</td>
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<tr>
<td></td>
<td>cancer</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>haemoptysis</td>
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<tr>
<td></td>
<td>clinical probability</td>
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<td>low</td>
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<td>high</td>
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<td>dichotomized rule</td>
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<tr>
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<td>likely</td>
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<td></td>
<td>revised Geneva score</td>
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<td>age &gt; 65 years</td>
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<tr>
<td></td>
<td>previous DVT or PE</td>
<td>+3</td>
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<tr>
<td></td>
<td>surgery or fracture within 1 month</td>
<td>+2</td>
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<tr>
<td></td>
<td>active malignancy (or consider as cured &lt; 1 year)</td>
<td>+2</td>
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<tr>
<td></td>
<td>heart rate</td>
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<td>75–94 bpm</td>
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<td>≥95 bpm</td>
<td>+5</td>
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<td>unilateral leg pain</td>
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<tr>
<td></td>
<td>pain on lower-limb deep vein palpation and unilateral oedema</td>
<td>+4</td>
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<td>haemoptysis</td>
<td>+2</td>
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<tr>
<td></td>
<td>clinical probability</td>
<td></td>
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</tr>
<tr>
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</tr>
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</table>

VTE: venous thromboembolism
Inpatients

The usefulness of a negative DD result in excluding VTE in hospitalized patients remains unclear. The test is less specific in acute medical illness due to enhanced fibrin production. Also, the clinical probability is frequently considered intermediate or high in hospitalized patients, thus limiting DD utility. Moreover, most of the above-mentioned studies mainly included outpatients. CDR and DD measurement therefore has lower utility in hospitalized patients and the clinician should probably proceed directly to an imaging test (23).

Elderly patients

The diagnosis of VTE is a major issue in elderly patients, explained in part by its increased prevalence, but also because co-morbidities may complicate the investigation and results interpretation (24). DD concentrations increase with age, reducing specificity of the test. For patients over 80 years of age, a DD assay rules out PE in only 5% of patients compared to 60% in patients under 40 years of age (25). DD testing has been reported to be non-cost-effective in elderly patients (> 79 years) due to the higher number of patients that need to be tested to rule out one diagnosis (26). However, DD sensitivity remains high and the test can be helpful in patients for whom imaging procedures are unwanted or contraindicated. A new DD cut-off value has been proposed (patient’s age × 10, μg/l) in an attempt to improve specificity and clinical utility (27). Calculated for patients over 50 years of age, this new cut-off point improves test performances, with a low failure rate. These promising results are presently being prospectively validated before implementation in practice can be recommended.

Cancer

In the majority of patients with an active malignancy who have suspected VTE, clinical probability is estimated to be high (28). Although DD sensitivity seems to remain unchanged, specificity is much lower, with 9 patients needing to be tested to exclude one diagnosis of PE (29). This explains why the vast majority of patients require further testing to rule out a diagnosis of VTE (28–31). Consequently, most of these patients should be directly referred for an imaging exam.

Others situations

Few other situations deserve to be mentioned. DD levels decrease in patients whose symptoms persist for many days or who are already receiving anticoagulant treatment and the test should not be used in these situations (32, 33). Otherwise, in patients with a previous VTE event, a negative DD result is reliable for ruling out a recurrence (34). However, a positive DD result has been reported more frequently in patients with previous VTE (in 32.7% vs. 15.9% of patients), decreasing the yield of the test. Interestingly, DD sensitivity varies according to thrombus location. Sensitivity for distal DVT and sub-segmental pulmonary embolism has been shown to be reduced, but it must be pointed out that the clinical significance of these thrombi remains unclear (35–37).

Although the clinical utility of DD testing is limited solely to the exclusion of diagnoses, some data suggest that a very high DD level is associated with an increased risk of VTE. Independently of the pre-test clinical probability, a DD value above 2000 μg/L was associated with an odds ratio of 6.9 for PE in a retrospective analysis (38). However, an elevated DD result is insufficient to confirm a diagnosis of VTE, so this observation if of limited clinical relevance. In conclusion, the comprehensive use of DD testing first involves determining whether or not VTE is part of the actual differential diagnosis. The indiscriminate use of DD assays would result in unjustified additional exams with a risk of false-positive results. Moreover, the clinician must determine the pre-test clinical probability prior to DD testing as knowledge of the DD result has been shown to influence clinical evaluation (39).

Lower limb venous compression ultrasonography

Historically, venography was considered the gold standard for the diagnosis of VTE. Nevertheless, it has largely been replaced by CUS, a less invasive and easily accessible imaging modality. CUS is the first-line exam in cases of suspected DVT, both for patients with a high clinical probability and for those with a low/intermediate probability and an increased DD level.

Three CUS methods are commonly used in clinical practice. The first option is...
to explore the proximal veins only (above the knee) and to repeat the CUS one week later if the first exam is normal. The proximal veins can be explored using the 2-point technique (by compressing only the common femoral veins and the popliteal fossa) or by examining the entire venous network segment above the popliteal veins (adding examination of the superficial and deep femoral veins). Irrespective of which protocol is used, a second CUS must be conducted one week later to exclude a proximal progression of a previously undiagnosed distal DVT. Several outcome studies have reported a low (<1%) 3-month VTE rate for patients with DVT excluded by this strategy, confirming the safety of this approach (9, 40–43). However, the second CUS has a low diagnostic yield and demonstrates few additional DVT at one week (around 1 to 2% positive results) at the expense of significant resource utilization (44, 45).

The second validated approach consists of performing a complete venous CUS, including compression of the entire deep venous system, from the groin down to the most distal veins (below the knee). This complete examination obviates the need to do a repeat CUS at one week. Both patients with a proximal and a distal DVT were treated using this strategy, with a low 3-month thromboembolic risk (46–49). These findings were confirmed in a recent meta-analysis of 4731 patients, with a 3-month VTE rate of 0.57% (50). It is relevant to mention that when compared to the CUS limited to the proximal veins, approximately 50% more patients received anticoagulation treatment for an isolated distal DVT with the complete CUS strategy (51, 52).

The last CUS approach combines a single proximal CUS with DD testing or clinical probability assessment in order to limit the number of exams required at one week. If the first CUS is negative, some authors propose that the exam be repeated at one week only in patients with an intermediate/high clinical probability, with a low 3-month VTE rate (9). Similarly, Bernardi et al. propose that a second proximal CUS be performed at one week exclusively in patients with elevated DD levels, allowing an 80% reduction in the number of exams required, with a reassuring 0.4% rate of VTE at 3-month for untreated patients (42).

These data raise questions about the significance of distal DVT. Indirect observations suggest a favorable clinical evolution for patients with an isolated distal DVT. The low rate of additional DVT diagnosed at one week with the serial proximal CUS strategy suggests that distal DVT rarely extends to the proximal veins. Furthermore, despite a higher number of patients receiving anticoagulation treatment with the complete CUS strategy, the 3-month VTE rate seems to remain unchanged (44, 52).

Distal DVT may have a lower embolic potential that may not justify the bleeding risk associated with anticoagulation treatment (53). Nevertheless, actual recommendations support the use of anticoagulation treatment regardless of DVT location (54). This issue is currently being addressed in the randomized CACTUS clinical trial (NCT 00539058) evaluating the pertinence of anticoagulation for isolated distal DVT.

In conclusion, both the complete and the serial proximal CUS perform equally well in DVT diagnosis, despite discordance concerning distal vein assessment. A recent trial directly compared complete CUS (proximal and distal veins) with a serial 2-point proximal CUS combined with a DD assay (55). In 2098 patients with suspected DVT, both strategies perform equally well, with similar 3-month VTE rates. However, despite the fact that 24% of patients were treated for isolated distal DVT in the complete CUS group, no difference was found in the 3-month VTE risk.

Limitations of CUS

The mentioned clinical outcome studies have demonstrated the excellent sensitivity of CUS for DVT diagnosis, with a low 3-month VTE rate in patients left untreated following a negative exam. However, clinicians should be aware of the potential limitations CUS revealed in some medical situations. Decreased performances have been observed with respect to the examination of the distal venous system, with reported sensitivity as low as 50 to 75% and specificity at around 90% (56, 57). Assessment of the distal veins may also be more affected by observer experience and anatomical considerations. Likewise, CUS performance is also reduced in asymptomatic patients and venography is superior in this circumstance. This consideration is mainly relevant for research purposes (58, 59).

The suspicion of recurrent DVT is another quite complex situation, as no objective test can reliably differentiate between a residual and a new thrombus. Approximately 50% of patients with a history of DVT will have a residual thrombus at one year (60, 61). A careful comparison with previous CUS, focusing on the appearance of the thrombus, its location and the diameter of the veins under compression can help to differentiate between these two conditions. When this information is not available, the choice of treatment should be based on the clinical context (history, physical examination and pretest probability). A repeat CUS examination may also be useful in this particular situation.

For obvious anatomical reasons, venous compressibility, a major criterion to confirm vein patency, cannot be assessed in the iliac veins and vena cava. Consequently, isolated iliac vein or vena cava thrombosis are challenging to diagnose by CUS. Nevertheless, some cues can be useful in this particular setting. A normal respiration-modulated flow pattern on a Doppler ultrasound at inguinal level strongly suggests the absence of an underlying more proximal DVT. However, confirmation or exclusion of a definitive thrombosis often requires a pelvic computed tomography scan to adequately assess the very proximal venous system, especially when there is a high clinical suspicion and an inconclusive CUS. It should be noted that additional imaging could also provide useful information about the differential diagnosis, such as an intra-abdominal compression of the venous system, which would account for the lower limb symptoms.

Role of CUS in patients with suspected pulmonary embolism

In a patient with suspected PE, investigating for DVT can be useful in certain situ-
ations. In a clinical context suggestive of PE, the identification of a proximal DVT allows a PE diagnosis to be established without thoracic imaging. Indeed, both conditions (proximal DVT and PE) represent different manifestations of the same pathologic process and both require the introduction of anticoagulation treatment. Importantly, DVT was found in only 9% of patients with suspected PE (15). Consequently, systematically proceeding withCUS in cases of suspected PE is an inefficient strategy as 11 patients needed to be tested to avoid one thoracic computed tomography scan. For patients with clinical features congruent with DVT, CUS could be proposed before pulmonary imaging as DVT is found more frequently in symptomatic patients. Likewise, CUS can be useful for PE investigation (instead of or prior to thoracic computed tomography) in patients with a history of contrast product allergy, renal insufficiency or during pregnancy, in an attempt to limit radiation exposure. Obviously, a negative CUS does not exclude PE and further investigation is warranted.

Conclusion

The diagnosis of VTE relies upon several, mainly non-invasive, diagnostic tools that must be used in a structured and adapted sequential approach. The implementation of a validated diagnostic algorithm can improve resource allocation and even patient outcomes. These strategies will continue to evolve with technological improvements in imaging modalities. Indeed, advances in medical imaging will increase the diagnosis of clinically unsuspected VTE and the detection of “low burden thrombi”, such as isolated distal vein thrombosis and sub-segmental PE.

The application of a rigorous diagnostic approach, including a clinical probability assessment and DD measurement, may eventually help distinguish high-risk VTE events from VTE events associated with a low risk of complications.

Forthcoming progress includes the refinement of diagnostic algorithms (e.g., age-adjusted DD cut-off value) and the improvement of knowledge concerning the prognosis factors associated with various VTE events (e.g., the clinical significance of distal DVT). Accordingly, the true issue in the near future may no longer be to simply detect clots but rather to identify which patients will benefit from anticoagulant treatment and how.

References


