Summary

D-dimer can be used to exclude venous thromboembolism (VTE) in outpatients. Together with a low pretest probability of VTE, a negative D-dimer can safely rule out VTE in 30-50% of patients with suspected VTE.

The use of D-dimer requires a method with particular performance characteristics, most importantly:

- A high sensitivity and negative predictive value (NPV)
- Acceptable diagnostic specificity
- Good reproducibility around the cut-off (decision limit)

Besides a sensitivity and NPV as close to 100% as possible, a high specificity is of importance to limit the number of unnecessary radiological imagings for the benefit of the patient and to improve logistics of the healthcare system.

Abbreviations and definitions

DVT: Deep venous thrombosis - disease where a blood clot is formed in the deep veins
NPV: Negative predictive value
PE: Pulmonary embolism
VTE: Venous thromboembolism (includes DVT and PE)

The presence of D-dimer indicates that thrombin has been formed and fibrin generated from fibrinogen in vivo as a result of activation of the coagulation system. D-dimer is the end product of degraded cross-linked fibrin, but it is a heterogeneous collection of fibrin fragments and thus not a well-defined analyte.

How is a D-dimer assay used?

Indications

D-dimer testing is used as an aid in the diagnosis of venous thromboembolism (VTE), and D-dimer testing is
widely accepted as the first-step test in the management of patients with suspected VTE [1].

The clinical problem is that the proportion of patients with a suspicion of VTE in whom the diagnosis is confirmed is low. It varies between studies, but is often around 20%. In order to minimize the number of radiological examinations performed on this patient group, D-dimer testing can be used to exclude VTE in outpatients. It can be used for this purpose when it is combined with a clinical probability score, and only a low score and a negative D-dimer test result can be used to exclude VTE.

Pretest probability score

There are different pretest probability scores, for example the original Wells score [2] and a score adopted for primary care [3]. The variables included are based on the differences in the prevalence of VTE in patients in hospital and primary care setting and also in the experience of the condition among the treating physicians. If the sum of the points are less than the decision limit, VTE is considered ruled out.

Flowchart for patients with high and low probabilities, respectively

Patients with a high clinical probability of VTE get either imaging at once or, if that is not possible, they get therapy at once whether a D-dimer test is positive or not [2].

Patients with a low probability of VTE have a D-dimer test performed and a negative test excludes VTE with a high sensitivity. If the D-dimer test is positive,
objective imaging has to be performed. With a careful combination of clinical assessment and D-dimer, VTE can be excluded.

Limitations

A number of limitations of the use of D-dimer for VTE diagnoses are listed in Table II [4]. In patients with a duration of symptoms >14 days, D-dimer is suspected to be negative due to the expected half-life. D-dimer cannot be used in hospitalized patients and patients with recurrent VTE, since the specificity of the test is too low, and thus a positive result can be expected also when the patient has other conditions, such as inflammation or even pregnancy.

Analytical challenges

Since the D-dimer analyte is not well-defined, different assays are based on different monoclonal antibodies that recognize different fibrin fragments or so-called D-dimer motifs. There is no reference preparation or calibrator that can be used as an international standard. There are also different measuring principles, from whole-blood methods based on agglutination, to automated latex agglutination tests (LIA) tests. Thus, different tests also have different decision limits for a negative test. The sensitivity and specificity depends on test characteristics (especially the monoclonal antibody used).

Performance characteristics

Performance characteristics - units, CLSI recommendations

The cut-off should be determined locally by clinical management studies, which is often a hard task for a laboratory to achieve [4]. A good reproducibility around the cut-off is preferred because the probability that a measured result for a specific person is below the cut-off, even though the “true” value is above the cut-off, depends on the “true” concentration and the reproducibility of the analytic method used. A high diagnostic sensitivity, a high negative predictive value, as well as an acceptable diagnostic specificity must be obtained.

Results are given either as mg/L D-dimer or as mg/L FEU (Fibrinogen Equivalent Units). 1 mg/L D-dimer is
approximately 2 mg/L FEU, but this is based on the assumption that 1 mg fibrinogen gives 0.5 mg D-dimer. It is not recommended to recalculate results to another unit, therefore it is also difficult to compare results from different tests and different studies, i.e. in a linear regression model [5]. The most important limitation with method comparisons is that the possibility of a method to differentiate non-VTE from VTE patients can only be evaluated in a clinical management study including radiological examination and follow-up for correct diagnosis.

It is known that D-dimer increases with age, which means that it is more difficult to exclude VTE in elderly patients. By using an age-adjusted cut-off, the number of elderly patients in which VTE can be excluded can be increased with equal sensitivity [6].

The CLSI document H59-A “Quantitative D-dimer for Exclusion of Venous Thromboembolic Disease; Approved Guideline” [7] states the recommendations for test to be used at low/intermediate clinical probability: NPV

<table>
<thead>
<tr>
<th>D-dimer cannot be used safely in the following situations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with symptoms of VTE for &gt;14 days</td>
</tr>
<tr>
<td>Patients with hypofibrinolysis</td>
</tr>
<tr>
<td>Patients with suspected VTE receiving therapeutic heparin or oral anticoagulants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D-dimer should be used with caution in the following situations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients presenting with recurrent VTE</td>
</tr>
<tr>
<td>Elderly patients</td>
</tr>
<tr>
<td>Hospitalized patients</td>
</tr>
</tbody>
</table>

TABLE II: Limitations of the use of D-dimer for VTE diagnosis (modified from [4])

FIG. 2: Flowchart for ruling out or diagnosing VTE
≥98 % (lower limit of 95 % confidence interval ≥95 %) and sensitivity ≥97 % (lower limit of 95 % confidence interval ≥90 %) guarantee that a VTE patient is classified correctly. This is of utmost importance since disease that is not diagnosed has serious consequences.

A high specificity is, however, also preferred since a specificity that is too low will result in a highly variable number of unnecessary radiological examinations [8]. A hypothetic example is shown below. One hundred patients without VTE are tested with three D-dimer methods that all have identical high sensitivity but differ in specificities. The number of false positives (who in the real world would be subject to imaging procedures) and true negatives are calculated for each method.

Many POC D-dimer methods have high sensitivity and NPV, but the specificity varies from 44 to 64 % [9], which will affect the number of false positive results obtained and thus, the lower the specificity, the more radiological examinations.

### SCORE study

The SCORE study was performed in seven centers in southern Sweden to verify the combined strategy of clinical assessment score followed by local D-dimer test to exclude deep venous thrombosis (DVT) [10]. Patients with a suspected first episode of DVT (n=357) were prospectively recruited and pretest probability score according to Wells was estimated. If categorized as low, D-dimer was analyzed and in case of a negative result DVT was considered ruled out and no further diagnostic imaging for DVT was performed.

Patients with positive D-dimer or intermediate/high pretest clinical probability underwent objective testing with compression ultrasound or contrast venography. The main outcome was any recurrent VTE during a 3-month follow-up. The prevalence of DVT was 23.5 % in our local population. With this strategy, we could safely rule out DVT. Only one out of 110 (0.9 %) of the patients with negative D-dimer was diagnosed with DVT.
during follow-up. The strategy could obviate the need for diagnostic imaging in about 30 % of outpatients with a suspected first episode of DVT.

**Conclusion**

D-dimer can be used to exclude venous thromboembolism (VTE) in outpatients. Together with a low pretest probability for VTE, a negative D-dimer can safely rule out VTE in 30-50 % of patients with suspected VTE.

The use of D-dimer requires a method with particular performance characteristics. The sensitivity and NPV needs to be as close to 100 % as possible. With a high specificity the number of unnecessary radiological imagings can be diminished for the benefit of the patient and to improve logistics of the healthcare system. Thus, the clinical use of D-dimer requires a validated method.

**References**