Clinical Use of the D-dimer Assay

What are D-dimers?
- D-dimer is a marker of fibrinolysis.
- Coagulation results in the formation of the fibrin clot.
- Fibrinolysis is the subsequent degradation of the fibrin clot.
- D-dimer is a protein that is released into the circulation during the process of fibrin clot breakdown.
- It is a specific product of cross-linked fibrin degradation by plasmin.

**Figure:** 1  
[From: Wikimedia Commons, the free media repository]

Fibrin degradation is formed by the sequential action of three enzymes: thrombin, factor XIIIa and plasmin. Thrombin cleaves fibrinogen-producing fibrin monomers that aggregate into proteofibrils (fibrin mesh). Factor XIII then cross-links the fibrin proteofibrils at the D fragment site leading to cross-linked fibrin. Plasmin degrades the cross-linked fibrin to release fibrin degradation products (FDPs) and the D-dimer antigen.

Clinical aspects
- Measurement of D-dimer may indicate a disturbance of the balance between the two processes of coagulation and fibrinolysis.

Clinical applications
D-dimer measurement has been validated in the following:
- The exclusion of venous thromboembolism (VTE) in certain patient populations:
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Prediction of recurrent VTE and risk stratification of patients for VTE recurrence
- Diagnosis and monitoring of disseminated intravascular coagulation (DIC)

Choice of D-dimer test
At AMPATH we use an assay that uses the principle of Enzyme-linked-immunosorbent-assay (ELISA).

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It meets the following criteria:
- Cut-off determined by clinical studies.
- High sensitivity (high predictive negative value) and acceptable specificity.
- Access available 24 hours a day, 7 days a week.
- Rapid turnaround time: less than one hour.
- Quantitative results.

Patient and sample collection
- Avoid trauma or stasis when venesecting.
- Collect sample into a citrate tube (blue top).
- Tube must be adequately filled (minimum 4 ml).
- Sample is stable for up to 24 hours at room temperature.

Reference range
- Normal range: <0.50 mg/l (μg/ml = mg/l).

D-dimer as a diagnostic tool
- It has a high negative predictive value for the diagnosis of VTE, especially if used in combination with the pre-test clinical probability.
- In low-risk patients, the absence of elevated D-dimer virtually “rules out” thrombosis-negative predictive value.
- It has been shown to have the most reliable negative predictive value when used to exclude DVT in younger patients, without co-morbidity, previous history of VTE and with a short duration of symptoms.
- In this scenario, it helps to eliminate unnecessary tests, venograms or lung scans and is an efficient cost-effective strategy to screen and manage patients.
- The presence of D-dimer cannot “rule in” a diagnosis - positive predictive value.

Limitations
- False positive
  - Recent surgery
  - Haemorrhage
  - Trauma
  - Malignancy
  - Sepsis and severe infection
  - Advanced age ± co-morbidity
  - Pregnancy
  - Liver disease

- False negative
  - Distal DVT
  - Upper extremity DVT
  - Hypofibrinolysis
  - Symposium older than 7–10 days
  - Patient started on therapeutic heparin or oral anticoagulation
  - Small or insufficient clot size
  - Distal DVT
  - Upper extremity DVT
  - Hypofibrinolysis

D-dimer and disseminated intravascular coagulation (DIC)
- DIC is a complex syndrome, secondary to several underlying disorders, leading to the following:
  - Activations of coagulation and fibrinolysis
  - Consumption of platelets and coagulation factors
  - The diagnosis of DIC should encompass both clinical and laboratory information.
  - The DIC scoring system of the International Society for Thrombosis and Haemostasis (ISTH) provides an objective measurement of DIC.

ISTH diagnostic scoring system for DIC
- Scoring system for overt DIC.
- Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
- If yes: Proceed. If no: Do not use this algorithm.
- Order coagulation tests and score the tests.
A negative D-dimer test was associated with lower annual risk of DVT/PE confirmed. Evidence supports the use of clinical prediction rules to establish pretest probability of VTE before further testing can be done. A negative D-dimer test in patients with a low pretest probability of VTE is sufficient to exclude VTE and prevent unnecessary testing. D-dimer levels as a determinant of recurrence risk. D-dimer therefore appears to be a useful biomarker in evaluating clinical pre-test probability of VTE using a validated clinical prediction rule (CPR) and then stratified into clinical probability groups: low, intermediate and high. The Wells prediction rules for DVT and for pulmonary embolism have been validated and are frequently used to estimate the probability of VTE before performing more definitive testing on patients. It is important to note that D-dimer levels are commonly elevated for various reasons in hospitalised patients.

D-dimer and venous thromboembolism

Upon presentation, all patients should be carefully evaluated for clinical pretest probability of VTE using a validated clinical prediction rule (CPR) and then stratified into clinical probability groups: low, intermediate and high. The Wells prediction rules for DVT and for pulmonary embolism have been validated and are frequently used to estimate the probability of VTE before performing more definitive testing on patients. It is important to note that D-dimer levels are commonly elevated for various reasons in hospitalised patients.

Table 1: Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Model for Predicting Pre-test Probability of Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, plaster on lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Bed-ridden &gt;3 days, major surgery &lt; 12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Local tenderness along deep vein system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm larger than asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema on asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

If both legs are symptomatic, score the more severe side.

Clinical probability

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt; 1</td>
</tr>
<tr>
<td>Intermediate 1-2</td>
</tr>
<tr>
<td>High &gt; 2</td>
</tr>
</tbody>
</table>

Table 2: Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Model for Predicting Pre-test Probability of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent surgery or immobilisation</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Clinical probability

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt; 2</td>
</tr>
<tr>
<td>Intermediate 2-4</td>
</tr>
<tr>
<td>High &gt; 4</td>
</tr>
</tbody>
</table>

Table 3: Methods available for diagnostic work-up of deep vein thrombosis (DVT) and pulmonary embolus (PE)

<table>
<thead>
<tr>
<th>Method</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Clinical pre-test probability</td>
<td>Clinical pre-test probability</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>D-dimer</td>
<td>D-dimer</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Compression ultrasound (CUS)</td>
<td>Perfusion-ventilation (V-Q scan)</td>
</tr>
<tr>
<td></td>
<td>Serial ultrasound</td>
<td>Spiral CT</td>
</tr>
<tr>
<td></td>
<td>Impedance plethysmography</td>
<td>MRI</td>
</tr>
<tr>
<td>Invasive</td>
<td>Contrast venography</td>
<td>Pulmonary angiography</td>
</tr>
</tbody>
</table>

Diagnostic algorithm for deep vein thrombosis and pulmonary embolus

Table 4: Wells Prediction Rule Pre-test Probability (PTP)

<table>
<thead>
<tr>
<th>Pre-test Probability (PTP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate/High</td>
</tr>
</tbody>
</table>

DVT/PE testing

Low: <0.5 mg/ℓ

Intermediate: 0.5–1 mg/ℓ

High: >1 mg/ℓ

DVT/PE not confirmed

Repeat imaging or consider other diagnosis

DVT/PE confirmed

Start treatment

Consider other diagnosis

DVT/PE ruled out

Stop exam for DVT/PE

Discussion

D-dimer should not be used as a stand-alone test to exclude/confirm venous thromboembolism.

Evidence supports the use of clinical prediction rules to establish pretest probability of VTE before further testing can be done.

D-dimer levels as a determinant of recurrence risk

• Current evidence suggests that quantitative D-dimer assays measured at the end of warfarin therapy and then one month after its discontinuation can help determine the recurrence risk.
• Warfarin reduces thrombin generation in vivo, resulting in decreased D-dimer levels.
• A negative D-dimer test was associated with lower annual risk of recurrence than a positive D-dimer test.
• D-dimer therefore appears to be a useful biomarker in evaluating recurrence risk and should be used in context along with consideration of individual risk factors for recurrence, risk of bleeding and individual patient preferences.

References