D-dimer and DVT

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LEARNING OBJECTIVES

1. Define and understand the causes, dangers, and problems of deep venous thrombosis (DVT)
2. Revise the structure of the fibrinogen molecule and the origin of D-Dimers
3. Discuss the causes of D-Dimer elevation
4. Describe the correct use of D-Dimers in the exclusion of DVT
5. Discuss a test algorithm for using D-Dimers
6. Be able to interpret clinical cases
By way of introduction...

- Deep Venous Thrombosis.
Deep vein of Leg
Inferior Vena cava
Right heart
Lung
Causes of Deep Venous Thrombosis

1) **Unprovoked**: older individuals (> 70 years), obesity, hypertension, metabolic syndrome

2) **Provoked**: Surgery, trauma, immobilization, acute inflammation, pregnancy, oral contraceptives

3) **Malignancy**

4) **Anti-phospholipid syndrome**

5) **Hereditary**: FV Leiden, prothrombin mutation
• 80% of DVTs are asymptomatic
Thrombosis and Coagulation Tests

NOT HELPFUL

• PT, PTT and fibrinogen & platelet function tests) are not helpful and are frequently normal.

• Fibrinogen may be elevated, but this is not specific for thrombosis
D-Dimer analysis is used in the diagnosis of deep venous thrombosis (DVT).

It is used solely for its negative predictive value and this applies to cases with a low probability of DVT.
1) D-Dimers are a marker of fibrin breakdown

2) Measurement is by immunoassay and NOT by a clot-based or color assay

3) The D-dimer test has very good SENSITIVITY but a rather poor specificity.
D-Dimer Formation Requires the Sequential Action of:-

1. Thrombin
2. Factor Xllla
3. Plasmin
Fibrinogen is a trinodular elongated molecule with a central “E” domain and two outer “D” domains.
ACTION OF THROMBIN
Release of Fibrinopeptides
Non-covalent Interaction

Non-covalent Interaction
FIBRIN STRAND
Action of transglutaminase

<table>
<thead>
<tr>
<th>Glutamine side-chain on protein 1</th>
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</thead>
<tbody>
<tr>
<td>Lysine side chain on protein 2</td>
</tr>
</tbody>
</table>
Cross-linked protein with isopeptidyl bond.
TRANSGLUTAMINASE CROSS-LINKING
Following Action of *plasmin* on FIBRIN

**D-Dimers**
Following Action of *plasmin* on FIBRINOGEN

Fibrin Split Products
Causes of D-Dimer Elevation

This is why the specificity is low

- Thrombosis
- DIC
- Recent Surgery
- Trauma
- Malignancy
- Pregnancy
- Liver Disease
- Renal Disease
• In the exclusion of DVT, D-Dimers are **positive or negative** (perhaps *borderline*).

• In the exclusion of DVT a D-dimer is not “less positive” or “more positive” i.e., 0.6 mg/L and 2.0 mg/L are both *positive*, while 0.3 is *negative*. 
<table>
<thead>
<tr>
<th>Deep vein thrombosis</th>
<th>Score&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PE</th>
<th>Clinical signs or symptoms</th>
<th>Score&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>1</td>
<td>Clinical signs and symptoms of deep vein thrombosis</td>
<td>Clinical signs and symptoms of deep vein thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Paralysis or recent immobilization (plaster) of the lower limbs</td>
<td>1</td>
<td>PE as likely as or more likely than alternative diagnosis</td>
<td>PE as likely as or more likely than alternative diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Recently bedridden (&gt;3 days) or recent major surgery</td>
<td>1</td>
<td>Heart rate &gt;100 bpm</td>
<td>Heart rate &gt;100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Localized tenderness</td>
<td>1</td>
<td>Previous immobilization or surgery (within 4 weeks)</td>
<td>Previous immobilization or surgery (within 4 weeks)</td>
<td>1.5</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>1</td>
<td>Previous deep vein thrombosis or PE</td>
<td>Previous deep vein thrombosis or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Calf swelling</td>
<td>1</td>
<td>Hemoptysis</td>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Edema (symptomatic leg)</td>
<td>1</td>
<td>Malignancy</td>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Collateral veins</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous VTE</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis</td>
<td>-2</td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Modified from Wells (13).

<sup>b</sup> Probability of deep vein thrombosis: <1, low; 1–2, moderate; >2, high.

<sup>c</sup> Probability of pulmonary embolism: <2, low; 2–6, moderate; >6, high.
D-Dimer cannot be used safely if

1. Patients have symptoms of VTE for > 14 days
2. Patients with suspected VTE receiving anticoagulants

D-dimer cannot be safely used in these patients because it can be falsely negative even in the presence of thrombosis.
D-Dimer in Pregnancy

- Normal pregnancy causes the D-dimer concentration to increase by an mean absolute magnitude of 0.69 μg/mL and that ~70% of women had an increase in D-dimer that exceeded 0.50 μg/mL

<table>
<thead>
<tr>
<th>Time point</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>1st trimester</td>
<td>0.163</td>
<td>0.421</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>0.409</td>
<td>0.480</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>0.690</td>
<td>0.580</td>
</tr>
<tr>
<td>Post partum</td>
<td>0.208</td>
<td>0.297</td>
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*Clinical Chemistry* 51:5 825–829 (2005)
Types of D-Dimer Assays

• (a) **ELISAs**, quantitative and highly sensitive, but time-consuming

• (b) Manual latex-based immunoassays with visual end-point: semiquantitative and less sensitive than the ELISA

• (c) **Latex-based assays with immunoturbidimetric detection**: quantitative, very sensitive and rapid and can be performed on a regular coagulation instrument.
ELISA
LATEX PARTICLES
Light is scattered by a particulate sample, reducing its intensity.
Specimen for D-Dimer
• **Reference Range** < 0.46 mg/L (or μg/mL)

Some laboratories use μg/L (or ng/mL).

Therefore 0.46 mg/L = 460 μg/L

• Technically, most D-Dimers are measured as “FEUs” or *Fibrinogen Equivalent Units*

• An alternative is to use **D-Dimer units**. 1 D-Dimer unit is 2 FEU.

• **Potential confusion!**

• 0.46 FEU μg/mL = 460 FEU μg/L = 230 DDU μg/L (!!)
## CLSI Recommendations

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<tbody>
<tr>
<td>NPV</td>
<td>$\geq 98%$</td>
</tr>
<tr>
<td>95% lower limit CI of the NPV</td>
<td>$\geq 95%$</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>$\geq 97%$</td>
</tr>
<tr>
<td>95% lower limit CI of the Sensitivity</td>
<td>$\geq 90%$</td>
</tr>
</tbody>
</table>
CASE 1

- A 35 year old male patient is admitted to the trauma unit after a motor vehicle accident. He has an exploratory laparotomy. Venous thromboembolism is a concern in these patients, so the resident diligently sends blood for D-Dimer the next day.

- **D-Dimer: 4.0 μg/mL (H) (RR < 0.46)**

- **Conclusion:** Must have a deep venous thrombosis
CASE 2

- A 50 year old female, previously well, is seen in the ED with pain in her leg. The limb is not tender, and there is no obvious swelling. The patient has no history of VTE and no recent surgery

- D-Dimer: 1.0 µg/L (H) (RR < 0.46)

Conclusion: Must have a deep venous thrombosis. No further studies, Commence therapy
CASE 3

• A 60 year old male is seen in the ED with pain in his leg. The limb is very tender and edematous, and his calf is swollen. He was recently immobilized for a long period because of an ankle fracture

• D-Dimer: 0.3 mg/L (RR < 0.46)

• Conclusion: No deep venous thrombosis
CASE 4

• A 50 year old female, previously well, is seen in the ED with pain in her leg. The limb is not tender, and there is no obvious swelling. The patient has no history of VTE and no recent surgery

• D-Dimer: **0.3 mg/L (RR < 0.46)**

• **Conclusion: DVT is excluded**

• **Yes!!**
END
Self-Assessment Question #1

Which statement is true regarding the biology of D-Dimers?

a) They form from the action of thrombin on fibrinogen.

b) They form from the sequential action of thrombin, FXIIIa & plasmin on fibrinogen.

c) They form from the action of factor VIII.

d) They are a by-product of platelet action.

e) They are derived from erythrocytes.

Explanation: D-Dimer formation requires the sequential action of thrombin on fibrinogen, followed by factor XIIIa (to produce the mature cross-linked fibrin) and finally, plasmin cleavage of the fibrin.
Self-Assessment Question #2

A patient who has recently undergone major surgery is noted to have markedly elevated plasma D-Dimers on the first post-operative day.

a) The patient must be treated for venous thrombosis

b) Surgery & trauma will lower D-Dimer concentration

c) D-Dimers are unhelpful in this situation

d) Surgery is not a risk factor for venous thrombosis

e) The PT & PTT are better tests in this situation.

Explanation: Surgery will significantly elevate plasma D-dimers, hence invalidating their use in excluding venous thromboembolism. Surgery certainly is a significant risk factor for venous thrombosis. The PT and PTT have no role to play in excluding thrombosis.
Self-Assessment Question #3

A patient with painful lower leg (calf) swelling is examined in the emergency room. He gives a history of having had a deep venous thrombosis 10 years ago. He was recently immobilized because of hip surgery. His D-dimer concentration is within normal limits.

a) The patient can be discharged with no further therapy needed.

b) The patient should be immediately tested for inherited thrombophilia (tendency to form venous clots).

c) Platelet function testing is strongly indicated.

d) The patient has hemophilia.

e) The patient requires imaging studies to exclude a deep venous thrombosis.

Explanation: The patient is at significant risk for a deep vein thrombosis; he suffered a previous DVT and has had recent limb immobilization. He presents with clinical signs suggestive of a calf vein thrombosis. He therefore has a high “pre-test probability” for DVT. A D-dimer in the reference range therefore cannot be used to exclude a thrombotic event. He will require further workup, including imaging studies before a decision can be reached.