The Role Of D-Dimer In Venous Thromboembolic Disease And Disseminated Intravascular Coagulation

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Selected slides courtesy Mike Laposata MD, PhD
Statement On Conflicts Of Interest

• The speaker has no conflicts of interest to declare and will receive no remuneration for this presentation
D-dimæh
The Appropriate Level of Hemostasis

Bleeding  Balance  Thrombosis
## The Elements Of Hemostasis

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Coagulation Factors</th>
<th>Blood Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibrinogen</td>
<td>Goal: Form Clot And Plug Vascular Leaks</td>
</tr>
<tr>
<td></td>
<td>Factor II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tissue Factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor V</td>
<td></td>
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<tr>
<td></td>
<td>Factor VII</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Von Willebrand Factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor IX</td>
<td></td>
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<tr>
<td></td>
<td>Factor X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor XI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor XII</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor XIII</td>
<td></td>
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Clot Formation

Vessel Wall Injury → Platelet Adhesion → Platelet Aggregation → Fibrin Formation → Vessel Wall Contraction → Vessel Wall Contraction
Coagulation Factors

Why Have A Cascade of Multiple Factors

Diagram showing the coagulation cascade with various factors and their interactions, including:
- **XI** → **XII** → **XIIa**
- **XI** → **XIa**
- **IX** → **IXa**
- **VIII** → **Ca++** → **VII** → **VIIa**
- **Ca++** → **III**
- **V** → **LiPID** → **Ca++**
- **(II) Prothrombin** → **Thrombin (IIa)**
- **(I) Fibrinogen** → **Fibrin**

Additional elements include:
- **Platelet** changes
- **Vessel Wall** interactions

Phases indicated as **Intrinsic** and **Extrinsic**.
Fibrinolysis

Very Complex Process

Final Stage: Degradation Of Fibrin Clot By Plasmin

Creates FDP including D-Dimer
Only D-dimer is useful for DVT and PE
Deep Vein Thrombosis (DVT)

- DVT is a blood clot (called “thrombus”) 
- It occurs in major veins, usually in the legs 
- More than two million Americans develop DVT each year

Ileo-femoral DVT

Picture from US National Library Of Medicine MedlinePlus
Venous Blood Clot
Pulmonary Embolism (PE)

- If a clot reaches the pulmonary artery and lung, blood circulation and gas exchange are impaired.
- In the US each year 600,000 people develop PE.
- Mortality = 10%.

Picture from National Library of Medicine.
Deep venous thrombosis (DVT) and pulmonary embolism (PE) collectively called venous thromboembolic disease (VTE)
Clinical appearance
Symptoms of DVT and PE

DVT
- Pain, swelling and redness of the leg

PE
- Shortness of breath
- Chest Pain
- Cough
- Hemoptysis (coughing up blood)
So What’s The Problem?

The clinical presentation of both DVT and PE may be subtle or asymptomatic.

Radiologic studies are expensive and not always readily available.

Need a simple, fast, inexpensive test that is highly sensitive and preferably specific.
Who Gets DVT and PE

Hereditary causes    Acquired causes

The common elements:
Stasis
Vascular injury
Hypercoagulable states
The Acquired Risk Factors

- Surgery / Trauma
- Immobilization
- Malignancy
- Pregnancy
- Oral Contraceptives / ERT
- Lupus Anticoagulant
- IgG (or IgM?) Anticardiolipin Antibody
- Obesity
- Nephrotic Syndrome
- Polycythemia Vera
- Smoking
The Hereditary Risk Factors

**Activated protein C resistance**
- Nearly always the factor V Leiden mutation
- May be heterozygous or homozygous

**Prothrombin G20210A mutation**
- May be heterozygous or homozygous

**Hyperhomocysteinemia**
- Acquired form: From decreased intake of folate, vitamin B6 and/or vitamin B12
- Congenital form: From enzyme deficiencies in homocysteine degradative pathways
Diagnosis Of DVT and PE
Utility Of The D-dimer Assay
Diagnostic Modalities: DVT

Physical exam and history
- Unreliable

D-dimer
- Sensitive but not specific

Duplex venous ultrasonography
- Most used test.
- Sensitivity 95% for proximal DVT and 75% for symptomatic calf vein thrombosis

MRI
- Most useful for vena cava and pelvic TE
- Venography: Invasive and requires dye injection
Ultrasound: The most common test for the diagnosis of DVT
Diagnostic Modalities: Pulmonary Embolism

Physical exam and history
• Unreliable

D-dimer
• Sensitive but not specific. Hence limited role in patients already hospitalized

ECG
• Right ventricular strain

Venous ultrasound
• Confirmed DVT is surrogate for PE

Chest CT
• Superceding lung scanning

Lung scanning
• Radiolabelled albumin aggregates injected IV---Filling defect

MRI
• Gadolinium contrast agent

Pulmonary venography
Radiologic Diagnosis Of PE

Computed tomography
  non-invasive
  high sensitivity
  Time consuming
  Expensive
  Requires expert interpretation

Lung Scan (V-Q Scan)

Angiography

General disadvantage: Instrument and skilled staff have to be available
What is D-Dimer?

Activation of Coagulation

Thrombin → F XIII a

Fibrin

Plasmin

Activation of Fibrinolysis

Increased D-Dimer level in blood indicates ongoing Fibrinolysis to dissolve unwanted blood clot.

D-Dimer assay optimized for high sensitivity for rule out diagnosis

By-product of Fibrin: D-Dimer
But Remember: D-dimer may be positive in other conditions

For example, disseminated intravascular coagulation, liver disease, surgery, etc

Hence a positive test does not prove the existence of DVT/PE
Risk Stratification For DVT: Pre-test Probability: The Wells Score

<table>
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<th>Symptom</th>
<th>Score</th>
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<td>Active cancer (treatment ongoing or within previous 6 months or palliative)</td>
<td>1</td>
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<td>Paralysis, paresis or recent plaster immobilization of the lower extremities</td>
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<td>Alternative diagnosis as likely or greater than that of DVT</td>
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0 = low risk of DVT
1 – 2 = medium risk of DVT
≥ 3 = high risk of DVT
Evaluation Of DVT

Note: The major role for D-dimer is the low risk outpatient or in ED
## Well’s Criteria for Pulmonary Embolism

<table>
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<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE more likely than alternatives</td>
<td>3</td>
</tr>
<tr>
<td>Suspected PE</td>
<td>3</td>
</tr>
<tr>
<td>Tachycardia (pulse &gt;100 beats per minute)</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery or immobilization in last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior DVT or pulmonary embolism</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 points</td>
<td>Low (3.6% risk)</td>
</tr>
<tr>
<td>3-6 points</td>
<td>Moderate (20.5% risk)</td>
</tr>
<tr>
<td>&gt;6 points</td>
<td>High (66.7% risk)</td>
</tr>
</tbody>
</table>
Strategy For Diagnosis Of PE

Note major role for D-dimer is the low risk outpatient or in ED

Suspicion Of PE Risk Assessment

Low Risk Measure D-Dimer

- Negative D-Dimer PE Excluded
- Positive D-Dimer Perform Scan

Moderate To High Risk Perform Scan
Not all D-dimer assays are the same:
1. Qualitative or quantitative
2. Citrate vs Whole blood
   EDTA
3. Cutoff
4. Assay turnaround time
5. Analytical range
6. Sensitivity and specificity

In the past there were a number of poor performing D-dimer assays.
The Historical Gold Standard

VIDAS® D-dimer Exclusion Test

FDA approved for the rule out of both DVT and PE in low risk patients

In recent years a number of new D-Dimer tests have come on the market with excellent sensitivity
High Sensitivity Is The Major Consideration

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Diseased</th>
<th>Non-Diseased</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Cutoff</td>
<td>( A ) (True-Positives)</td>
<td>( C ) (False-Positives)</td>
</tr>
<tr>
<td>&lt; Cutoff</td>
<td>( B ) (False-Negatives)</td>
<td>( D ) (True-Negatives)</td>
</tr>
</tbody>
</table>

D-Dimer Assay Should Have A Minimum Number Of False Negative Results

Sensitivity = \( \frac{A}{(A+B)} \)
Specificity = \( \frac{D}{(C+D)} \)
NPV = \( \frac{D}{(B+D)} \)
PPV = \( \frac{A}{(A+C)} \)
What Are The Advantages Of A Point-Of-Care D-Dimer

D-Dimer is used for rule out of low risk patients

Emergency department

Large multi-specialty practice

Acute care clinic
## Point-Of-Care: ED Length Of Stay (Hours) For Patients Tested For D-Dimer Before and After POCT

<table>
<thead>
<tr>
<th></th>
<th>Before POCT D-Dimer</th>
<th>After POCT D-Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LOS</td>
<td>8.46</td>
<td>7.14</td>
</tr>
<tr>
<td>Median LOS</td>
<td>6.20</td>
<td>5.88</td>
</tr>
<tr>
<td>p</td>
<td>0.016</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Rate (percent) of hospital admission, discharge and admit to observe for patients before and after implementation of the rapid whole blood D-dimer test in the emergency department

<table>
<thead>
<tr>
<th></th>
<th>Before Implementation</th>
<th>After Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted</td>
<td>36.5</td>
<td>22.7</td>
</tr>
<tr>
<td>Discharged</td>
<td>42.9</td>
<td>50.2</td>
</tr>
<tr>
<td>Admit to observe</td>
<td>20.6</td>
<td>27.0</td>
</tr>
</tbody>
</table>
Issues Concerning Cutoff Values

• Many laboratory tests have established cutoff values (e.g. troponin, D-dimer, et al)

• Cutoff values are set to achieve a balance between a desired sensitivity and specificity

• Virtually never are both 100%

• In the case of D-dimer the cutoff should be optimized to maximize sensitivity without excessive loss of specificity

• You do not want to miss a VTE and will therefore accept a certain percentage of false positives
Issues Concerning Cutoff Values

- For an assay that yields continuous quantitative values over a linear range there is rarely an absolute “cutoff” value.

- Thus virtually all assays will have some false positive and false negative results.

- Example troponin I cutoff set at the 99th percentile of the normal range.

- By definition 1% of normals will be positive and some patients with myocardial infarction will fall below the cutoff.
Possible Solutions

1. Optimize the cutoff to balance sensitivity and specificity
2. Utilize a borderline range such that values are either negative, borderline or positive

MGH reporting of D-dimer values
- < 350: Negative
- 350-400: Borderline
- > 400: Positive

• How did we arrive at this: Internal study of hundreds of cases and literature review
• In the past there were a number of poor quality D-dimer tests on the market

• The Vidas D-dimer was the first assay to achieve an exclusion claim for DVT/PE and was the best assay on the market

• A negative Vidas D-dimer could be used to exclude DVT/PE with a relatively high degree of certainty in LOW RISK PATIENTS

• Today there are other D-dimer assays with an exclusion claim and other good assays without the claim
What Does An Exclusion Claim Mean

• To have an exclusion claim the company must perform a large and very expensive clinical study that is submitted to the FDA.
• Assays without exclusion claims may work just as well (or even better).
• Using an assay without an exclusion claim may require literature review, internal data and/or consultation with peer hospitals to establish the assay’s performance.
Conclusion

D-dimer tests that are equivalent in performance to the Vidas are acceptable and may be preferable in terms of:

- Sample type (WB vs Citrated plasma)
- Assay speed
- Specificity without loss of sensitivity
- Cost including QC and reagents
- Other menu: cardiac markers, NT-proBNP, etc
One MGH Study Of Triage Versus Vidas D-dimer

• 211 patients evaluated in emergency department for DVT/PE
• Assays agreed on classification in 200 cases (94.5%)
• 11 discrepant results
  All were Vidas positive, Triage negative
  All were ruled out for DVT/PE
• In this study Triage was equally sensitive but more specific

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vidas</td>
<td>100%</td>
<td>67.9%</td>
</tr>
<tr>
<td>Triage</td>
<td>100%</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

Caveat: In reality no assay is 100% sensitive

Disseminated Intravascular Coagulation (DIC)

DIC is always a response to an underlying process.

Patients exhibit a consumptive coagulopathy where they are both clotting and bleeding due to consumption of coagulation factors.

It results in a generalized activation of hemostatic mechanism.

The mortality in DIC is related to the underlying disease.
Conditions Associated with the Development of DIC

- Malignancies
- Massive tissue trauma
- Hemorrhagic shock
- Burns
- Severe infections
- Severe liver disease
- Amniotic fluid embolism
- Premature separation of the placenta
- Septic abortion
- Retained dead fetus
- Retained fetal products after delivery
- Complications of pregnancy
Disseminated Intravascular Coagulation (DIC)

- Infection
- Complications of Pregnancy
- Malignancy
- Massive Tissue Trauma

Fibrin Formation

Thrombin

Platelet Activation

Fibrin Degradation Products
Practical Laboratory Evaluation for DIC

Changes in DIC

<table>
<thead>
<tr>
<th>Parameter</th>
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Diagnostic and Therapeutic Approach to DIC

1. DIC risk factor present
   - No
   - Yes

2. Laboratory tests results consistent with DIC?
   - No
   - Yes

3. DIC is present
   - No
   - Yes

4. Is the patient bleeding?
   - No
   - Yes
   - Plasma and platelets, possibly cryoprecipitate for hemostasis, and packed red blood cells
   - No
   - Yes

5. Bleeding controlled?
   - No
   - Yes

Watch for bleeding
Case 1:

65 y/o man in intensive care unit with bleeding from multiple sites and respiratory failure

Any role for D-Dimer?
**Laboratory Evaluation for DIC**

<table>
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<th>Changes in DIC</th>
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Case 2:

25 year old woman in good health presents to ED with mild bilateral swelling in her legs following a 4 hour car ride

Role for D-dimer?
## Risk Stratification The Wells - Score

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This patient is a low risk rule out.
Case 3:

37 y/o woman, obese and heavy smoker presents to ED with acute shortness of breath and a painful edematous right leg. She has a history of 2 prior DVT’s

Role for D-dimer
Case 3:

Sounds high risk but criteria are not clear
Sounds like DVT and PE
D-dimer may be useful but ultrasound/ chest CT inevitable
Note 3rd DVT … Think hypercoagulable state
Case 4:

35 y/o man presents to 24 hour clinic with right lower leg pain. There is no swelling

What to do?
Case 4:

D-dimer useful but will take 2 days to get back from reference lab
Ultrasound not available on site

Sure would be nice to have a rapid rule out test here
Case 5:

57 y/o man presents with chest pain and shortness of breath. He is a heavy smoker.

Role for D-dimer
Case 5:

Considerations
PE
Acute coronary syndrome
Congestive heart failure
COPD exacerbation

Ideally want Tn, natriuretic peptide, D-dimer