Evolution of the D-dimer Assay in Clinical Medicine

Monet N. Sayegh, M.D.
Senior Medical/Clinical Consultant
Objectives

1. Describe VTE as DVT and PE
2. Discuss D-dimer and its role in DVT/PE
3. Well’s pre-test probability & clinical models
4. Describe evaluation of D-dimer assay results
5. Discuss RAPID Rule Out of PE in The ER
6. The relationship of PE & Healthcare Reform
Did You Know?

**VTE** is one of the most common causes of maternal death in developed countries.

40% of these patients had been seen by a physician in the weeks prior to their death.

The variability of presentation sets the patient and clinician up for potentially missing the diagnosis.
Venous Thromboembolism: Incidence & mortality

630,000 cases/y
100%

Survived >1h
89%

Diagnosis missed
63%

Diagnosed & treated
26%

Died undiagnosed
21%

Died despite Tx
<2%

Died <1h
11%

Survived

Undiagnosed

Treated & Survived

Total survivors
~66%

Total Death
~34% (214,200)

Hastings, Glen E. et.al. February 8, 2004
What do the symptoms look like?

Chest Pain
Chest Wall Tenderness

Back Pain
Shoulder Pain

Pain Upper Abdominal Hemopysis

Shortness of Breath. Painful Respiration

New Onset Wheezing

New Cardiac Arrhythmia
# Epidemiology of Chest Pain in Primary Care and Emergency Department Settings

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>% of Patients w CP</th>
<th>% of Patients w CP</th>
<th>% of Patients w CP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary care US</td>
<td>Primary care Euro</td>
<td>ED US</td>
</tr>
<tr>
<td>Musculoskeletal condition</td>
<td>36</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>19</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Serious CVD†</td>
<td>16</td>
<td>13</td>
<td>54(4.16mil)</td>
</tr>
<tr>
<td>Unstable CAD</td>
<td>1.5</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>10</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary disease‡</td>
<td>5</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td>16</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>8</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

# Incidence of VTE Disease: Age and Gender

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence of Thrombosis/100,000</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>1-2</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>50-59</td>
<td>30</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>60-69</td>
<td>100</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>70-79</td>
<td>258</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>&gt;80</td>
<td>747</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>
# VTE Predisposing Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilization &gt;4 days past 2 months</td>
<td>31</td>
</tr>
<tr>
<td>Cancer</td>
<td>20.5</td>
</tr>
<tr>
<td>Varicose Veins</td>
<td>20.0</td>
</tr>
<tr>
<td>Prior History of Thromboembolism</td>
<td>17.5</td>
</tr>
<tr>
<td>Surgery in the past 2 months</td>
<td>14.6</td>
</tr>
<tr>
<td>Estrogen Therapy</td>
<td>6.1</td>
</tr>
<tr>
<td>Postpartum</td>
<td>5.5</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>5.0</td>
</tr>
<tr>
<td>Travel ≥12 hours by car/ plane within 3 weeks</td>
<td>4.2</td>
</tr>
<tr>
<td>Known Thrombophilia (Antithrombin III deficiency, Protein C&amp;S deficiency &amp; Factor V Leiden)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Ann Inter Med 1997;126:454-457*
The Pathophysiology of Pulmonary Embolism
Types of Pulmonary Embolism

- **Massive Pulmonary Embolism**
  - Effects 4-4.5% of Patients
  - Mortality rate is 30-60%

- **Non-Massive Pulmonary Embolism**
  - 95.5-96% of the patients
  - <5% Mortality Rate
The classic triad of signs and symptoms of PE:

- <20% occurrence
- 60% with dyspnea
- 17% with chest pain
- 3% with hemoptysis

Diagnosing DVT/PE

- History and Exam
- Clinical Probability
- Clinical Outcome
- Guides Choices
- Diagnostic Studies
Clinical Models for Suspected VTE

Why Use a Clinical Model ("Probability")?

• Optimize predictive value of diagnostic test
• Reduce reliance on imaging
• Reduce the number of tests required

Principles of Clinical Assessment:

• Pre-test probability can be estimated
• Pre-test probability influences final outcome
## Wells pretest probability for PE

<table>
<thead>
<tr>
<th>Clinical finding*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (i.e., objectively measured leg swelling or pain with palpation of deep leg veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>PE as likely or more likely than an alternative diagnosis</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate more than 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (i.e., bedrest except for bathroom access for at least three consecutive days) or surgery in the past four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous objectively diagnosed DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (treatment for cancer that is ongoing, within the past six months, or palliative)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total points</th>
<th>Risk of PE</th>
<th>LR+</th>
<th>% PE Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 low</td>
<td>0.13</td>
<td>1-28</td>
<td></td>
</tr>
<tr>
<td>2-6 Mod</td>
<td>1.82</td>
<td>28-40</td>
<td></td>
</tr>
<tr>
<td>&gt;6 High</td>
<td>6.75</td>
<td>38-91</td>
<td></td>
</tr>
</tbody>
</table>

*Findings are listed in order of clinical importance. DVT = deep venous thrombosis; PE = pulmonary embolism; LR+ = positive likelihood ratio.

## Wells Pretest probability for DVT

<table>
<thead>
<tr>
<th><strong>Clinical finding</strong></th>
<th><strong>Points</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cancer (treated now or within 6 months or only palliatively)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paralysis, paresis or recent leg cast immobilization.</td>
<td>1.0</td>
</tr>
<tr>
<td>Recently bedridden &gt;3 days or major surgery within 4 weeks</td>
<td>1.0</td>
</tr>
<tr>
<td>Localized tenderness along distribution of the deep venous system.</td>
<td>1.0</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1.0</td>
</tr>
<tr>
<td>Affected calf 3cm bigger @ 10cm below the tibial tuberosity.</td>
<td>1.0</td>
</tr>
<tr>
<td>Pitting edema only on affected leg</td>
<td>1.0</td>
</tr>
<tr>
<td>Collateral nonvaricose superficial veins.</td>
<td>1.0</td>
</tr>
<tr>
<td>Alternative diagnosis is as probable or more than is DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total points</th>
<th>Risk of DVT</th>
<th>% DVT Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>High</td>
<td>75</td>
</tr>
<tr>
<td>1-2</td>
<td>Mod</td>
<td>17</td>
</tr>
<tr>
<td>&lt;1</td>
<td>Low</td>
<td>3</td>
</tr>
</tbody>
</table>

Goals of Diagnostic tests

- Provide reliable diagnosis
- Shortest Possible Time
- Least Discomfort To Patient
- Reasonable Cost
Standard Imaging and Laboratory Diagnostic Methods

**DVT**
- Ascending contrast venography
- Compression Ultrasound
- Duplex Scanning
- Impedance Plethysmography
- Doppler ultrasound

**PE**
- Pulmonary Angiography
- Ventilation-perfusion lung scan (VQ)
- Spiral computed tomographic angiography
- CXR(ABG,EKG,D-dimer)
Lower Extremities Imaging Modalities:

- Venography
- Impedance Plethysmography
- Duplex Doppler
- Compression Ultrasound
PE Diagnostic Tests:

**Definitive Imaging Modalities**
- Pulmonary angiography
- Ventilation–perfusion scanning
- Computed tomography
- MR Angiography or Real Time MR
- Emergency Transthoracic (TTE)
- Transesophageal (TEE) Echocardiography

**Non-Definitive Diagnostic Tests**
- D-dimer
- ABG
- CXR
- ECG
Why is VTE is Underdiagnosed?

Diagnosis is difficult!

History and clinical exam......
- Subjective
- Overlapping symptoms with other conditions

Imaging methods......
- Expensive ($600-2000)
- Not always available
- Poor turn-around-time
- Some methods are invasive and increase risk
- Require highly skilled personnel

Is imaging being used for all suspected patients? Can we afford it?
Chest Pain . . . is it from the Lung, or not?

Musculoskeletal Pain
Cardiomyopathy
Breast Abcess
Aortic Stenosis/ Dissection
Tietze's disease
Myocarditis
Pericarditis
Herpes
Zoster
Breast Cancer
Subdiaphrag Abcess
Lung Cancer
COPD/Emphysema
Pneumothorax
Anxiety
CHF/ACS
Blunt Chest Trauma
Empyema
Mediastinitis
Panic Attack
Pneumonia
Breast Implant
Mondor's Syndrome
GERD
Asthma
Septic shock
Mallory-Weiss
Sickle cell Anemia
Boerhaave Syndrome

Pulmonary Pain
How Can We Improve?

Send all suspected patients to imaging?

Not logistically or economically feasible

or

Utilize a simple, fast, non-invasive, economical diagnostic test for reliable exclusion of DVT/PE

D-dimer
What is D-dimer?

D-dimer is the specific breakdown product of a fibrin clot.

XL-FDPs cross-linked fibrin degradation products
The implications of D-dimer

- **D-dimer**
  - Presence of on-going coagulation activation & reactive fibrinolysis process

- **Fibrinogen** → **PLASMIN** → **Fibrin Clot**
  - Breakdown

- **Breakdown**
  - NO: D-dimer

- **D-dimer**
Fibrin Split Products (FSP) and D-dimer

- **General term for all fibrin-related products**
  - Measured with antibody to fibrinogen

- **FSP can be comprised of:**
  - Fibrinogen fragments
  - Incomplete fibrinogen molecules

- **D-dimer:**
  - Products generated during coagulation and fibrinolysis
  - Measured with antibody specific to D-dimer
  - D-dimer quantified whereas FSP are semi-quantified
  - D-dimer used to ascertain lower levels of active (or pathologic) Hemostasis
D-Dimer for Diagnosis of VTE Theory

- D-dimers form after coagulation generates and then starts to break down fibrin clot
- D-dimers become elevated in blood after the formation of VTE
- However, D-dimers also elevate in other pathological processes
- Therefore, D-dimer levels are NOT a specific marker of VTE (negative predictor only)
Non-VTE with Elevated D-Dimer
Positive D-dimer but Negative VTE

- Atherosclerosis
- Diabetes
- Anticoagulant
- Cancer
- Age
- Hemorrhage
- Hospitalized patients
- DIC
- Trauma
- Hepatic Disease
- Inflammation
- Pregnancy
- Recent Surgery
- Hematoma
# D-dimer Methods

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>present in venous thromboembolism (DVT / PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>ELISA</td>
<td></td>
</tr>
<tr>
<td>Manual latex agglutination</td>
<td></td>
</tr>
<tr>
<td>Red cell agglutination</td>
<td></td>
</tr>
<tr>
<td>Immuno-Turbidimetric</td>
<td></td>
</tr>
<tr>
<td>Clinical application</td>
<td>As an aid in the diagnosis of thromboembolic events</td>
</tr>
</tbody>
</table>
D-dimer Assay Methods Criteria

- Accurate values around cut off value
- Available 24 hours
- Available on routine equipment
- Rapid TAT (<60 min)
- Inexpensive
- Single sample measurement
- High sensitivity
- High Negative Predictive Value
D-Dimer Assay Methods: Methodological Problems

- Antibodies differ, therefore different results
- Different results from different tests
- Different standards and calibrators
- Different units and different names for units
  - D-dimer units
  - Fibrinogen Equivalence Units
  - ~1 FEU = ~ 2 D-dimer Units
- No reference standards
D-dimer Assay Methods: Assigned Cut Off Value

- Many of the automated assays now have a cut-off established by manufacturer and cleared by the FDA!
- Lab does not have to determine cut-off.
- Established for high NPV cutoff value.
- D-dimer assay must be verified that it works to manufacturer’s specification.
- Can exclude 30-40% of cases.
D-dimer Clinical Studies
All methods had comparable NPV’s

Table 1
Performance of Advanced d-Dimer, Stratus® CS d-dimer, STA Liatest® D-Di and VIDAS® d-Dimer New for exclusion of deep venous thrombosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Cut-off, mg/l (FEU(^a))</th>
<th>Sensitivity, % (95% CI(^b))</th>
<th>Specificity, % (95% CI(^b))</th>
<th>NPV(^c), % (95% CI(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced d-Dimer/CA-7000</strong></td>
<td>1.00</td>
<td>95.0 (88.7–98.4)</td>
<td>34.0 (28.1–40.3)</td>
<td>94.3 (87.2–98.1)</td>
</tr>
<tr>
<td></td>
<td>1.10</td>
<td>95.0 (88.7–98.4)</td>
<td>38.1 (32.0–44.5)</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>1.20</td>
<td>94.0 (87.4–97.8)</td>
<td>42.2 (35.9–48.7)</td>
<td>94.5</td>
</tr>
<tr>
<td><strong>Advanced d-Dimer/CA-560</strong></td>
<td>1.00</td>
<td>96.0 (90.1–98.9)</td>
<td>23.4 (18.2–29.2)</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td>1.10</td>
<td>96.0 (90.1–98.9)</td>
<td>29.5 (23.9–35.7)</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>1.20</td>
<td>94.0 (87.4–97.8)</td>
<td>35.2 (29.3–41.6)</td>
<td>93.5</td>
</tr>
<tr>
<td><strong>Stratus® CS d-dimer</strong></td>
<td>0.30</td>
<td>96.0 (90.1–98.9)</td>
<td>38.9 (32.8–45.4)</td>
<td>96.0</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>93.0 (86.1–97.1)</td>
<td>49.2 (42.8–55.6)</td>
<td>94.5</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>92.0 (84.8–96.5)</td>
<td>55.3 (48.9–61.7)</td>
<td>94.4</td>
</tr>
<tr>
<td><strong>STA Liatest® D-Di</strong></td>
<td>0.30</td>
<td>97.0 (91.5–99.4)</td>
<td>23.0 (17.8–28.7)</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>95.0 (88.7–98.4)</td>
<td>41.0 (34.8–47.4)</td>
<td>95.2</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>94.0 (87.4–97.8)</td>
<td>48.0 (41.5–54.4)</td>
<td>95.1</td>
</tr>
<tr>
<td><strong>VIDAS® d-Dimer New</strong></td>
<td>0.30</td>
<td>98.0 (93.0–99.8)</td>
<td>21.3 (16.4–27.0)</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>95.0 (88.7–98.4)</td>
<td>30.3 (24.6–36.5)</td>
<td>93.7</td>
</tr>
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<td></td>
<td>0.50</td>
<td>93.0 (86.1–97.1)</td>
<td>41.8 (35.5–48.3)</td>
<td>93.6</td>
</tr>
</tbody>
</table>

\(^a\) Fibrinogen Equivalent Units.
\(^b\) Confidence interval.
\(^c\) Negative predictive value.
The Future for the D-dimer Assay

Future looks very positive for the use of the D-dimer assay in other clinical situations:
- Following patients on anticoagulant therapy.
- Determine risk for recurrent VTE at the end of Oral Anticoagulation Therapy.
- Follow post-VTE after stopping Oral Anticoagulation Therapy.
- Follow cancer patients for risk of development of DVT.
- Assess VTE risk in patients prior to procedure.
- Clinical criteria and D-dimer will become more refined for use as an aid in the diagnosis of DVT and PE.
Comparison of postoperative survival after curative resection (Colon Cancer) between patients with two different preoperative plasma D-dimer levels.

Algorithm for suspected DVT by ACEP

DVT Clinical Algorithm

Pre-test Probability For DVT

Low

D-dimer positive

Perform emergency bedside ultrasound for DVT

Negative-Repeat in 5-7 days

Positive-Anticoagulate

D-dimer negative

DVT excluded

Moderate to High

Perform emergency bedside ultrasound for DVT

Negative-Obtain D-dimer

Positive-Anticoagulate

DVT excluded

Negative-DVT excluded

Positive-Repeat ultrasound in 5-7 days or obtain confirmatory study

Example of Algorithm for Diagnosis of PE

- Low Clinical Probability of embolism
- Highly sensitive D-dimer assay
  - Negative: Diagnosis ruled out
  - Positive: Ventilation-perfusion scanning or CT scanning

The D-dimer & Cardiac Marker Match

D-dimer + Cardiac Markers + NT-proBNP = Better Chest Pain Differentiation

Estimated 8 million ED visits per year for chest pain alone!
In Summary

- Patients with VTE have elevated D-dimer
- D-dimer assay can be useful in VTE diagnosis
- Assay can be cost effective
- The D-dimer assay has important limitations:
  - Can not be used as the only diagnostic tool for VTE
  - Can only be used to rule-out patients without VTE

- D-dimer test must be:
  - Automated and easy to perform
  - Rapid TAT
  - Available 24 hrs

- Test must be set up for:
  - High Negative Predictive Value
  - Maximum sensitivity
  - However, test is NOT standardized
In Summary

- Use only in ED or outpatient settings
- Clinical model for use ("Staging") must be established
- Should not routinely be used on in-patients
- Should not be used on patients receiving anticoagulation therapy
- Establish cut off value based on FDA cleared level or clinical outcome studies
The Evolution of D-Dimer

Lab Quality Results Brought Closer to the Patient

Nancy Gunther-Orsatti
For FY2013, Inpatient Prospective Payment System (IPPS) hospitals do not receive the higher payment for cases when one of the selected conditions is acquired during hospitalization (**BOLD** are new for FY2013)

<table>
<thead>
<tr>
<th>Hospital-Acquired Conditions (HACs)</th>
<th>Pay Not Made Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign Object Retained After Surgery</td>
<td>Manifestations of Poor Glycemic Control</td>
</tr>
<tr>
<td>Air Embolism</td>
<td>Surgical Site Infection, Mediastinitis, following Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>Blood Incompatibility</td>
<td>Surgical Site Infection Following Certain Orthopedic Procedures</td>
</tr>
<tr>
<td>Pressure Ulcer Stages III &amp; IV</td>
<td>Surgical Site Infection Following Bariatric Surgery for Obesity</td>
</tr>
<tr>
<td>Falls and Trauma</td>
<td>Surgical Site Infection Following Cardiac Implantable Electronic Device (CIED)</td>
</tr>
<tr>
<td>Catheter-Associated Urinary Tract Infection</td>
<td>Deep Vein Thrombosis and Pulmonary Embolism Following Certain Orthopedic Procedures</td>
</tr>
<tr>
<td>Vascular Catheter-Associated Infection</td>
<td>Latrogenic Pneumothorax with Venous Catheterization</td>
</tr>
</tbody>
</table>
Complete End To End Solution

BCS XP System

Sysmex CA-620 and 660 Systems

Sysmex CA-1500 System

Stratus CS
Menu Breadth: Select Assays Individually Based on Patient Need

Cardiac-Specific Assays
- hsTroponin I
- CKMB
- Myoglobin
- Cardiophase hsCRP
- NTproBNP

VTE* Assessment
- D-Dimer – with PE Exclusion Claim**

Pregnancy Assessment
- Quantitative ßhCG

* Venous Thromboembolism
** In conjunction with non-high Pre-Test Probability Score
Three Simple Steps to Process a Sample

Sample → TestPak → Start → Results
Thank you for your attention!