VTE Screening and Diagnosis: The Role of D-dimer Testing vs. Imaging
Paul Riley, PhD, MBA

Disclosures
- Salaried employee of Diagnostica Stago, Inc.

Learning Objectives
- Define and differentiate DVT, PE and VTE
- Learn PE prevalence, risk factors, mechanism of disease, symptoms, and clinical decision rules for risk stratification
- Explain the role of clinical decision rules and D-dimer in the diagnostic algorithm and their impact on imaging utilization

Presentation Outline
- Overview of Venous Thromboembolism (VTE)
  - Define deep vein thrombosis (DVT) and Pulmonary Embolism (PE)
  - Prevalence, risk factors, and treatment
  - Post-thrombotic syndrome
- Clinical decision rules
  - PERC Score
  - Wells Score
- Diagnostic algorithm (including use of D-dimer)
- Case studies
- Use of D-dimer vs. imaging techniques
- Recent clinical studies of different D-dimer assays; extending utility of the assay
  - Age adjusted cutoffs
  - Prospective use of the D-dimer

Overview of Venous Thromboembolism (VTE)
- VTE is one disease entity with two patterns of clinical presentation:
  - Deep Vein Thrombosis (DVT) is blood clot in leg veins
  - Pulmonary Embolism (PE) involves clot migrating from leg veins to the lung, associated with significant morbidity & mortality
- VTE affects 300,000 to 600,000 Americans annually, results in ~100,000 deaths
- ~30% of patients presenting with suspected VTE have PE, with 20 - 25% presenting as sudden death, diagnosed at autopsy (27,000 people)
- PE is the leading cause of preventable hospital death and maternal mortality in the US
- Treat with anticoagulation for customized length depending on patient needs, family history, comorbidities, bleeding risk, other medications, etc.

**Women’s Health Initiative Data 1993-2012**

In a study of women’s health based on Medicare claims, VTE rates are different between ethnic groups along with associated clinical factors.

**PE Incidence US vs. Outside US (Europe + Canada)**

Due to differences in clinical practices, there is a much higher number of patients suspected of PE in the US and prescribed imaging to confirm PE compared to outside US suggesting the higher rates of unnecessary imaging procedures in the US compared to Europe and Canada.

**Signs and Symptoms are Nonspecific**

- **DVT**
  - Pain tenderness and/or swelling in the calf or leg
  - Discoloration of the calf that can extend to the foot
  - Symptoms of PE

- **PE**
  - Difficulty breathing
  - Sharp chest pain worsened by taking a deep breath
  - Blood in the sputum
  - Rapid heart rate

**Anatomy of a Clot**

**Risk Factors for DVT and PE**

**Virchow’s Triad**

- Venous stasis
- Hypercoagulability of the blood
- Endothelial injury
Recently Paralysis, Active extremities

High Moderate Low

Localized palliative)

Alternative Collateral Pitting Calf ENTIRED system

D-dimer Formation

Well's Pre-Test Probability for DVT and PE

American College of Physicians PE Guideline

PE Rule Out Criteria (PERC Score)
D-dimer is Sensitive but Not Specific for PE

- Non-VTE causes of elevated D-dimer
  - Cancer
  - Rheumatoid arthritis
  - Conditions requiring intensive care
  - Advanced age (>65 years)
  - Developing DIC
  - Sepsis
  - Inflammation
  - Pregnancy

- The greatest utility of D-dimer is its negative predictive value

Diagnosis of DVT

- Difficult diagnosis as clinical symptoms (leg pain, etc.) are nonspecific

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<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Advantages</th>
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<tbody>
<tr>
<td>Contrast</td>
<td>&quot;Gold standard&quot;</td>
<td>Invasive, equipment, rare serious side effects</td>
</tr>
<tr>
<td>Impedance</td>
<td>Non invasive</td>
<td>Inadequate specificity and sensitivity</td>
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<tr>
<td>Compression</td>
<td>Non invasive</td>
<td>Not accurate for all DVT</td>
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Diagnosis of PE

- Difficult diagnosis as clinical symptoms (cough, dyspnea, etc.) are nonspecific
- Non specific tests (EEC, blood gas)

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<td>Sensitivity low overall</td>
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<td>Spiral Computed Tomography</td>
<td>Invasive, equipment, rare serious side effects</td>
<td>&quot;Gold standard&quot;</td>
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Imaging methods are considered the gold standard for DVT and PE diagnosis, but expose the patient to high amounts of radiation, are expensive, and only available in limited times and centers as they require specialized equipment and expertise to operate and interpret results.

Compression Ultrasound

Venography – Femoral Vein

CT Pulmonary Angiogram (CTPA)

Source: James Heilman, MD March 2011
DVT Case - Presentation

- 52 year old man presents in ER with dyspnea (shortness of breath), wheezing and chest tightness.
- Blood pressure is 145/88 mmHg, pulse rate >110 bpm and respiratory rate >30/min. Blood gas results reveal hypoxia (low oxygen) and cardiac exam found tachycardia (rapid heart rate).
- Clinical history includes long history of seasonal allergy and bone fracture 1 month prior with 3 weeks immobilization. A diagnostic workup is prescribed.

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<th>RESULT</th>
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<td>D-dimer (STA-Liatest D-Di)</td>
<td>0.38 μg/mL FEU</td>
<td>&lt; 0.50 μg/mL FEU</td>
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PE Case

- 39 year-old male with sickle cell trait presented to hospital with shortness of breath and pleuritic chest pain following flight from Trinidad to Jamaica via Miami.
- Blood pressure was 135/79 mmHg, pulse was 92 beats/min, respiratory rate was 24/min, O2 saturation was 85%, BMI 34 kg/m²
- Wells score was calculated as 3 (moderate risk for PE), D-Dimer test was >10,000 μg/L
- Diagnosed with bilateral PE, subQ enoxaparin started followed by rivaroxaban.

CTPA Overuse Study – Patients

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Patients were predominantly middle-aged females
Risk factors included:
- History of prior VTE
- Active malignancy
- Recent surgery or trauma
- Exogenous estrogen use (BCP, HRT)

PE positive by CTPA on initial ED visit: 18 (11.8%)
PE positive on 10-day follow-up: 0

D-dimer vs. Imaging for VTE Diagnosis

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CTPA Overuse Study – Results of Wells/D-dimer

13.8% of the “D-dimer” patients were found to be PE negative upon follow-up and did not require CT-PA.

CTPA Overuse Study - Results

Of the 110 (72%) patients with Wells score indicating PE is unlikely, only 35% had a D-dimer result. Why?

CTPA Overuse Study - PE Negative Patients

Results – Likelihood Ratio (LR) Analysis

CTPA Overuse Study - False Positives / True Negatives

Results of CT-PA time & ED Length of Stay (LOS)

CT-PA accounted for more than ½ of the ED LOS
- Median time for a CT-PA is 160 minutes (2 hrs 40 min.)
- Median ED LOS was 295 minutes (4 hrs 55 min.)
- Without an appropriate comparison group, impact of LOS by avoidance of CT-PA cannot be determined

Time waiting for potentially unnecessary imaging may contribute to ED crowding
- Associated with poor care in the ED
- Delays in medications
- Increased mortality rates
- Increased healthcare cost
Supporting Studies

- CT-PA requests had increased 56% between 2000 and 2005 w/o significant increase of PE positive rate (3.1%)
- Inappropriate use of CT-PA was suggested
- Guidelines using the Wells/D-dimer were placed in the order entry menu of a VA hospital
- Over 24 months on 252 patients (57% inpatient/43% outpatients) were enrolled (mostly men)
- PE prevalence was 19%
- Detection rate increased from 3.1% to 16.5% w/ CT-PA
- In patients with suspected PE, implementation of a clinical decision rule (Wells/D-dimer) significantly increased the yield of PE using CT-PA and improved its utilization


A review article of evidence supporting use of the algorithm below including clinical decision rule/D-dimer (validated in > 5000 consecutive patients) may reduce the number of unnecessary imaging tests by 20 to 30% with reductions in health care costs and complications.

Exclusion of PE – Large Management Trial

- A large trial of 5,141 patients from 9 centers in Europe and North America was conducted to evaluate performance of the STA Liatest D-d for exclusion of PE

The performance of STA Liatest D-di was confirmed for this application, and was the first D-dimer assay to receive clearance in a study design compliant with the latest and most stringent guideline on VTE exclusion by the CLSI.


Recent Clinical Studies Featuring D-dimer; Extending the Utility of the Assay

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Using D-dimer Prospectively - MAGELLAN

Patients with elevated baseline D-dimer have higher rates of VTE whether patient is taking rivaroxaban or enoxaparin; shows which patients would benefit most from receiving extended duration anticoagulation


Conclusions

- VTE/PE/DVT are a significant public health issues
- D-dimer assays are most useful when demonstrated to have high sensitivity and specificity
- Specificity saves healthcare dollars by preventing false positives
- Last, D-dimer assays with high negative predictive value (NPV) demonstrate the ability of the test to identify disease-free individuals
- D-dimer assay continues to be a mainstay of the clinical laboratory

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