VTE Screening and Diagnosis: The Role of D-dimer Testing vs. Imaging

Paul Riley, PhD, MBA
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 venous 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)**

- **Use of D-dimer vs. imaging techniques**

- **Recent clinical studies of different D-dimer assays; extending utility of the assay**
  - Prospective use of the D-dimer assay
  - Age adjusted cutoffs
  - Clinical probability cutoffs
Overview of Venous Thromboembolism (VTE)
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.

Monetary Cost of VTE

- Two thirds of cases occur in outpatients
- Diagnostics and prescription costs between $7,594 - $16,644 per patient
- Contributes well over $2 billion in total cost to the healthcare system annually

Risk Factors for DVT and PE

- Physical immobility
  - Long-distance travel – car or plane
  - Lengthy illness
- Recent major surgery
- Trauma
- Malignancy
- Pregnancy
- Oral contraceptive/hormone replacement therapy
- Genetic predisposition
  - Factor V Leiden
  - Prothrombin G20210A
  - Protein C, protein S, AT deficiency
  - Sickle cell trait
- Obesity
- Varicose veins
- Previous DVT

Stasis

Inflammation
According to PROLONG, anticoagulant treatment should be continued in patients with increased D-dimer levels one month after anticoagulant discontinuation.
VTE Risk, Gender, and Ethnic Background

- Seven centers collected demographic and baseline data from 2003-09 on 2002 whites and 395 blacks.
- When compared with whites, blacks had significantly higher proportion with PE (especially idiopathic PE in black women).
- Blacks had significantly higher mean BMI, higher proportion with hypertension, diabetes, chronic renal disease, and sickle cell disease.
- Whites had higher proportion with recent surgery, trauma infection, family VTE history, and inherited thrombophilia.
- Whites and blacks have differing demographic characteristics and baseline risk translating into distinct VTE risk.
- Transient VTE risk factors are lower in blacks but idiopathic VTE is higher.

Due to difference in clinician 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

**Risk Factors**

- **Hypercoagulable State**
  - Malignancy
  - Pregnancy and peri-partum period
  - Oestrogen therapy
  - Trauma or surgery of lower extremity, hip, abdomen or pelvis
  - Inflammatory bowel disease
  - Nephrotic syndrome
  - Sepsis
  - Thrombophilia

- **Vascular Wall Injury**
  - Trauma or surgery
  - Venepuncture
  - Chemical irritation
  - Heart valve disease or replacement
  - Atherosclerosis
  - Indwelling catheters

- **Circulatory Stasis**
  - Atrial fibrillation
  - Left ventricular dysfunction
  - Immobility or paralysis
  - Venous insufficiency or varicose veins
  - Venous obstruction from tumour, obesity or pregnancy

**Virchow’s Triad**

- Endothelial injury
- Hypercoagulability
- Stasis of blood flow

Post Thrombotic Syndrome

### Post Thrombotic Syndrome Frequency

<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Number of patients</th>
<th>Type of patient</th>
<th>Follow-up, years</th>
<th>Treatment</th>
<th>Frequency of PTS, %</th>
<th>All</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franzek et al., 1996 [8]</td>
<td>39</td>
<td>Low-risk patients (no previous DVT or PE)</td>
<td>12</td>
<td>54% with regular GCS</td>
<td>36</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Stain et al., 2005 [9]</td>
<td>406</td>
<td>Patients receiving VKAs after symptomatic VTE</td>
<td>5</td>
<td>GCS</td>
<td>43</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Ginsberg et al., 2001 [33]</td>
<td>110 (symptomatic DVT)/82 (asymptomatic DVT)</td>
<td>1 year after confirmed proximal DVT</td>
<td>1</td>
<td>GCS</td>
<td>27/4</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ginsberg et al., 2000 [26]</td>
<td>25 (proximal DVT) 66 (distal DVT) 164 (no DVT)</td>
<td>Hip or knee arthroplasty within previous 2–7 years</td>
<td>5</td>
<td>Different prophylactic regimens</td>
<td>4</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Schulman et al., 2006 [11]</td>
<td>897</td>
<td>Objectively verified DVT (cancer patients excluded)</td>
<td>10</td>
<td>VKAs</td>
<td>56</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

DVT = deep-vein thrombosis; GCS = graduated compression stockings; NR = not reported; PE = pulmonary embolism; PTS = post-thrombotic syndrome; VKAs = vitamin K antagonists; VTE = venous thromboembolism.

VTE Diagnostic Strategies and Scoring Algorithms
Diagnostic Strategy for VTE

- **Clinical assessment (with pre-test scoring system)**
  - Signs & symptoms of DVT/PE
  - Risk factors for DVT/PE
  - Potential alternative diagnosis
  - Used to calculate *pre-test probability* of disease
    - Stratifies patients into low, moderate or high categories

- **Quantitative & sensitive D-dimer testing**

- **Objective testing – Imaging studies**
  - i.e. CUS, CTPA, Venography

Physicians must rapidly assess patients with nonspecific symptoms such as chest pain, dyspnea and palpitations and decide if testing for PE is indicated.
# Well’s Pre-Test Probability for DVT and PE

## Well’s Pre-Test Probability for DVT

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within previous 6 months, or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for &gt; 3 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>ENTIRE leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt; 3 cm when compared with the asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely as or greater than that of DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>High pretest probability &gt;3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate pretest probability 1-2 points</td>
</tr>
<tr>
<td>Low pretest probability zero or negative points</td>
</tr>
</tbody>
</table>

## Well’s Pre-Test Probability for PE

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternate diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart Rate &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis (coughing up blood)</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in past 6 months, or palliative)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>High pretest probability &gt;6 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate pretest probability 2-6 points</td>
</tr>
<tr>
<td>Low pretest probability &lt;2 points</td>
</tr>
</tbody>
</table>

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## PE Rule Out Criteria (PERC) Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Meets Criterion</th>
<th>Does Not Meet Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50 y</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Initial heart rate &lt; 100 beats/min</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Initial oxygen saturation &gt; 94% on room air</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No unilateral leg swelling</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No hemoptysis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No surgery or trauma within 4 wk</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No history of venous thromboembolism</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No estrogen use</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

If the answer to all questions is NO, the patient has met PERC and no further testing is indicated.

CLSI Guideline on D-dimer Exclusion

Fibrinolysis and D-dimer Formation

accessed Aug 28, 2017
D-dimer Formation

Fibrinogen

Thrombin

Soluble Fibrin Monomer Complexes

Fibrin Monomer + fibrinopeptides

XIIIa

Fibrin clot

Plasmin

Fibrin Degradation Products

Pre-thrombotic

Post-thrombotic

Fibrinogen Degradation Products

D-Dimer

Fibrin Degradation Products
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
Quick Review of Statistical Terms

Clinical/Diagnostic Performance Stats

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False Negatives</th>
<th>False Positives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative Predictive Value (NPV)</strong></td>
<td><strong>DECREASED BY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Diagnostic Sensitivity** (TP/TP+FN):
  - ability of a test to detect disease
- **Diagnostic Specificity** (TN/TN+FP):
  - ability of a test to recognize *absence* of disease
- **Negative Predictive Value** (TN/TN+FN):
  - ability of test to identify disease-free individual among total population of patients with negative test result

D-dimer tests are best for VTE screening when they have high sensitivity, specificity, and NPV; quantitative immunoturbidimetric assays are the most likely to possess these characteristics as demonstrated in the literature.
Diagnosis of DVT

- Difficult diagnosis as clinical symptoms (leg pain, etc.) are nonspecific
- Imaging diagnostic methods:

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast venography</td>
<td>&quot;Gold standard&quot;</td>
<td>Invasive, equipment, rare serious side effects</td>
</tr>
<tr>
<td>Impedance Plethysmography</td>
<td>Non invasive</td>
<td>Inadequate specificity and sensitivity</td>
</tr>
<tr>
<td>Compression Ultrasound</td>
<td>Non invasive</td>
<td>Not accurate for all DVT</td>
</tr>
</tbody>
</table>
Difficult diagnosis as clinical symptoms (cough, dyspnea, etc.) are nonspecific

Non specific tests (EEC, blood gas)

Imaging diagnostic methods:

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Angiography</td>
<td>&quot;Gold standard&quot;</td>
<td>Invasive, equipment, rare serious side effects</td>
</tr>
<tr>
<td>Spiral Computed Tomography</td>
<td>Non invasive</td>
<td>Sensitivity low overall</td>
</tr>
<tr>
<td>Perfusion scanning</td>
<td>Non invasive</td>
<td>Many scans non diagnostic</td>
</tr>
</tbody>
</table>

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

CT Pulmonary Angiogram (CTPA)

Source: James Heilman, MD March 2011
D-dimer vs. Imaging for VTE Diagnosis
CTPA Overuse Study Overview

Title: Overuse of Computed Tomography Pulmonary Angiography (CTPA) in the Evaluation of Patients with Suspected Pulmonary Embolism in the Emergency Department

- Conducted at Hospital of the University of Pennsylvania
- Design was a prospective cohort study of adult ED patients. The objective was to assess the percentage of CT-PAs that could have been avoided by using the Well’s Score coupled with D-dimer or the PERC in patients with suspected PE.
- Primary outcome: diagnosis of PE
- Secondary outcomes: ED LOS and CT-PA time

CTPA Overuse Study Methods - 1

- 152 patients enrolled from HUP ED between 7 am - 7 pm, 7 days/week over 6 months
  - Aged 18 or over
  - Undergoing CT-PA for suspected PE
- Clinical info needed to calculate the Wells score or PERC was collected by treating physicians prior to knowledge of CT-PA result
- ED Length of Stay (LOS) determined
  - Time between room placement and bed request for admission or discharge
- CT-PA time determined
  - Time between initial order placement and initial radiology interpretation

Results of D-dimer (VIDAS) were obtained (cut-off 0.5 μg/mL)
- As part of ED evaluation
- As an outpatient in the health system w/in 24 hrs of ED presentation
- For patients not receiving D-dimer testing as part of their ED evaluation, D-dimers were performed from archived samples at a later date

Patients with negative CT-PAs were contacted after 90 days to determine if they had a subsequent diagnosis of PE

All evaluation and management decisions were independent of the study or study investigators

CTPA Overuse Study – Patients

<table>
<thead>
<tr>
<th>Most Common Signs and Symptoms</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>77.0%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>74.3%</td>
</tr>
<tr>
<td>Lower extremity pain or swelling</td>
<td>44.1%</td>
</tr>
</tbody>
</table>

- 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 CT-PA on initial ED visit            | 18 (11.8%)     |
| PE positive on 90-day follow-up                     | 0              |

PERC is recommended for patients with low pre-test probability by clinical gestalt

14 (9.2%) patients met PERC

All were PE negative on follow-up

Could have safely foregone CT-PA

Sensitivity findings were similar to other prospective evaluations

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

CTPA Overuse Study - Results

- Per the Well’s algorithm, all 72% of patients should have had a D-dimer test before CT-PA; Only 35% were tested
- Authors suggest some reservations about Wells leading to fewer D-dimers
  - Clinician concern over false-positive results
    - 81% had elevated D-dimer results of whom only 8 (9%) met the primary outcome of PE (results were similar in other studies)
    - Hence clinicians perform D-dimers on patients they are confident will be negative (lowest of the low PTP group)
  - Wells may not be entirely objective
    - “alternate diagnosis is more likely than PE”
    - Clinician judgment can move patients into higher of lower risk groups
  - Other variables that are more predictive are not included in Wells
    - non-CA thrombophilia, family history of VTE, pleuritic chest pain

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 - False Positives / True Negatives

Results – Likelihood Ratios

- Sensitivity and NPV are impacted by false-negatives
- Specificity is impacted by false-positives
- LR at 0 indicates strong likelihood that Wells or PERC is associated with absence of disease

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 (2hrs 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

CTPA Overuse Study - Discussion

- Use of CT in the US has increased dramatically
  - 14% of all ED patients undergo CT scans
    - **Economic impacts**
      - Impacts resource utilization
      - Increases cost
      - Increases ED LOS
    - **Patient impacts**
      - Patient exposure to IV contrast media
        - Contrast-induced nephropathy (11% risk)
        - Allergic reactions
        - Extravasation (rare)
      - Radiation exposure (increased CA risk)

“Validated clinical decision rules have the potential to reduce unnecessary CT-PA and adverse consequences.”

- Such rules were underutilized in the study setting
- One potential barrier was clinician feeling that gestalt is similar or superior to clinical decision rules
- Some physicians order “unnecessary” CT-PAs for fear of litigation
- Studies show only of physicians who are familiar with clinical decision rules use them in more than half of their patients
- Physician’s recall of the “rules” was low to moderate

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 in LA
- 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

Supporting Studies

Review article of evidence supporting use of the algorithm below including clinical decision rule/D-dimer (validated in > 5000 consecutive patients at LUMC) may reduce the number of unnecessary imaging tests by 20 to 30% with reductions in health care costs and complications. Effective management decision in 98% of patients.

Figure 1. Preferred diagnostic algorithm for clinically suspected acute PE. CDR, clinical decision rule; HS, highly sensitive.
Author’s concerns about increased use of CT-PA

- Use of CT-PA as screening test for PE leads to very low prevalence (<10%) of diagnosed PE
  - Low diagnostic yield seems consistent with a trend of overdiagnosis and observed rise in PE incidence with minimal change in mortality and lower morbidity

- Increasing fear of complications
  - Allergic reactions to IV contrast
  - Contrast-induced nephropathy

- Questionable clinical relevance of subsegmental emboli

CTPA Overuse Conclusions

There is a potential overuse of CT-PA in suspected PE patients and the potential impact of the Wells/D-dimer algorithm

- Today's ED study demonstrated that 9.2 and 13.8% of CT-PA procedure could be avoided by use of PERC and Wells/D-dimer, respectively\(^1\)
- Use of CT-PA in ED patients is increasing substantially (>70 million performed in US in 2007)\(^2\)
- Other studies show 20 to 30% of imaging studies may be avoided using a clinical decision rule and D-dimer\(^3\)

Recent Clinical Studies Featuring D-dimer; Extending the Utility of the Assay
A large trial of 1,141 patients from 9 centers in Europe and North America was conducted to evaluate performance of the STA Liatest D-di for exclusion of PE.

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

Baseline D-dimer and Recurrence Risk

Unprovoked VTE patients

DVT patients

The D-dimer is thought to be inaccurate for looking at VTE recurrence, but by tracking D-dimer over time after first incidence, quartile analysis shows increased risk of VTE or DVT for those patients with increased D-dimer values (higher quartiles).

Using D-dimer Prospectively - MAGELLAN

Subanalysis of larger study; 7,581 patients with elevated baseline D-dimer (any assay) have higher rates of VTE regardless of anticoagulant; shows which patients would benefit most from receiving extended duration anticoagulation

D-dimer independently associated with VTE risk

Using a clinical probability adjusted cutoff (2 x moderate probability cutoff for low probability patients) allows for potential to safely exclude VTE in a greater number of patients compared to AADD, and prevents unnecessary imaging procedures, especially for younger patients.

Conclusions

- VTE is a significant public health issue with well published diagnostic and treatment strategies but standardization not uniform.
- D-dimer assays most useful when demonstrated to have high sensitivity to detect all potential patients and specificity to rule out those patients with no DVT/PE.
- Specificity saves healthcare dollars by preventing false positives, resulting in fewer unneeded imaging procedures.
- D-dimer assays with high negative predictive value (NPV) demonstrate the ability of the test to identify disease-free individuals among a total population of patients with true negative test results.
- D-dimer assay featured in many multicenter clinical trials to extend the utility and applicability of the assay.