Objectives

- Define a venous thromboembolism (VTE).
- Describe how VTE is diagnosed or excluded with current testing guidelines.
- Review the types of D-Dimer assays and the significance of their results.

What is Venous Thrombotic Embolism? (VTE)

- Intravascular deposits of fibrin, RBCs and platelets
- Associated with hemostasis activation, venous stasis or vascular injury
- Deep-Vein Thrombosis (DVT)
- Pulmonary Embolism (PE)
Venous Thrombosis Statistics

- **Deep-Vein Thrombosis**
  - ~2 million Americans/year\(^1\)
- **300,000 - 600,000 cases of Pulmonary Embolism/year**
  - If untreated, ~30% of cases/year are fatal

\(^1\) [www.preventdvt.org](http://www.preventdvt.org)

Diagnosis of DVT/PE

- **Physical Symptoms**
  - **DVT**
    - Pain
    - Tenderness
    - Swelling
    - Edema
    - Discoloration of the skin
  - **PE**
    - Chest pain or discomfort
    - Suddenly getting short of breath
    - Dizziness
    - Coughing up blood
    - Rapid pulse or sweating
    - Getting anxious

Diagnosis of DVT/PE

- **DVT** Diagnosis
  - Imaging
    - Venous ultrasound (compression)
    - Venography
    - Impedence plethysmography (IPG)
  ✓ DVT Fact: Only 20-30% + by imaging study

- **PE** Diagnosis
  - Imaging
    - Pulmonary angiography
    - Helical computed tomography (HCT)
    - Perfusion scan
  - Positive for DVT venous ultrasound or venography
  ✓ PE Facts: 70%+PE, asymptomatic DVT
    2 hours from onset of symptoms to treat...

- Imaging Studies
  - Not 100% Sensitive
  - Expensive
  - Some are Invasive — Risk of Morbidity or Mortality
  - Often Not Available
Diagnosis of DVT/PE

- Diagnostic Algorithms
- Stratify Risk Based on Symptoms
  - Triage - Patient Care Protocol
  - Cost

Diagnosis of DVT/PE

- DVT Algorithm
  - Wells Pretest Probability (PTP) Index
    

<table>
<thead>
<tr>
<th>Wells' Criteria for DVT</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent surgery or severe trauma?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent severe illness, injury?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitting edema?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prominent veins?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf tenderness along the deep venous system?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf tenderness between the toes and the ankle?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient temperature?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous documented DVT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis to DVT?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- PE Algorithm
  - Wells Pretest Probability (PTP) Index

<table>
<thead>
<tr>
<th>Wells' Criteria for Pulmonary Embolism (PE)</th>
<th>Low</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Signs and Symptoms of DVT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE in V, Diagnosis, or Recurrence?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate &gt; 100?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilization at least 3 days, or surgery in the previous 4 weeks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous, objectively diagnosed PE or DVT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anasarca?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnourished?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment within 6 mo, or palliative?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

> 6  High probability
2-6  Moderate
<2  Low probability
Diagnosis of DVT/PE

• Diagnostic Algorithms
  • Stratify Risk Based on Symptoms
    – Triage - Patient Care Protocol
    – Cost

• High # of Imaging Studies Negative for D-Dimer....

Clinical Applications

Clinical Aspects

• D-Dimer is a specific marker of Fibrinolysis subsequent to Thrombosis

• Measurement of D-Dimer may indicate a disturbance of the balance between the two processes
Clinical Applications

• D-Dimer serves as an aid in the clinical diagnosis and management of three classes of thrombotic disorders:

  • Disseminated Intravascular Coagulation (DIC) - can be described as a loss of balance between the body's procoagulant (clot forming) and fibrinolytic (clot lysing) capacities

  • Arterial Thrombosis
    – M.I.
    – Stroke
    – Unstable Angina
    – Dissecting aneurism

  • Venous Thromboembolism (VTE) - Pathologic clots formed in veins due to hypercoagulability and associated with significant morbidity and mortality
    – Deep Vein Thrombosis (DVT)
    – Pulmonary Embolism (PE)
Additional Applications

• Sickle cell disease
• Liver disease
• Severe infections/sepsis
• Pre-eclampsia
• Conditions that activate hemostatic system (increase D-Dimer levels)
  • Trauma
  • Surgery
  • Malignancy
  • Inflammation
  • Pregnancy
  • Exercise
  • Rheumatoid Factor

Who is susceptible to venous thrombosis?

Talk about a brutal coincidence. Dr. John Royle will never forget that gray August morning in 1993 when the Melbourne vascular surgeon was climbing the 40 steps between his consulting rooms and operating theatre at Austin Hospital. It was a routine walk for the then 60-year-old who had only the day before flown back from a conference in Hawaii, where he had presented a paper suggesting Australians could be at greater risk of flight-related deep vein thrombosis (DVT) than previously believed.

The phenomena had already struck Royle personally; one of his colleagues had recently died after a long-haul flight and the father of one of his daughter's schoolmates had been struck down by a fatal DVT soon after returning home on a flight from Europe. But Royle's customary stride was interrupted by a sharp, cramping pain in his left calf. Ten seconds. Maybe 20. That’s all it took for him to recognize the telltale signs of a thrombus (blood clot) in a deep vein of his leg which he knew had a risk of breaking free from the vein wall and traveling to his heart or lungs, where it could block the flow of blood and cause a fatal pulmonary embolism.

Royle took a detour to the hospital’s lab for an ultrasound, where it was found he had a six-centimetre long clot in his leg which, although not life-threatening, had a risk of lengthening.

Royle was immediately hooked up to a drip of an anti-coagulant drug and returned to the hospital for five days.
Deep Venous Thrombosis

- **Proximal thrombosis** – thrombi are present above the knee
- **Distal thrombosis** – thrombi confined to the calf veins

Deep Vein Thrombosis

- Approximately 1 per 1,000 people each year are affected by DVT
- Incidence increases with age
- Hospitalization for 5 to 7 days
- 50% of patients with DVT are asymptomatic

Evaluation of DVT

- Clinical suspicion confirmed by objective tests
  - **Non-Invasive** - Compression Ultrasound (CUS)
    - < 100% sensitivity
    - Operator dependent
  - **Invasive** - Venography – “gold standard”
    - Risk of thrombosis
Pulmonary Embolism

- Dislodged blood clot entering the pulmonary circulation
- Accounts for 10% of all hospital deaths
- Estimated 200,000 die of PE each year
- 80% of patients who die from PE do so within the first 2 hours of symptom onset

Evaluation of PE

- Ventilation-perfusion (V/Q) lung scans
  - Initial diagnostic procedure of choice
  - Diagnostic in only 20-30%
- Pulmonary angiography
  - Diagnostic gold standard
  - 3% morbidity/0.5% mortality
- Spiral CT and MRI
  - Becoming more widely used
Diagnosis of DVT/PE

- PE onset of symptoms - 120 minutes to treat
  40 + minutes - decide to go to ER
  20 minutes - admission and evaluation
  15 minutes - order blood work, draw & transport to lab
  15 minutes - centrifuge
  Time remaining ?

10 minute or 35 minute assay?????

Current Testing Algorithms

- Clinical Probability - risk of VTE using a clinical scoring system
- Quantitative D-Dimer - High NPV and sensitivity
- Non-invasive diagnostic tests
  - ultra-sound
  - V/Q lung scan
  - MRI
  - spiral CT

D-Dimer as a Diagnostic Tool

- The presence of D-Dimer cannot “rule in” a diagnosis - Positive Predictive Value
- The absence of elevated D-Dimer virtually “rules out” thrombosis - Negative Predictive Value
Purpose of the D-Dimer Assay

- **Patients w/VTE symptoms**
  - 75% - VTE
  - 25% + VTE
  - 70% + DVT
  - 30% + PE
  - 10% Fatal

---

Annals of Emergency Medicine

  - Level B recommendations
  - “In patients with a low pretest probability of PE, use the following tests to exclude PE: A negative quantitative D-Dimer (turbidimetric or ELISA)”

- **Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting With Suspected Pulmonary Embolism**
  - Level B recommendations
  - “In patients with a low pretest probability of PE, use the following tests to exclude PE: A negative quantitative D-Dimer (turbidimetric or ELISA)”

---

Diagnosis of DVT/PE

- **Diagnostic Algorithms**
  - Fastest Triage of the Patient
  - Providing Optimal Care
  - Apply GOMER...

  **GOMER?**

  (Get Out of My Emergency Room)
Algorithm Using D-Dimer in PE/DVT

Suspected PE or DVT

Pretest Probability Index for PE or DVT

High

Appropriate Diagnostic Imaging Studies

Algorithm Using D-Dimer in PE/DVT

Suspected PE or DVT

Pretest Probability Index for PE or DVT

Low - Moderate

Perform D-dimer

High

Appropriate Diagnostic Imaging Studies
Algorithm Using D-Dimer in PE/DVT

Suspected PE or DVT

Pretest Probability Index for PE or DVT

Low - Moderate

Perform D-dimer

High

DVT/PE Excluded

Appropriate Diagnostic Imaging Studies

Financial Impact Using D-Dimer

- Reduced the number of ultrasound by 20%\(^1\)
- Minimized risk of inappropriate therapy
- Improved diagnosis of PE
- Global cost savings of 10% for DVT\(^2\) and PE\(^3\)


Diagnosis of DVT/PE

- Hemostasis Marker
  Screening Assay to Rule Out VTE

D-Dimer

Formation of D-Dimer

D-Dimer is Elevated with:
- DVT and PE
- Disseminated intravascular coagulation (DIC)
- Other states – Cancer, Pregnancy, Age

Hemostatic Balance

- Under normal physiological conditions there is a balance between:
  - Fibrin Formation (Thrombin mediated)
  - Fibrin Dissolution (Plasmin mediated)
Fibrin Degradation Products

• The action of plasmin on cross-linked fibrin generates a heterogeneous mixture of fragments

D-Dimer

• The smallest of the crosslinked fibrin degradation products (XL-FbDP) generated by plasmin-mediated lysis of crosslinked fibrin
Reporting D-dimer Results
Due to the variable specificity of D-Dimer antibodies, different commercial kits report in different units. Lack of an International Reference Standard.

Laboratory Interpretation

Clinical Decision Threshold

- Problem: Derive a qualitative (positive or negative disease state) clinical answer from quantitative data

- Solution: Select a cut-off value to distinguish normal from abnormal
Sensitivity and Specificity

- Diagnostic Sensitivity – the ability of a test to recognize the presence of disease
- Diagnostic Specificity – the ability of a test to recognize the absence of disease

The “Perfect” Diagnostic Test

- Discriminates the population with disease from the population without disease perfectly
- Achieves a sensitivity and specificity of 100%

More Common Case

- For most diagnostic tests there is some overlap in the populations with and without disease
**Typical Case**
For every possible clinical cut-off point you select there will be the following cases:

- **Individuals with the disease classified as positive** (TP = True Positive)
- **Individuals with the disease misclassified as negative** (FN = False Negative)
- **Individuals without disease classified as negative** (TN = True Negative)
**Typical Case**
For every possible clinical cut-off point you select there will be the following cases:

- Individuals with the disease classified as positive (TP = True Positive)
- Individuals with the disease misclassified as negative (FN = False Negative)
- Individuals without disease classified as negative (TN = True Negative)
- Individuals without disease misclassified as positive (FP = False Positive)

**TYPES OF D-DIMER ASSAYS**

**Recommendations for Selection and Use of D-Dimer Assay for Exclusion of DVT / PE**

- Quantitative assay with a large measuring range
- Time to result < 15 min, available at any time
- Evaluated in appropriate clinical trials
- Validated - like sampling of patient population
- High sensitivity (100% NPV)
- Validated Cut-off value – If a D-Dimer method is used in the evaluation of VTE, has the method been validated for this purpose?
- Impact on preanalytical variables – i.e. Iemia, hemolysis

3. CAP Checklist Oct 2006 – HEM.37925: "the cut-off value for exclusion of these conditions should be validated..."

**HEMOSTASIS INNOVATION IS HERE**
Types of D-Dimer Assays

Generation:

1. 3-hour ELISA
   - Sensitive
   - Quantitative
   - Manual (Robotic)
   - Requires multiple incubations
   - Takes too long...
   - Not practical for PE...

2. Semi-Quantitative/Qualitative
   - Easy to use
   - Short turn-around-time
Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative/Qualitative
   - Easy to use
   - Short turn-around time
   - Qualitative – no cut-off
   - Manual: risk of operator error
   - Limited sensitivity
   - Intended use claim: “Aids in assessment and evaluation...DIC, DVT & PE”
   - Cannot be used for the exclusion of DVT or PE

Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
   - Intended use claim: “For exclusion of DVT and PE...”
   - Mostly automated procedure
   - Quantitative results
   - Good NPV and sensitivity

**NEW**
HEML7435 Phase 1 N/A YES NO

If a D-dimer test is not used for exclusion of deep vein thrombosis and/or pulmonary embolism, does the laboratory inform clinicians that the test should not be used to exclude deep vein thrombosis or pulmonary embolism?

NOTE: This disclaimer may be included in the laboratory report, or in a written memorandum to clinicians. The former is preferable.
Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA

• Intended use claim: “For exclusion of DVT and PE…”
• Mostly automated procedure
• Quantitative results
• Good NPV and sensitivity
• Turn-around-time – 20 min.
• Too long for PE
• Manually pipette & load sample

Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
• 15 minute turn-around-time
• Quantitative

Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
• 15 minute turn-around-time
• Quantitative
• “Aid in the assessment & evaluation of DIC & PE (DVT not referenced)”
• No cut-off - uses normal range
• Manually load blood & cartridge
• Runs one at a time…
Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
4. Quantitative & Automated on Hemostasis Analyzers

KEY:
- Antigen-antibody complex
- Cross-linked D-Dimer

Abs

TIME
Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
4. Quantitative & Automated on Hemostasis Analyzers
   - Available on most Hemostasis analyzers
   - Rapid
   - Minimized Operator Error
   - Intended Use Claims – Vary
   - Different Sensitivity, NPV & Specificity

Types of D-Dimer Assays

Generation:
1. 3-hour ELISA
2. Semi-Quantitative
3. Rapid ELISA
4. Quantitative & Automated on Hemostasis Analyzers
5. High Specificity, Automated & Quantitative

Elevated D-Dimer Levels

- VTE
- DIC
- Pregnancy
- Cancer
- Age
**Elevated D-Dimer Levels**
- VTE
- DIC
- Pregnancy
- Cancer
- Age

**Falsely Elevated Rheumatoid Factor**

Rheumatoid Factor (RF)
- RF is a protein which binds to the Fc portion of antibodies.
- Patients with RF will have falsely elevated or false positive immunoassay results.

**Rheumatoid Factor (RF)**
- Incidence of RF
  - 6.5% of an unselected population*
  - Age-related, varying 5-10% depending on population age


Therefore it is hypothesized that 5-10% of D-dimer false-positives may be due to RF interference…
Removing RF Interference

- Cleaving the Fc portion off the antibody eliminates RF interference.
Types of D-Dimer Assays

- Generation:
  - 3 hour ELISA
  - Semi Quantitative
  - Rapid ELISA
  - Quantitative & Automated on Hemostasis Analyzers
  - High Specificity, Automated & Quantitative

More Specific
- Reducing False Positives
- Reducing Imaging Studies on VTE “Negative” Patients
- Cost Savings for the Hospital

Note on Statistics

- Sensitivity
  - True Positives vs. False Negatives
  - Want 100%
- Negative Predictive Value (NPV)
  - True Negatives vs. False Negatives
  - Want 100%
- Specificity
  - False Positives vs. True Negatives
  - The higher the better

Performances of the Hemostasis D-dimer HS assay for the exclusion of venous thromboembolism

http://www.clpmag.com/graphics/mags/0507/pt_fig01.gif
Performance Data

N= 300 (78 VTE+, 222 VTE-)  

<table>
<thead>
<tr>
<th></th>
<th>HemosIL D-Dimer HS 500</th>
<th>HemosIL D-Dimer</th>
<th>VIDAS DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>%NPV (95% CI)</td>
<td>100% (96.5-100)</td>
<td>100% (95.4-100)</td>
<td>100% (95.3-100)</td>
</tr>
<tr>
<td>% Sensitivity (95% CI)</td>
<td>100% (95.4-100)</td>
<td>100% (95.1-100)</td>
<td>100% (95.4-100)</td>
</tr>
<tr>
<td>% Specificity (95% CI)</td>
<td>46.8% (40.1-53.6)</td>
<td>35.9% (29.6-42.6)</td>
<td>34.7% (28.4-41.3)</td>
</tr>
</tbody>
</table>

*De Moerloose Performances of HemosIL D-dimer HS Assay for the Exclusion of Venous Thromboembolism. 2005 ISTH 2361-2363.

Interferences

- Hemoglobin
- Bilirubin
- Lipemia
- Rheumatoid Factor

Lack of Standardization

- No international standard.
  - D-dimer “monomers”, “dimers” as calibrators
  - Pooled patient plasma - harmonization factor
  - ISTH SSC 1993-1997
- Antibody reactivity
- Matrix effect – Assay and Instrument
- Measurement units
  - D-dimer units or FEU units
Reporting D-dimer Results

Due to the variable specificity of D-Dimer antibodies, different commercial kits report in different units.

Lack of a International Reference Standard.

D-dimer units
(DD) 250 ng/ml

Fibrinogen Equivalent Units (FEU) 500 ng/ml

Formula: 1 FEU = 2 D-Dimer units

EXCLUSION CLAIM

EXCLUSION CLAIM

HEMOSTASIS INNOVATION IS HERE

HEMOSTASIS INNOVATION IS HERE
EXCLUSION CLAIM

**Exclusion of Venous Thromboembolism** - a claim that can apply to any method, the results of which can reliably exclude venous thromboembolism (VTE). **NOTE 1:** Regarding a D-Dimer assay, studies must demonstrate that the negative predictive value (NPV), sensitivity, and coefficient of variation at the threshold have sufficient power to exclude VTE when the test is applied to patients judged to have a low or intermediate probability of VTE determined using a posttest probability (PTP) scoring algorithm. **NOTE 2:** As defined by the US Food and Drug Administration, a D-dimer assay with an exclusionary claim is used in conjunction with a PTP assessment to exclude the presence of a pulmonary embolism/thrombus and/or a deep vein/thrombosis. In addition to validating the assay's threshold and establishing assay sensitivity, specificity, and NPV's compared with imaging studies, the clinical study must include patient follow-up to obtain clearance.

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**HEMOSTASIS INNOVATION IS HERE.**

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EXCLUSION CLAIM

**Single-Center Management Study**

**Enhancing Diagnosis of DVT and PE**

An outcome study was performed on 300 frozen samples from patients suspected of PE or DVT (15% frequency of VTE). Positive samples were confirmed through standard imaging techniques. Patient samples were also tested with a traditional automated, latex-based method and an ELISA assay, using manufacturer recommended cut-off values. Results, shown below, are based on a 230 ng/ml, D-DU cut-off value.

<table>
<thead>
<tr>
<th>VTE Performance</th>
<th>REMESIS D-Dimer HS</th>
<th>Traditional Automated Latex</th>
<th>ELISA Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples (n)</td>
<td>300</td>
<td>207</td>
<td>300</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>100 (95.1–100)</td>
<td>100 (95.1–100)</td>
<td>100 (95.1–100)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>68.8 (61.1–76.4)</td>
<td>55.1 (50.5–60.6)</td>
<td>54.7 (50.4–60.3)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>100 (95.1–100)</td>
<td>100 (95.1–100)</td>
<td>100 (95.1–100)</td>
</tr>
</tbody>
</table>

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**HEMOSTASIS INNOVATION IS HERE.**

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EXCLUSION CLAIM

**Multi-Center Management Study**

**Excluding DVT and PE**

A multi-center management study was performed at four hospitals on 668 samples from patients suspected of PE (n=361) or DVT (n=307). Patient management was based on a study-specific diagnostic algorithm involving PTP scoring. Positive samples were confirmed through standard imaging techniques. Negative results were confirmed at a three-month follow-up.

For patients with a negative D-Dimer test result and a moderate PTP, physicians determined if a three-month follow-up or imaging techniques were required. The overall prevalence in the total population of samples was 10.1% (66/668) for PE and 20.2% (136/668) for DVT. Results, shown below, are based on a 230 ng/ml, D-DU cut-off value for the AGI TOP.
EXCLUSION CLAIM

DVT PERFORMANCE

<table>
<thead>
<tr>
<th>Samples (n)</th>
<th>ALL SAMPLES</th>
<th>HIGH PTP</th>
<th>LOW &amp; MODERATE PTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>100 (96/0.9)</td>
<td>100 (98/0.9)</td>
<td>100 (94/0.9)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96.2–100</td>
<td>97.2–100</td>
<td>97.2–100</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>100 (96/0.9)</td>
<td>100 (98/0.9)</td>
<td>100 (94/0.9)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>96.2–100</td>
<td>97.2–100</td>
<td>97.2–100</td>
</tr>
</tbody>
</table>

EXCLUSION CLAIM

PE PERFORMANCE

<table>
<thead>
<tr>
<th>Samples (n)</th>
<th>361</th>
<th>28</th>
<th>333</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>100 (98/0.9)</td>
<td>100 (100/1)</td>
<td>100 (98/0.9)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96.2–100</td>
<td>99.2–100</td>
<td>99.2–100</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>100 (98/0.9)</td>
<td>100 (100/1)</td>
<td>100 (98/0.9)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>96.2–100</td>
<td>99.2–100</td>
<td>99.2–100</td>
</tr>
</tbody>
</table>

EXCLUSION CLAIM

Multi-Center Management Study to support DVT and PE Exclusion

A prospective management study was conducted to demonstrate the usefulness of Hemostil D-Dimer HS to exclude DVT and PE, in conjunction with a pretest probability score (Wells model). The 4 sites involved were:

- Dimitrios Scarvulis, MD; University of Ottawa, Ottawa, Canada
- Gualtiero Palareti, MD; University Hospital S. Croce-Malpighi, Bologna, Italy
- Jong R. Wu, PhD; Duke University Medical Center, Durham, NC, USA
- Pierre Toulin, MD, PhD; CHU Hospital Cimiez, Nice, France
EXCLUSION CLAIM

The patients were enrolled from consecutively eligible outpatients presented to the emergency department with first suspicion of VTE (either DVT or PE). The patients underwent a standard diagnostic algorithm that began with a pretest probability score and D-Dimer testing using the hospital's validated D-Dimer assay. Then, imaging tests were conducted to confirm or exclude the diagnosis of DVT or PE. Patients with no conclusive diagnosis underwent venography, angiography, or other appropriate testing defined by the institution in order to be diagnosed positively or negatively with DVT or PE. Patients excluded for VTE at the hospital admission were then followed up for 3-months. The algorithm is shown in the following figure.

HEMOSTASIS INNOVATION IS HERE.

Hemast D-Dimer HS
510(k) Summary (Summary of Safety and Effectiveness)

Applicant Contact Information:
Applicant: Instrumentation Laboratory Co.
Address: 113 Hartwell Avenue
Lexington, MA 02421
Contact Person: Carol Marble, Regulatory Affairs Director
Phone Number: 781-861-4465
Fax Number: 781-861-4307
Preparation Date: August 15, 2007
Device Trade Name: Hemast D-Dimer HS

Regulatory Information:
Classification: Fibrisol and Fibrom Split Products, Antigen, Antisera, Control
Device Class: Class II
Regulation No.: 884.7220
Product Code: DAP
Panel: Hematology

Prediccate Device: Bioreference D-Dimer Exclusion Assay

Device Intended Use:
Hemast D-Dimer HS is an automated latex enhanced immunoassay for the quantitative determination of D-Dimer in human citrated plasma on the ACL TOP for use in conjunction with a clinical pretest probability (PTT) assessment model to exclude venous thromboembolism (VTE) in outpatients suspected of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Device Description:
The D-Dimer HS Latex Reagent is a suspension of polystyrene latex particles of uniform size coated with the Polyclonal antibody highly specific for the D-Dimer domain in fibrin soluble derivatives. The use of the Polyclonal antibody allows a more specific D-Dimer detection avoiding the interference of some endogenous factors like the Rheumatoid Factor. When a plasma containing D-Dimer is mixed with the Latex Reagent and the Reaction Buffer included in the D-Dimer HS kit, the coated latex particles agglutinate. The degree of agglutination is directly proportional to the concentration of D-Dimer in the sample and is determined by measuring the decrease of the transmitted light caused by the aggregates (turbidimetric immunoassay).

HEMOSTASIS INNOVATION IS HERE.
A multi-center management study was performed.
Exclusion Claim

A multi-center management study was performed at four hospitals on 468 samples from patients admitted consecutively to the emergency unit with suspected DVT or PE. 307 patients were suspected of DVT and 361 patients were suspected of PE. As part of the study, patients underwent venous Doppler ultrasound, a clinical assessment, and a D-Dimer test. A high, moderate or low probability of DVT or PE was determined. Patients with a negative D-Dimer test result and a low PT score underwent no further diagnostic testing and were followed up after 3 months for development of DVT or PE. For patients with a negative D-Dimer test result and a moderate PT score, it was the physician’s decision whether to follow up after 3 months or to undergo imaging techniques. Patients with a positive D-Dimer test result or a high PT score underwent imaging techniques.

Recommendations for Selection and Use of D-Dimer Assay for Exclusion of DVT / PE

- Quantitative assay with a large measuring range
- Time to result < 15 min, available at any time
- Evaluated in appropriate clinical trials
- Validated - like sampling of patient population
- High sensitivity (100% NPV)
- Validated cut-off value – if a D-Dimer method is used in the evaluation of VTE, has the method been validated for this purpose?
- Impact on preanalytical variables – i.e. Lipemia, hemolysis

3. CAP Checklist Oct 2006 - HEM.3792:5 “...the cut-off value for exclusion of these conditions should be validated...”

CLSI Guidelines H58-A: “The threshold may be determined by the manufacturer and the value may be cleared by a regulatory agency for use with the method. Such information is published in the package insert of the reagents, and provided.”
• Trauma /Urgent Setting
  – Patients aren’t fasting – lipemia
  – Rapid blood draws – hemolysis
• False Negative Results
  – Wrong diagnosis – patients at risk
  – Puts Hospital at risk for liability
• False Positive Results
  – Unnecessary imaging studies
  – Increased Hospital costs – uninsured
• 2014-Affordable Care Act
  – Drive to decrease unnecessary testing
  – Lower healthcare costs

Q&A

Mahalo