Deep Venous Thrombosis Pulmonary Embolism, D-dimer and Point-of-Care

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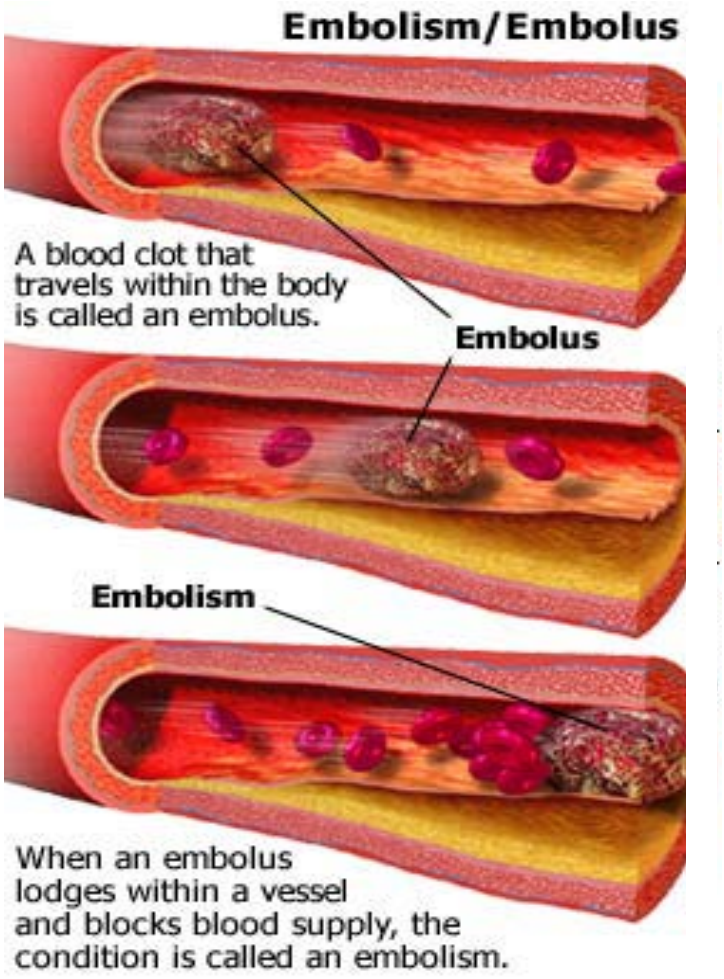
Objectives

- Review of Pathophysiology of DVT and PE
- Diagnosis
  - History & Physical examination
  - Imaging
  - Lab work
- D-dimer Tests
  - Latex
  - Immunometric
  - Specificity
  - Point of Care

Venous Thromboembolism

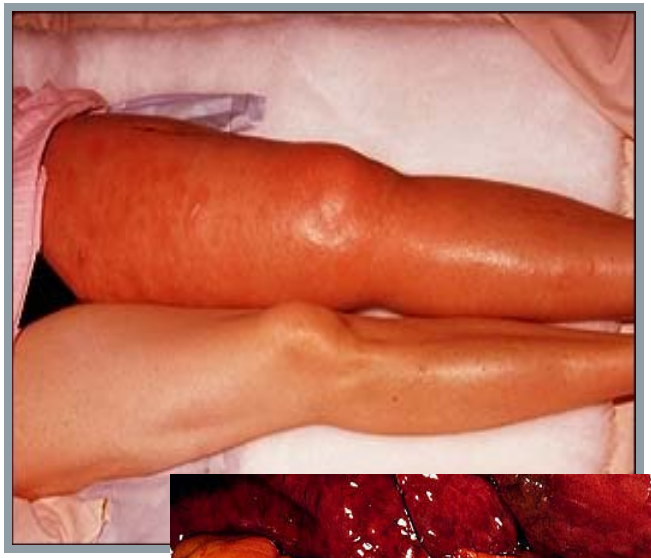
- A blood clot, or thrombosis, develops abnormally in the blood vessel; usually the extremities.
- A deep vein thrombosis (DVT) forms primarily in the deep calf or thigh veins behind a valve.
  - May cause swelling if it persists
  - Most are relatively minor and go unnoticed
  - Pain occurs once extended along the vein and enters into thigh vein
- If DVT is not treated immediately, the blood clot may reach the lungs and cause a potentially fatal pulmonary embolism
- 90% of blood clots resulting in a PE stem from a DVT

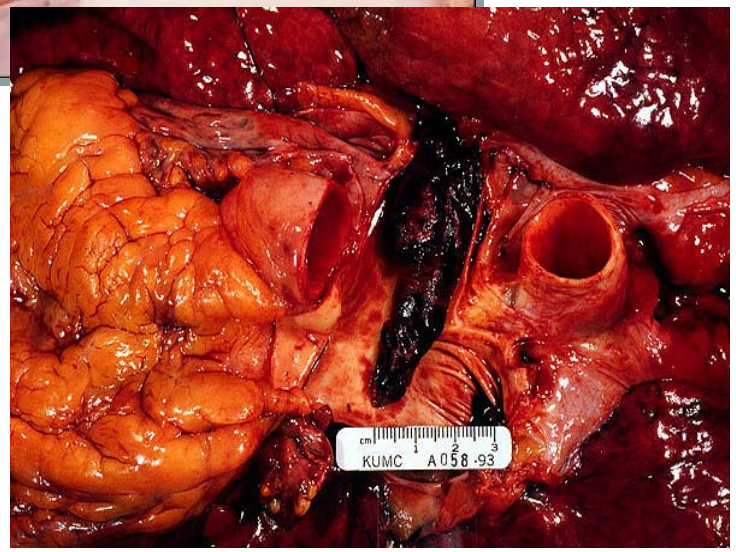


Venous Thromboembolism (VTE)

- 3rd most common cardiovascular disease
- Encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE)

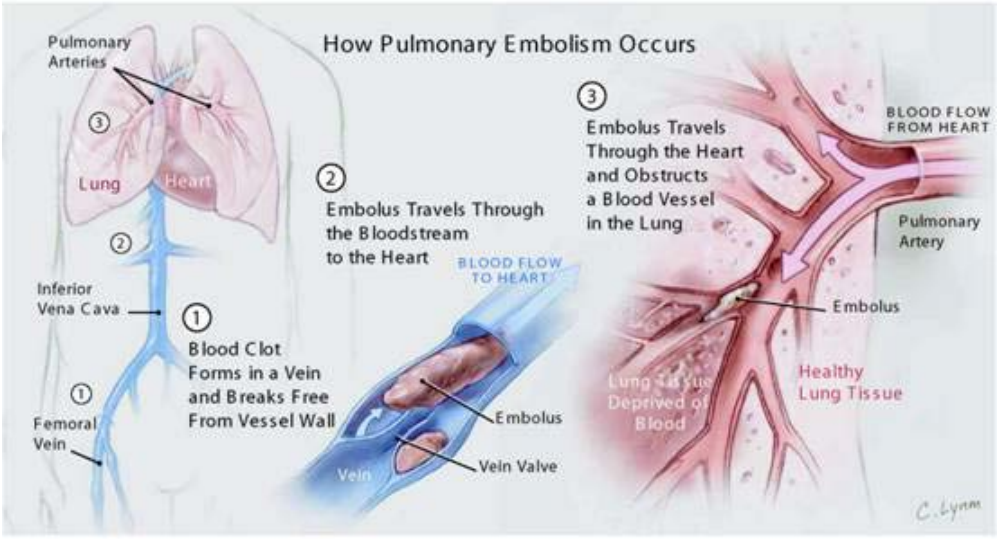
Ileo-femoral DVT





Pulmonary Embolism (PE)

- Clots that travel through the venous system to reach and block a pulmonary vessel.
- If a clot reaches the pulmonary arteries, blood circulation is disturbed and subsequently gas exchange is partly hindered



Partial List of Risk Factors

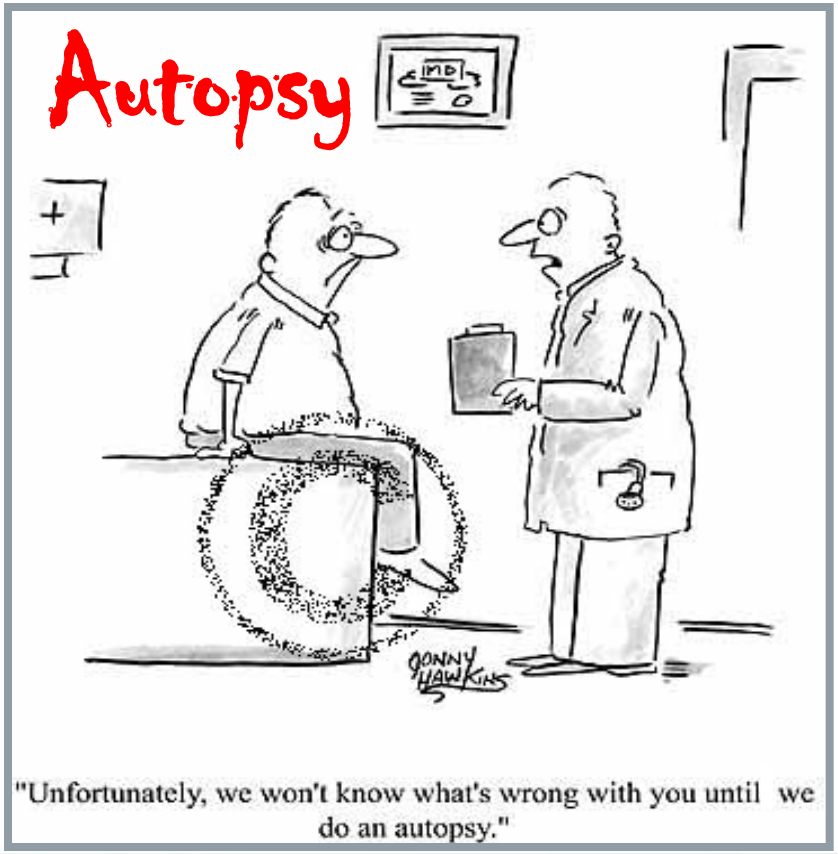
- Age >40 yr
- History of VTE
- Surgery/Trauma
- Prolonged immobilization
- Congestive heart failure
- Fracture of pelvis, femur or tibia

- Cancer
- Obesity
- Pregnancy or recent delivery
- Oral contraceptives/Estrogen therapy
- Inflammatory bowel disease
- Burns
- Genetic or acquired thrombophilia

Clinical Symptoms of PE and/or DVT

- Shortness of breath 73%
- Chest Pain 66%
- Leg Pain or Swelling 33% (due to DVT)
- Cough 43%, sometimes with blood 15%
- Tachycardia
- Dizziness
- Syncope
- Tachypnea
- Crackles
- Jugular venous distention
- Fever
- EKG changes

#1 method for diagnosis:



Issues in Diagnosing Patients with SOB

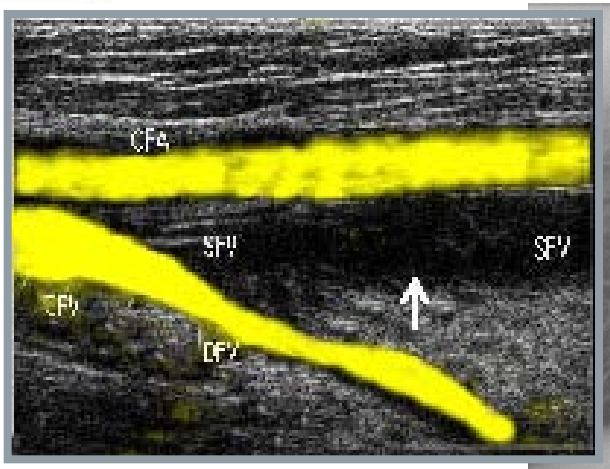
- Differential diagnoses
  - PE
  - Myocardial Infarction
  - Congestive Heart Failure
  - Pneumonia
  - COPD
  - Cardiac Tamponade
- Diagnostic testing
  - Cardiac markers
  - D- dimer
  - CBC, chemistry, lipid panel
  - EKG
  - CXR
  - VQ scan/CT scan
  - Cultures
  - Echocardiogram
  - Stress test
  - Left/Right Heart Catheterization
  - Pulmonary Function Test

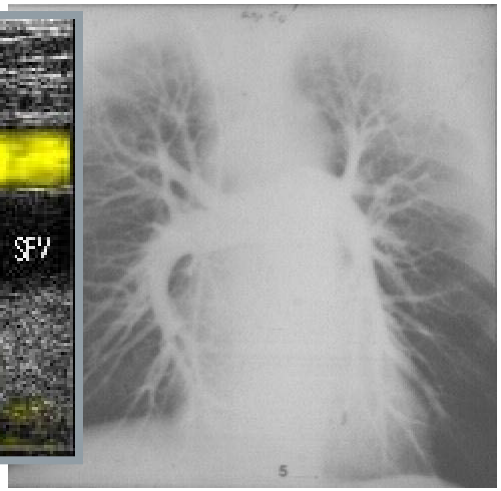
Other Causes of D-dimer Elevation

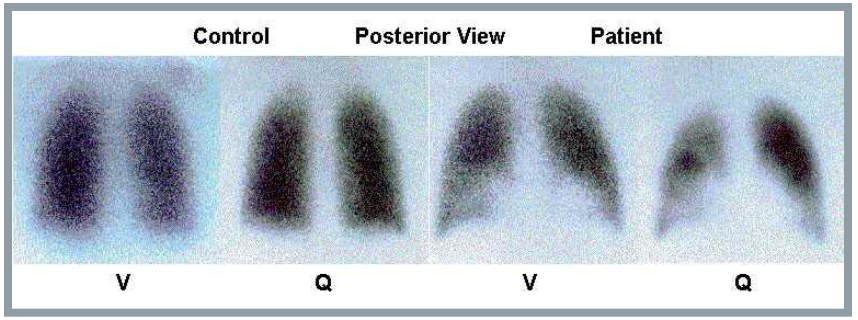
- DIC
- AMI
- Atherosclerosis
- Trauma
- Hepatic disease
- Sepsis
- Surgery
- Infection
- Pregnancy
- Inflammation
- Age
- Cancer
- Thrombolytic therapy

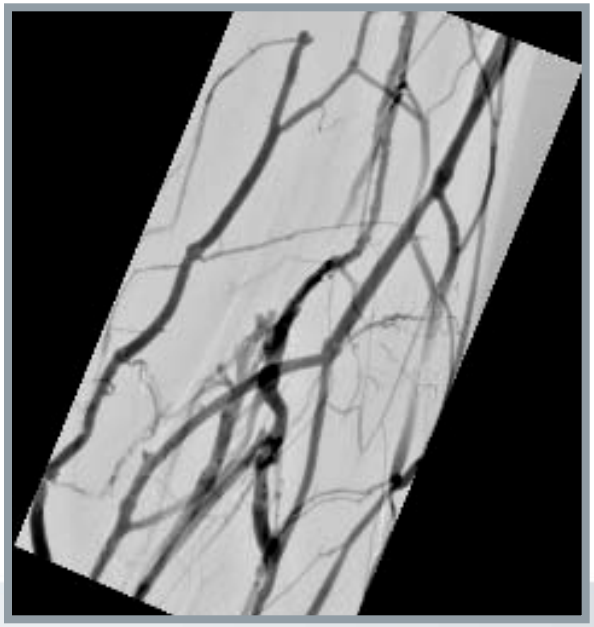
- **Hence a positive test does not prove the existence of DVT/PE**

Current practice in PE diagnosis?









General disadvantages:

1. **Instrument and skilled staff have to be available**
2. **Potential of renal damage as a result of imaging dye administration**

So What's The Problem?

- The clinical presentation of both DVT and PE may be misinterpreted, subtle or asymptomatic
- Radiologic studies are expensive, subjective and often non-diagnostic, potentially harmful to the patient and not always readily available
- Need a simple, fast, inexpensive test that is highly sensitive and preferably specific

Challenges Associated With D-dimer

- Not specific to a disease, detects breakdown of clot
  - May encounter false positives for PE/DVT
  - Value is in ability to reduce further evaluation of patients with a negative D-dimer
- No standard for D-dimer; results vary, correlation is difficult
  - Latex agglutination subjective and has 80% sensitivity, vs. sandwich immunoassays (ELISA and FIA) assays with nearly 100% sensitivity

van der Graaf, *et al*. *Thromb Haemost* 2000; 83: 191–8.

How is D-dimer Being Used ?

D-dimer often used inappropriately

- No pretest probability assessment
- Blanket test of all chest pain patients
  - Overuse diminishes the value of the test
    - Lowers specificity / increases FP rate, decreases clinician/lab confidence in test!
  - Shortens life of the scanner
    - With D-dimer screening, the positive rate of CT scans for PE is 11%* - 15%**
    - Without D-dimer screening, the positive rate is 5%** - 8%*
  - Irradiates patients
    - The radiation from one chest CT ≥ 40 chest x-rays
- D-dimer TATs insufficient to make rapid clinical decisions for imaging
  - Ordering D-dimer, but sending concurrently for imaging, if available

*** Kline, et al, *Annals of Emergency Medicine*, Nov 2004**

**** Night Radiologist et al. Sharp Hospital. Unpublished**

Appropriate Use of D-dimer

American College of Emergency Physicians Clinical Policy Statement

- In most cases, low probability patients are candidates
- Screen patients with a Pre-test Probability Score (Wells, Hamilton, Charlotte, Geneva, etc)
- Use in out-patient population
  - Hospitalized, pregnant, post surgical patients will likely be elevated due to other clinical conditions/risk factors
- When used appropriately, D-dimer assists in reducing the number of patients requiring CT scans
- Physician education will be VERY useful
  - Use on low probability patients that would otherwise be sent for imaging/scanning as part of a PE or DVT workup

Fesmire FM, *et al.*, *Ann Emerg Med. 2003;41:257-270*.

ACEP Clinical Policy

- In patients with low pre-test probability the following can be used to exclude PE:
  - Negative quantitative D-dimer
  - Negative whole blood qualitative D-dimer AND Wells' score < 2

Low Probability <2.0
(3.6% Risk)

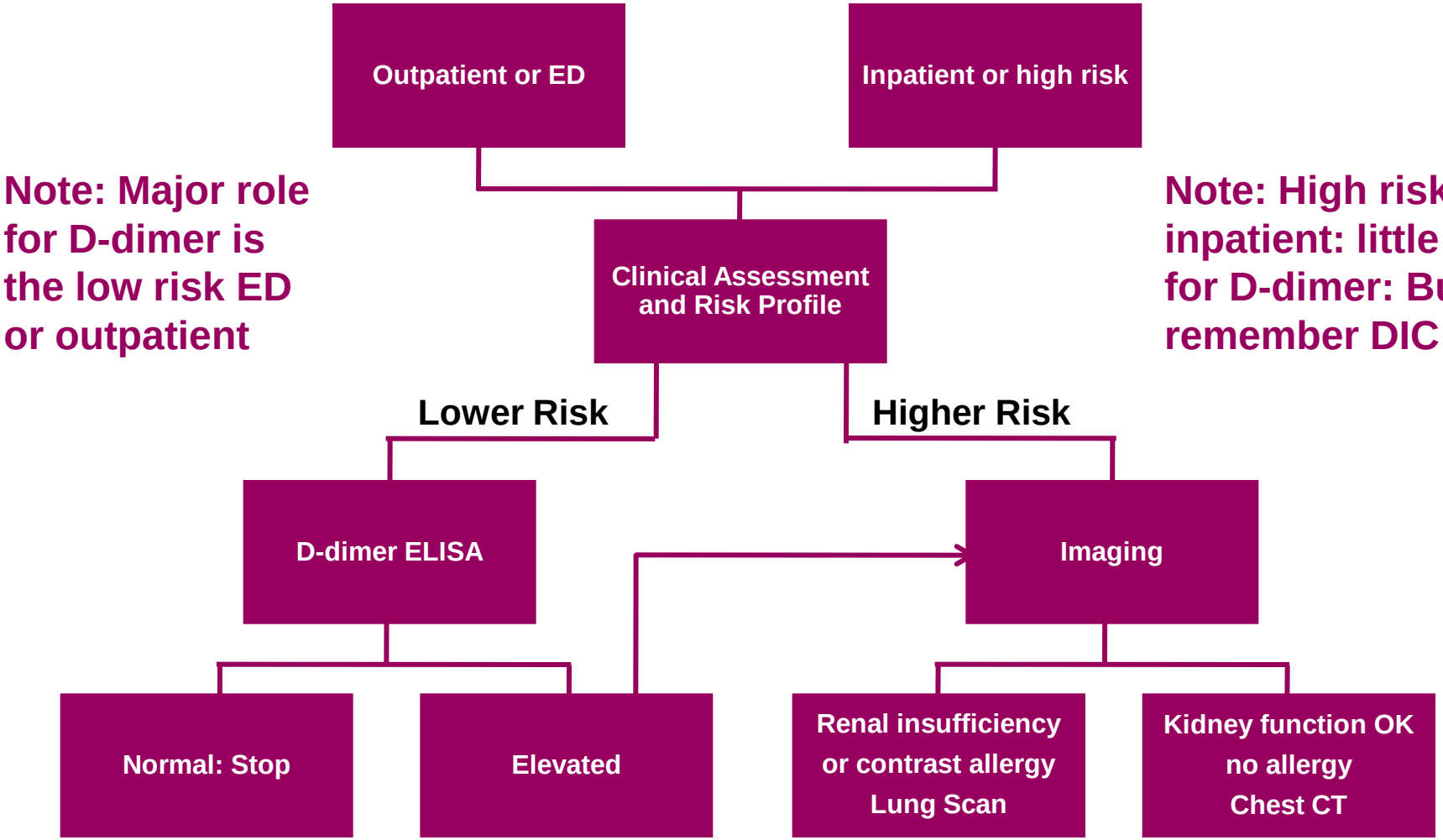
Moderate 2.0 – 6.0
(20.5% Risk)

High Probability >6.0
(66.7% Risk)

Clinical Characteristics	Score
Clinical signs and symptoms of DVT	3
PE likely or more likely than alternative diagnosis	3
Heart rate greater than 100 beats/min	1.5
Immobilization (bedrest ≥ 30 days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (Receiving treatment, treated in the last 6 months, or palliative care)	1.0

Wells PS, *et al., Thromb Haemost* 2000;83:416-420.

Strategy For Diagnosis of PE



Note: Major role for D-dimer is the low risk ED or outpatient

Note: High risk or inpatient: little role for D-dimer: But remember DIC

Implementation of a Rapid Whole Blood D-Dimer Test in the Emergency Department

Lewandrowski *et al., Am J Clin Pathol* 2009;132:326-331

Rapid Whole Blood Test in the ED

- Study Objectives – To Assess:
  - ED length of stay pre- and post-implementation of POC D-dimer;
  - Admission and discharge rates pre- and post-implementation of POC D-dimer; and
  - Utilization of imaging test rates pre- and post-implementation of POC D-dimer.

Lewandrowski *et al., Am J Clin Pathol* 2009;132:326-331.

Methods and Materials

- 252 patients pre-implementation and 211 patients post-implementation were evaluated for:
  - test results, turnaround times, and test volumes
  - ED LOS
  - patient chart reviews

Results

- Following implementation of the rapid D-dimer test the total test turnaround time (from blood draw to availability of the test result) decreased from approximately 2 hours (central laboratory, depending on the shift and time of day) to 25 minutes, representing an approximately 79% decrease.

Lewandrowski *et al., Am J Clin Pathol* 2009;132:326-331.

Results

- The volume of D-dimer tests requested by the ED increased from a mean of 127 per month before implementation of the rapid D-dimer test to a mean of 154 tests per month (a 21.3% increase; P = 0.037), reflecting increased utilization.
  - Some of this increase can be explained by an approximately 6% increase in ED visits during the study period (daily average of 221 before to 235 after implementation).

Results

Rates 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

	Before Implementation	After Implementation
Admitted (%)	36.5	22.7
Discharged (%)	42.9	50.2
Admit to observe (%)	20.6	27.0

- The difference pre- and post-implementation was significant (P = 0.005), indicating that the availability of the rapid test may have influenced patient disposition decisions.

Results

Rates of Follow-up Radiologic Testing* Before and After Implementation of the Rapid Whole Blood D-Dimer Test in the Emergency Department

Radiologic Study	Before Implementation	After Implementation
No (%)	60.3	61.1
Yes (%)	39.7	38.9

* Venous ultrasound, lung scan, or computed tomography.

- There was no statistical difference in imaging rates, i.e., implementation of POC D-dimer did not increase imaging.

Key Points

- The POC test performed as well as the Lab test while producing
  - A significantly shorter ED LOS
  - Fewer admissions
  - No change in the rate of imaging
- These changes should result in decreased costs.

Lewandrowski *et al., Am J Clin Pathol* 2009;132:326-331.

Diagnostic Accuracy and User-Friendliness of 5 Point-of-Care D-Dimer Tests for the exclusion of Deep Vein Thrombosis

Geersing *et al. Clin Chem* 2010;56:1758-66

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DVT Rule Out Study

- Study Objectives – To Assess:
  - Accuracy of five POC D-dimer tests in the assessment of deep vein thrombosis (DVT);
  - Nursing opinion on the ease of use of the tests.

Methods

- Protocol
  - 577 patients suspected of having a DVT were evaluated using:
    - Vidas (bioMerieux)
    - Pathfast (Mitsubishi)
    - Triage (Alere)
    - Cardiac (Roche)
    - Clearview Simplify (Alere)
- Ease of Use
  - Twenty nurses completed questionnaires dealing the ease of use of the five test methods.

Results

- Accuracy:
  - Differences in the calculated sensitivities and specificities and negative predictive values were largely a result of differences in the cutoffs used.
  - There were no significant differences in the area under the curves (AUC) for the ROC analyses.

Table 2. Diagnostic accuracy measures of the 5 point-of-care D-dimer tests for the exclusion of DVT (N = 577).

D-dimer assay	Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	LR−[a] (95% CI)	NPV (95% CI)	AUC (95% CI)
Vidas	500 μg/L FEU	0.99 (0.96–1.0)	0.42 (0.37–0.46)	0.03 (0.01–0.24)	99.5 (98–100)	0.89 (0.82–0.97)
Pathfast	570 μg/L FEU	0.98 (0.94–1.0)	0.39 (0.35–0.44)	0.06 (0.02–0.29)	99.2 (98–100)	0.89 (0.81–0.97)
Triage	196 μg/L FEU	0.97 (0.93–1.0)	0.48 (0.44–0.53)	0.06 (0.03–0.23)	99.2 (98–100)	0.88 (0.80–0.97)
Cardiac	500 μg/L FEU	0.94 (0.88–0.99)	0.62 (0.58–0.67)	0.10 (0.07–0.25)	98.6 (97–100)	0.88 (0.80–0.96)
Clearview Simplify	80 μg/L	0.91 (0.85–0.98)	0.64 (0.60–0.69)	0.14 (0.09–0.29)	98.1 (97–100)	NA

[a] LR−, likelihood ratio negative; NPV, negative predictive value; NA, not applicable because it is a qualitative assay.

Results

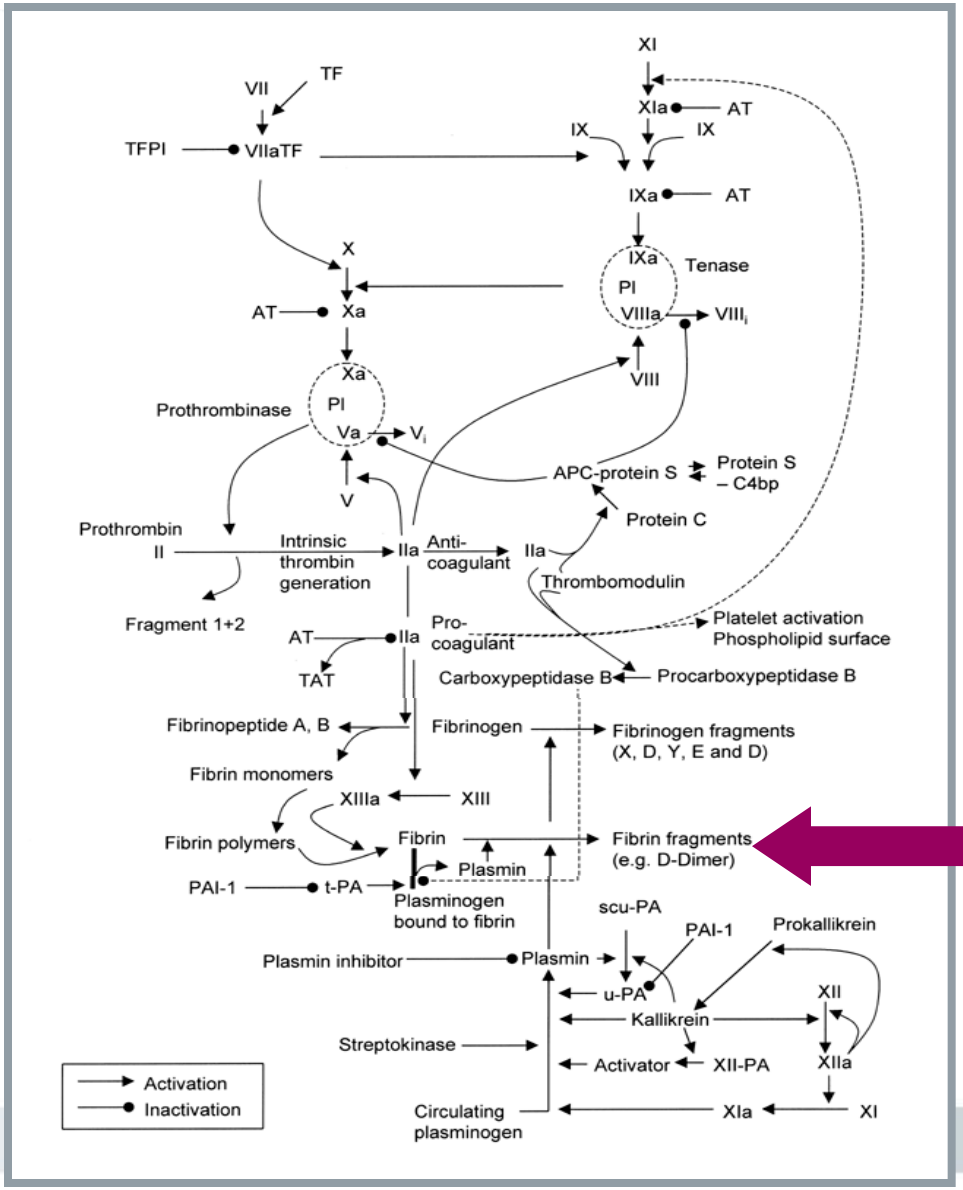
- Ease of use:
  - “On the basis of user-friendliness the Cardiac and Triage devices may be preferred for use in an emergency department setting or small primary care clinics. In addition, these tests produce a D-dimer test result within 15 min and can provide measurements of other (cardiovascular) biomarkers …”
  - “The Clearview Simplify test is also user-friendly for primary care, because it is easily portable, requires no analyzer, can be performed on capillary whole blood, and requires no calibration.”
  - The drawback to the Clearview Simplify is that the interpretation of test results was rated more difficult because of the subjective nature of the reading.

D-dimer tests-Choices and Challenges

- Latex Agglutination
  - Qualitative or semi-quantitative
  - Relatively insensitive
- Whole Blood Agglutination
  - More sensitive than latex
  - Somewhat subjective
- Turbidimetric
  - Much less subjective
- ELISA/Immunoassay
  - High analytical sensitivity
  - Historically laborious

- Standardization challenges
  - No recognized standard
  - Purified D-dimer from plasmin digested clots (ng/mL)
  - D-dimer from totally lysed fibrin clots (Fibrin Equivalent Units, FEU)
- Patient variables

Tests of Fibrinolysis

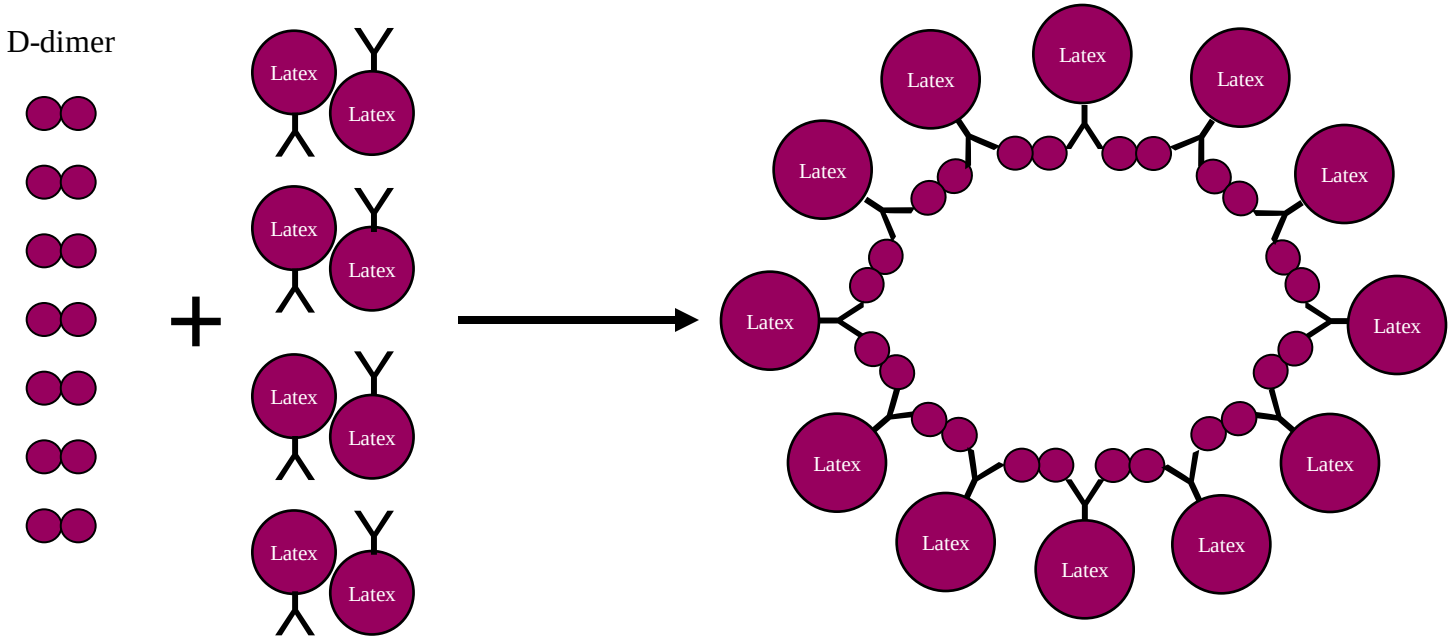


- Fibrinogen
- Platelet count
- Fibrin degradation products
  - FpA
  - FpB
  - Fragment D
  - Fragment E
  - D-dimer (“cross-linked” fibrin degradation product)

- Only D-dimer is useful for DVT and PE

How Were D-Dimers Measured?

- Latex Agglutination:
  - Big clumps that are visible to the naked eye



- Turbidimetric assays:
  - Big clumps that scatter light – the less light detected, the more analyte is present

Turbidimetric Assays

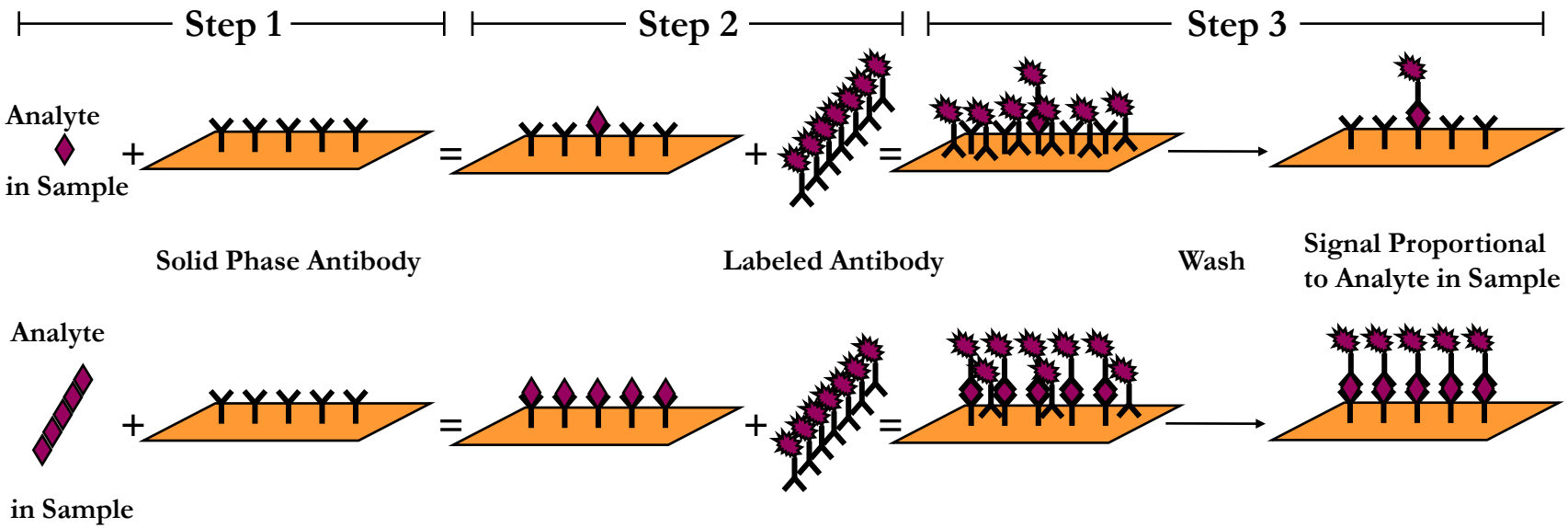
- Shine a light on one side and measure the light coming through on the other side

ELISA / EIA

- Enzyme-Linked Immunosorbent Assay
  - Synonymous with Enzyme Immunoassay (EIA)
  - 1st ELISAs were run in microtiter plates (aka ELISA plates)
- Member of a class of immunoassays (Immunometric or “Sandwich”)
  - All involve capturing the analyte
  - All involve measuring captured analyte using a form of signal generator
    - EIA uses an enzyme-labeled antibody to convert an “invisible” molecule into a “visible” molecule
    - FIA (Fluorescence immunoassays, or IFA, immunofluorometric assay) are similar to EIA except that they use a fluorescent-labeled antibody as the signal
    - ELFA-Enzyme linked fluorescent immunoassay
  - FIA can be just as sensitive as EIA (e.g., TnI or BNP)

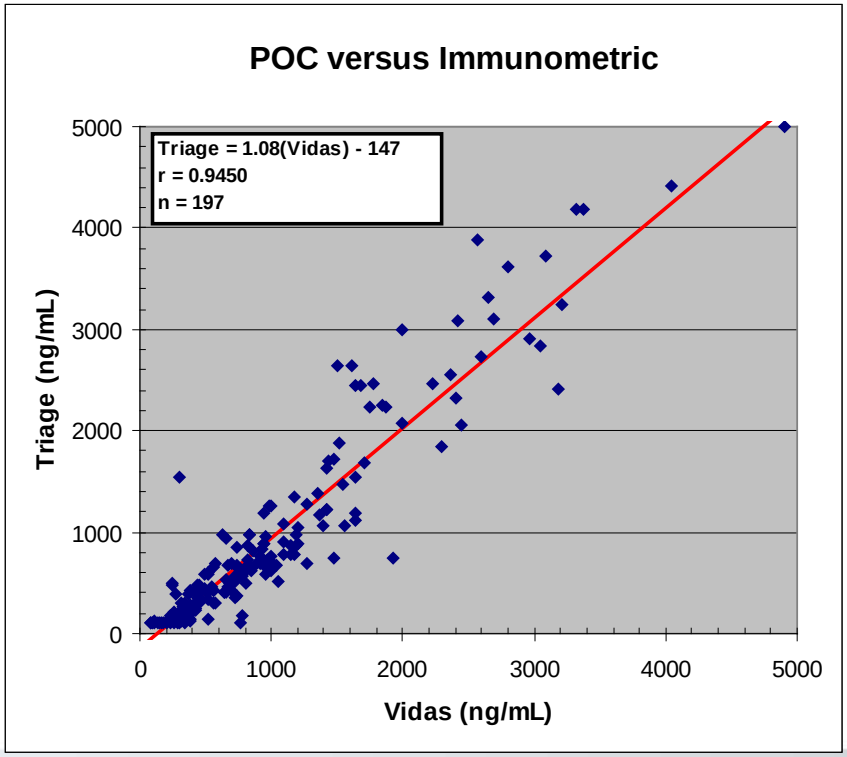
“Sandwich” Immunoassay

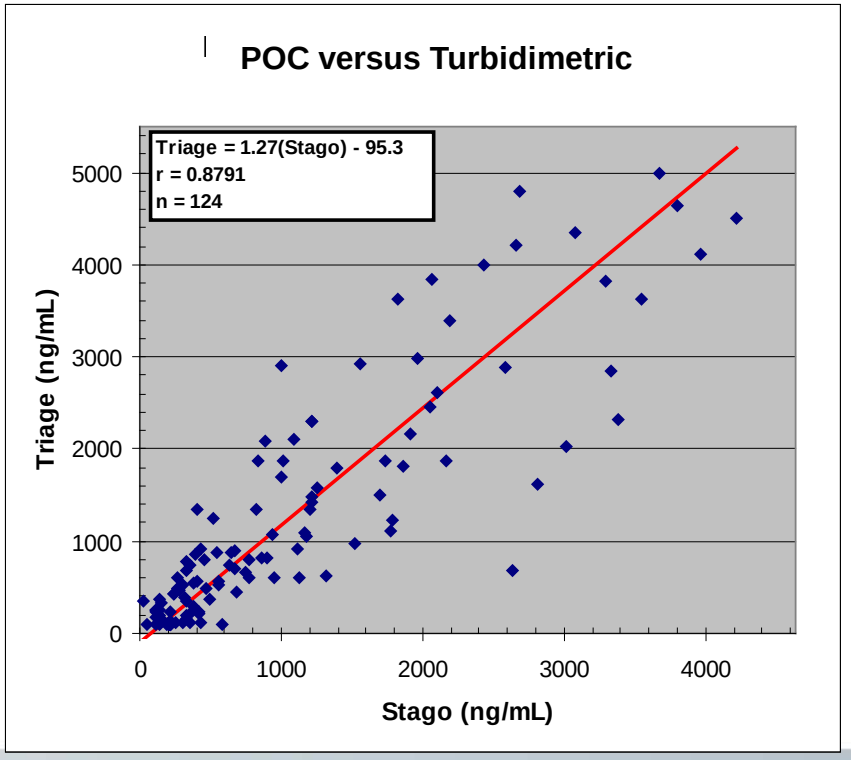
- Typically used for analytes with multiple epitopes (Cardiac Markers, D-dimer, Microbiology).



Assays Compared

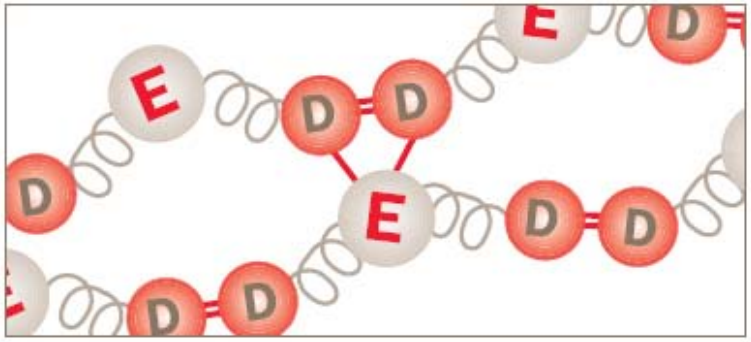
- Shown below is a POC immunometric (sandwich) assay versus an immunometric Lab assay (left panel) and the POC assay versus a turbidimetric Lab assay (right panel).

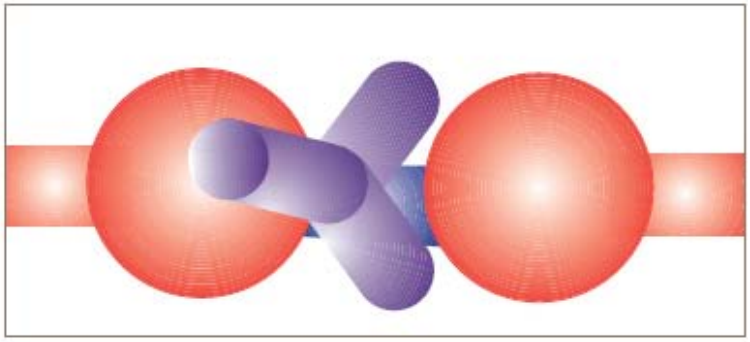




Value of D-dimer Antibody Specificity

- False positives reduce the value of D-dimer and increase clinician and lab frustration.
- Tests with high affinity antibodies for D-dimer reduce false positives.

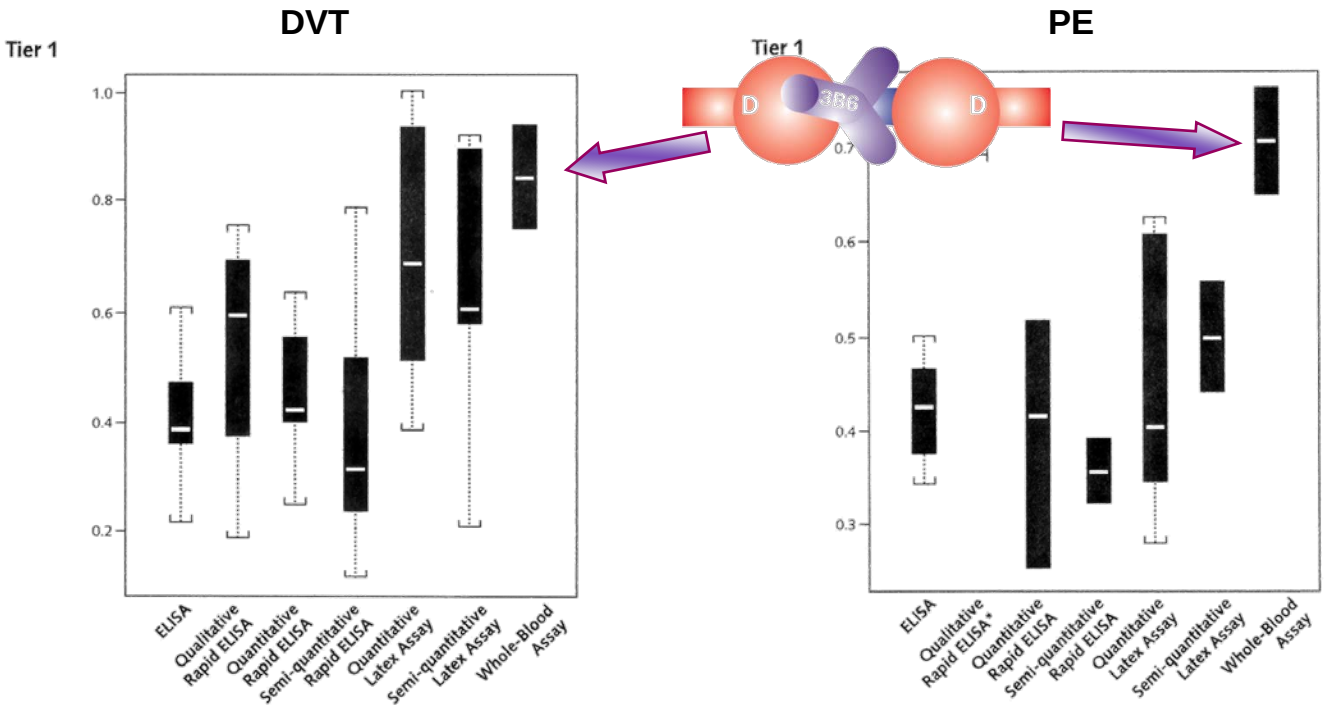




- The 3B6 monoclonal antibody offers high specificity due to its affinity to the cross-linking epitope (recognition site) of D-dimer.

Review of 78 DVT/PE Studies

- 78 prospective clinical studies investigated the use of D-dimer for the exclusion of acute VTE and PE
- The specificity the 3B6-based whole blood assay was identified as clinically and statistically superior to the rapid ELISA and automated latex immunoassay methods for acute DVT and PE.



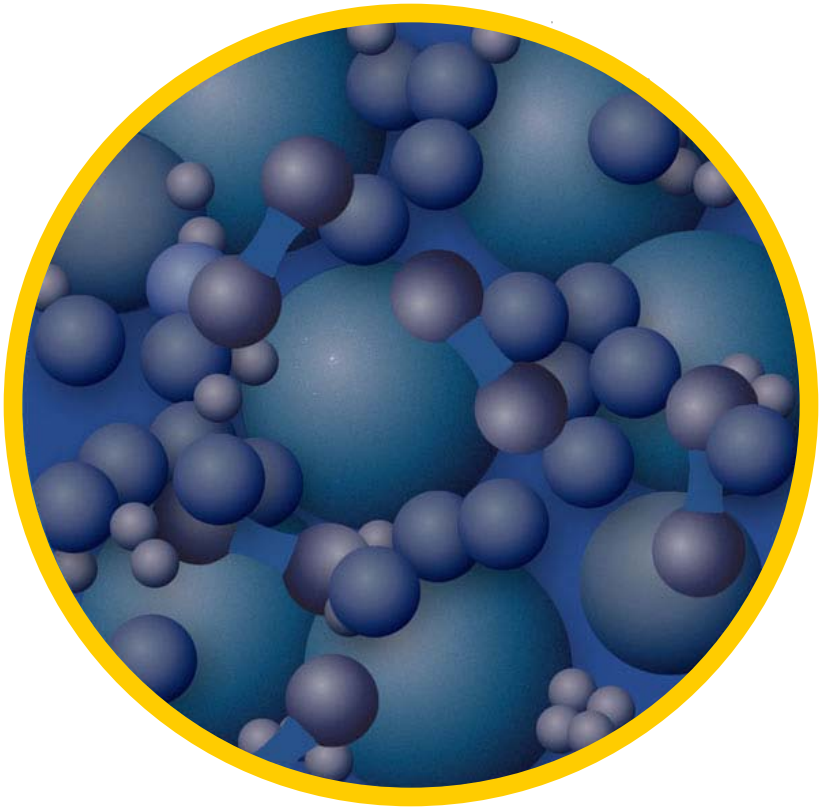
Stein PD, *et al., Ann Intern Med* 2004;140:589-602.

Fibrin Assay Comparison Trial (FACT)

- Study Findings:
  - The main reason for differences between D-dimer assays is due to differences in antibody specificity
  - Assays displaying cross-reactivity with non-cross linked fibrinogen and fibrin derivatives will show falsely high
    - Diagnostica Stago assays (MAbs 8D2, 2.1.16) showed greater than 30% cross-reactivity
  - Assays using 3B6 antibodies were identified as the most specific for D-dimer. 3B6 assays had the least false positives.

Dempfle CE*, et al. Thrombo Haemost* 2001;86:671-8.

Distinguish from other FDPs



- FpA
- FpB
- D-dimer
- Fragment D
- Fragment E

Plasmin-derived FDPs may be detected in addition to D-dimer, resulting in an erroneously elevated result

Distinguish from other FDPs

- False positives reduce the value of D-dimer and increase clinician and lab frustration
- Tests with high affinity antibodies for D-dimer reduce false positives
  ⇒ D-dimer
- The 3B6 monoclonal antibody offers high specificity due to its affinity to the cross-linking epitope of D-dimer

Is D-dimer useful for DIC?

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation.

- Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

- If yes, proceed. If no, do not use this algorithm;

1. Order global coagulation tests (platelet count, PT, fibrinogen, soluble fibrin monomers, or fibrin degradation products).

Is D-dimer useful for DIC?

2. Score global coagulation test results:
   - Platelet count
     - (>100 x 10^9/L = 0, <100 x 10^9/L = 1, <50 x 10^9/L = 2)
   - Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products - **D-dimer**)
     - Historical abnormal D-dimers can be split into tertiles
       - no increase scores a 0; mild increase (1st tertile) scores a 1; moderate increase (2nd tertile) scores a 2; strong increase (3rd tertile) scores a 3.
   - Prolonged prothrombin time
     - (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
   - Fibrinogen level
     - (>1.0 g/l = 0, <1.0 g/l = 1)

Is D-dimer useful for DIC?

3. Calculate score.

- If ≥ 5: compatible with overt DIC; repeat scoring daily.
- If < 5: suggestive (not affirmative) for non-overt DIC; repeat next day.

D-dimer, conclusions

- Most appropriate for ED patients as hospitalized will usually have elevated levels
- When used appropriately, D-dimer is a useful tool for ruling out venous thromboembolism and reducing costs and adverse outcomes that result from unnecessary imaging studies.
- D-dimer can be used on in-patients to help assess disseminated intravascular coagulation (DIC).

Questions????