Venous Thromboembolism: The Role of D-dimer at the Point-of-Care

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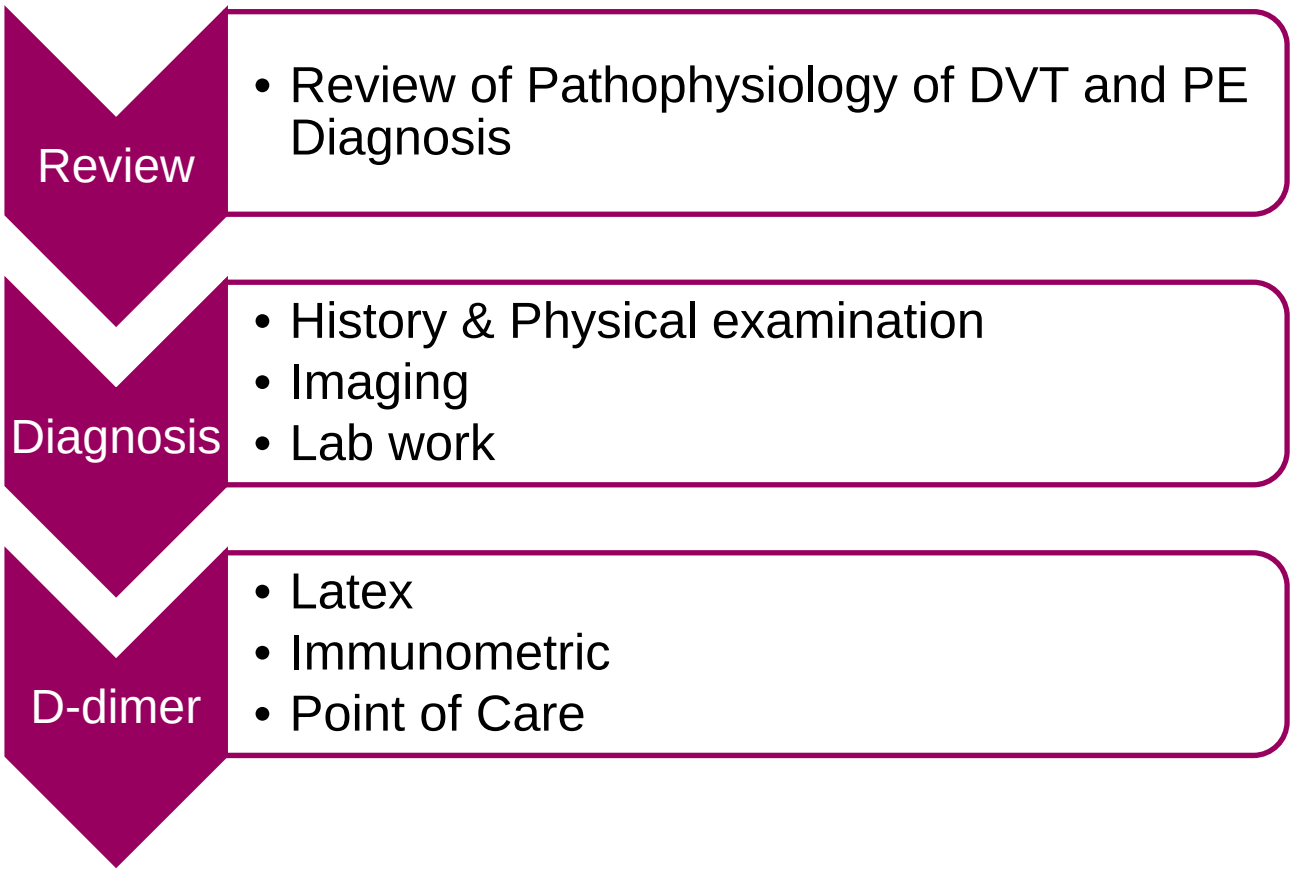
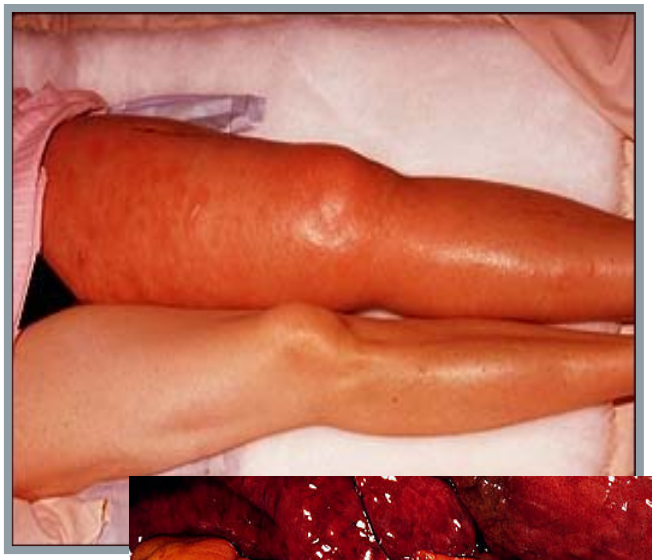
Objectives

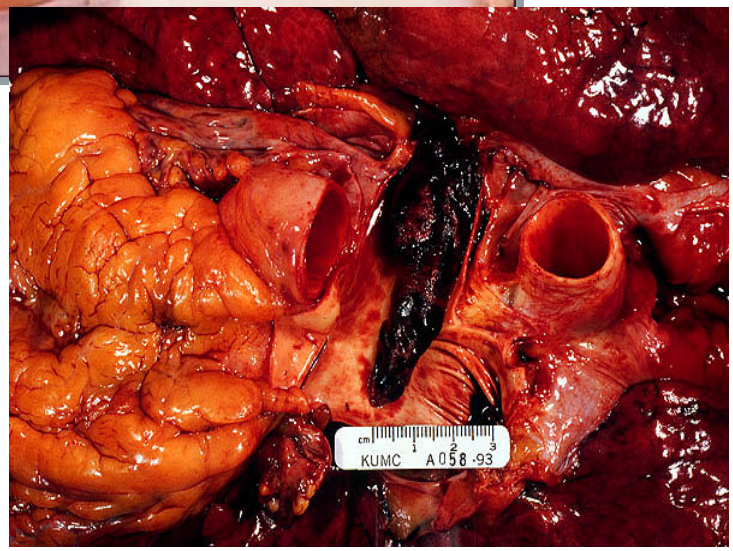

Review
• Review of Pathophysiology of DVT and PE Diagnosis
Diagnosis
• History & Physical examination
• Imaging
• Lab work
D-dimer
• Latex
• Immunometric
• Point of Care

Venous Thromboembolism (VTE)

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

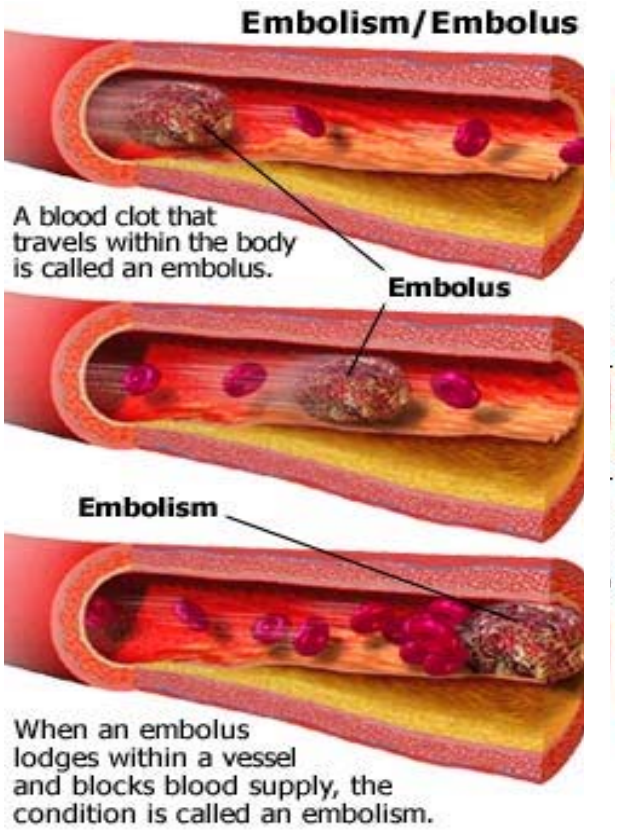
Ileo-femoral DVT





Venous Thromboembolism

A blood clot (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**

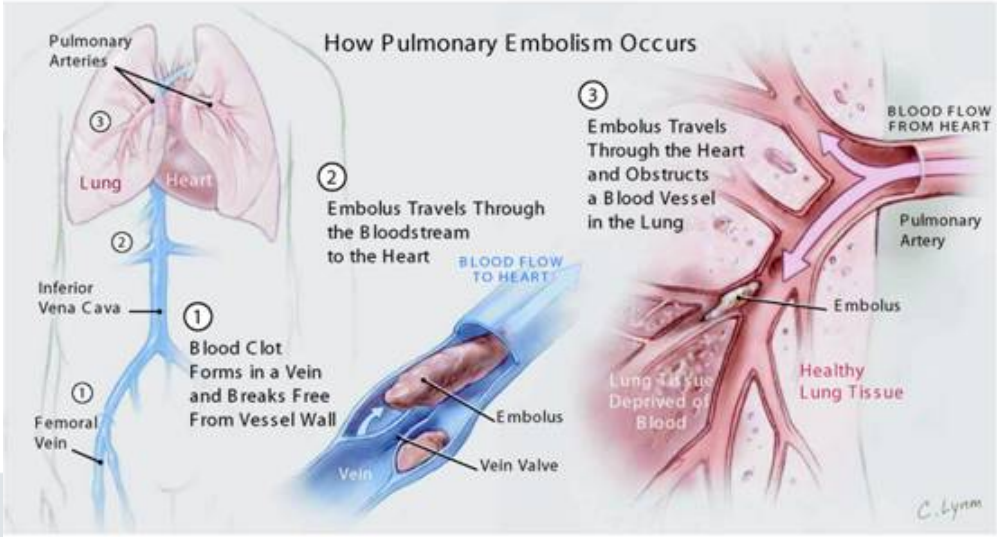
90% of blood clots resulting in a PE stem from a DVT

If DVT is not treated immediately, the blood clot may reach the lungs and cause a potentially fatal pulmonary embolism

Pulmonary Embolism (PE)

PEs are clots that travel through the venous system to reach and block a pulmonary vessel.

When a PE is present, circulation is disturbed and subsequently gas exchange is hindered



Partial List of Risk Factors

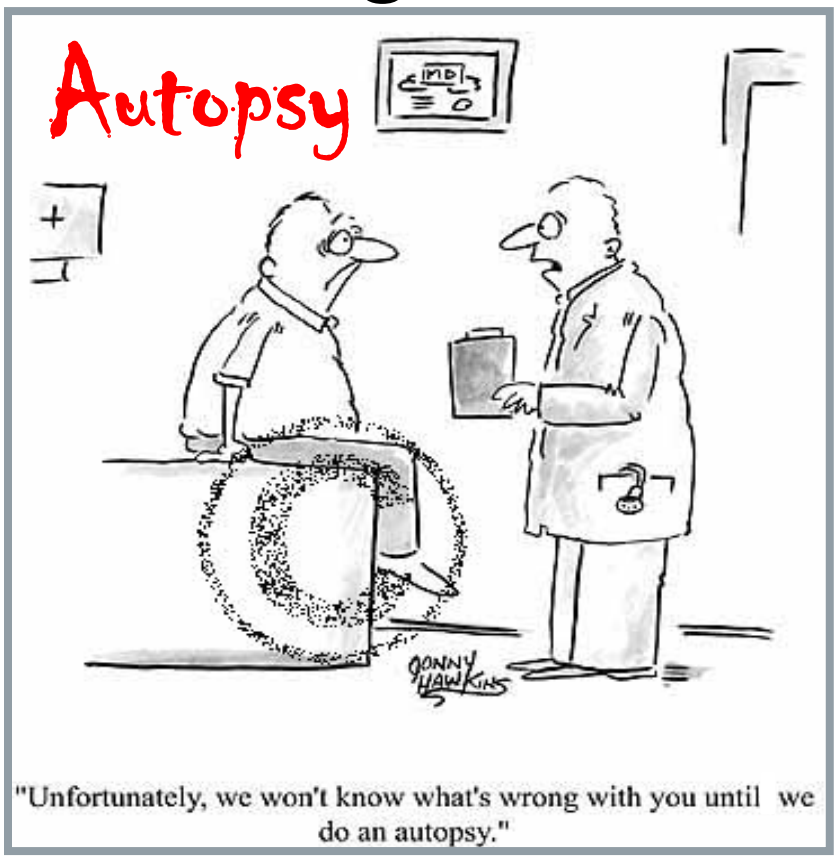
- Age >40 yr
- History of VTE
- Surgery/Trauma
- Prolonged immobilization
- Congestive heart failure
- Fracture of pelvis, femur or tibia

- 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

73%	• Shortness of breath
66%	• Chest pain
43%	• Cough • Sometimes with blood (~15%)
Other	• Tachycardia • Tachypnea
Other	• Syncope • Dizziness
Other	• Crackles • Jugular venous distention
Other	• Fever • ECG changes
33%	• Leg pain or swelling (DVT)

#1 method for diagnosis:



"Unfortunately, we won't know what's wrong with you until we do an autopsy."

Issues in Diagnosing Patients with SOB

Differential diagnoses	PE
	MI
	CHF
	Pneumonia
	COPD
	Cardiac Tamponade

Issues in Diagnosing Patients with SOB

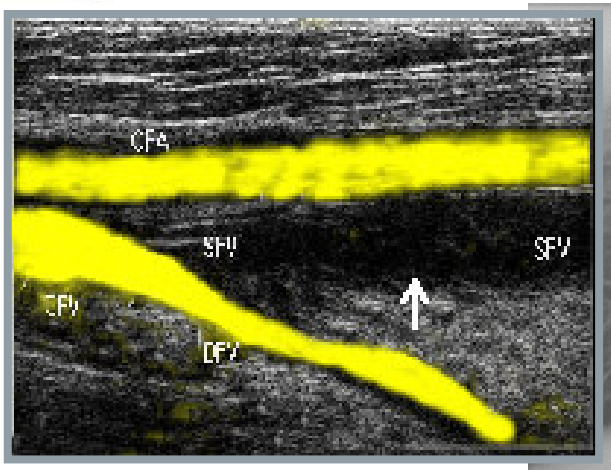
Diagnostic Testing

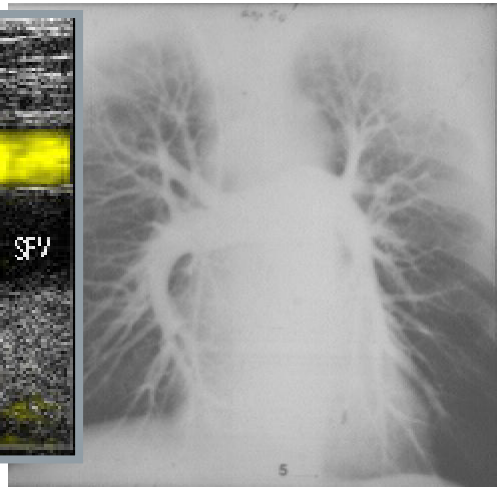
- Cardiac markers
- D-dimer
- CBC
- Chemistry, lipid panel

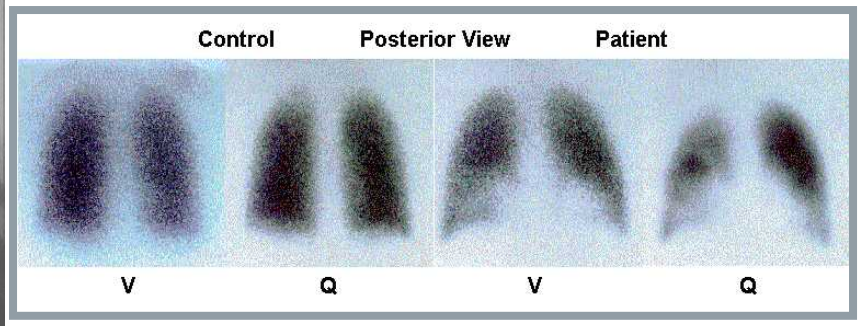
- ECG
- CXR
- VQ scan/CT scan
- Pulmonary function test

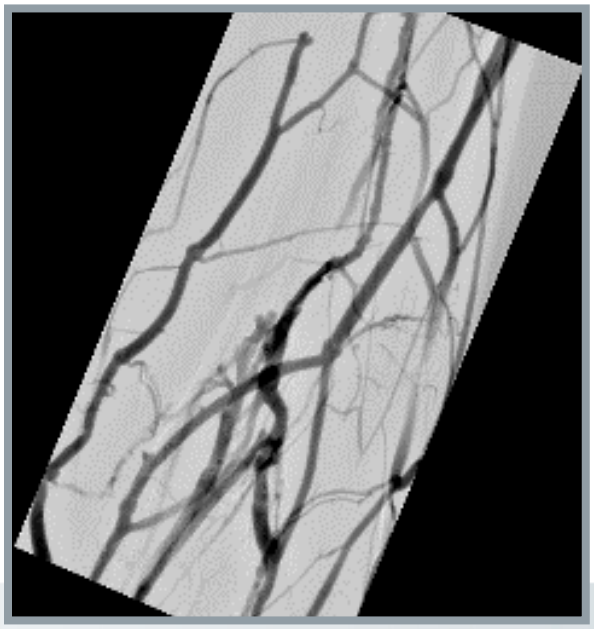
- Cultures
- Echocardiogram
- Stress test
- Cardiac catheterization

Current practice in PE diagnosis?









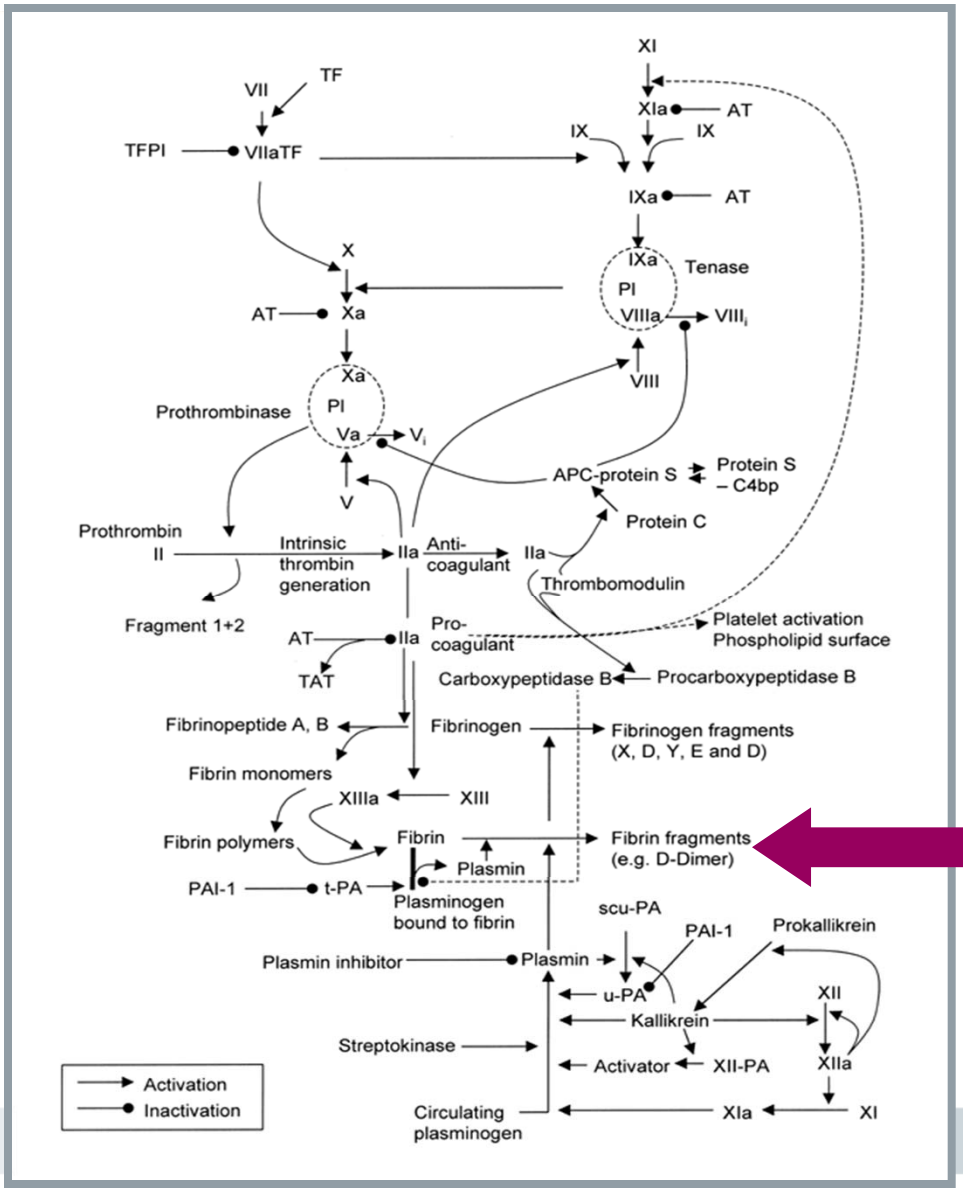
General disadvantages:

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?

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

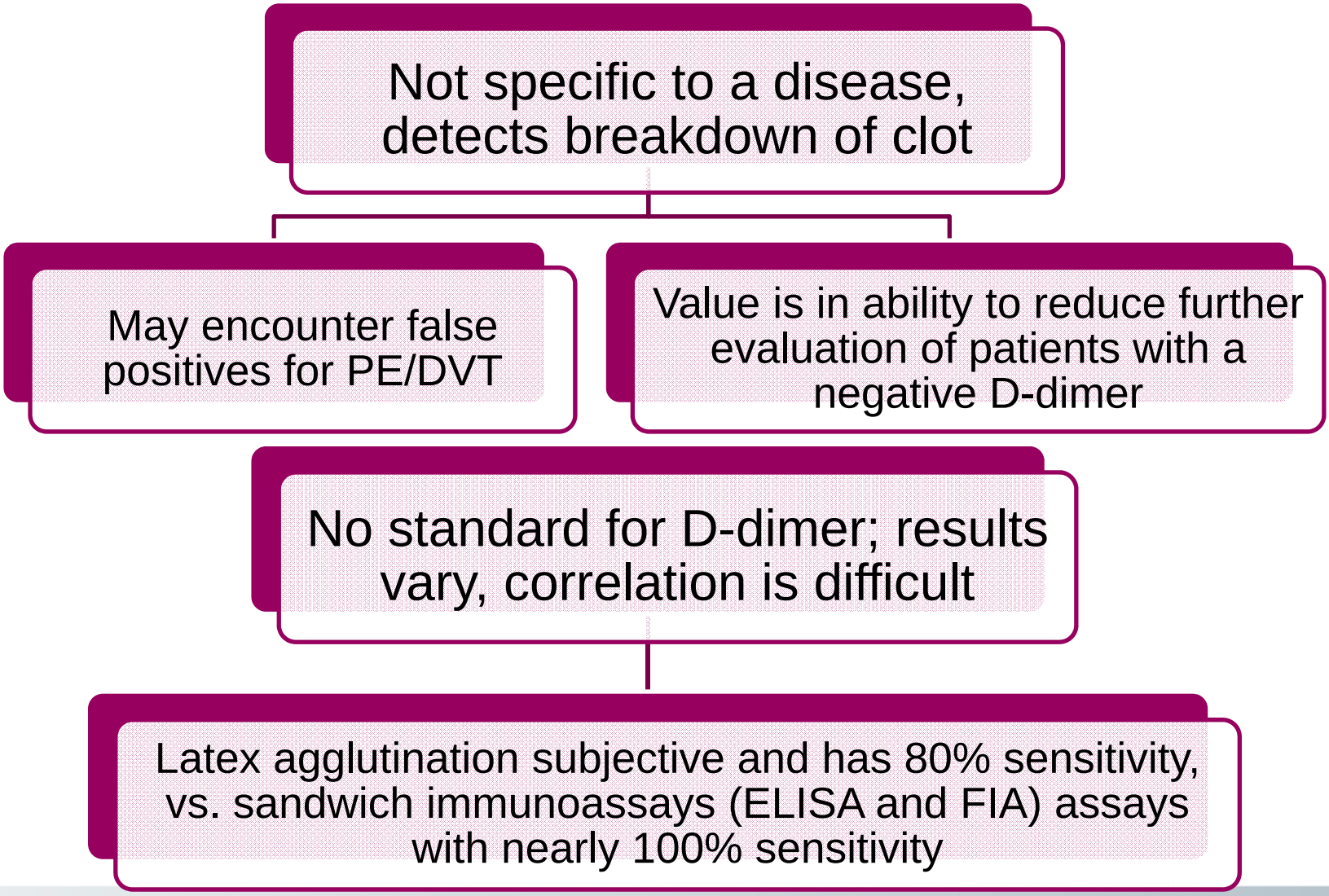
Tests of Fibrinolysis – Why D-dimer?



- 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

Challenges Associated With D-dimer



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
- Laboratory 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

Low Probability <2.0
(3.6% Risk)

Moderate 2.0 – 6.0
(20.5% Risk)

High Probability >6.0
(66.7% Risk)

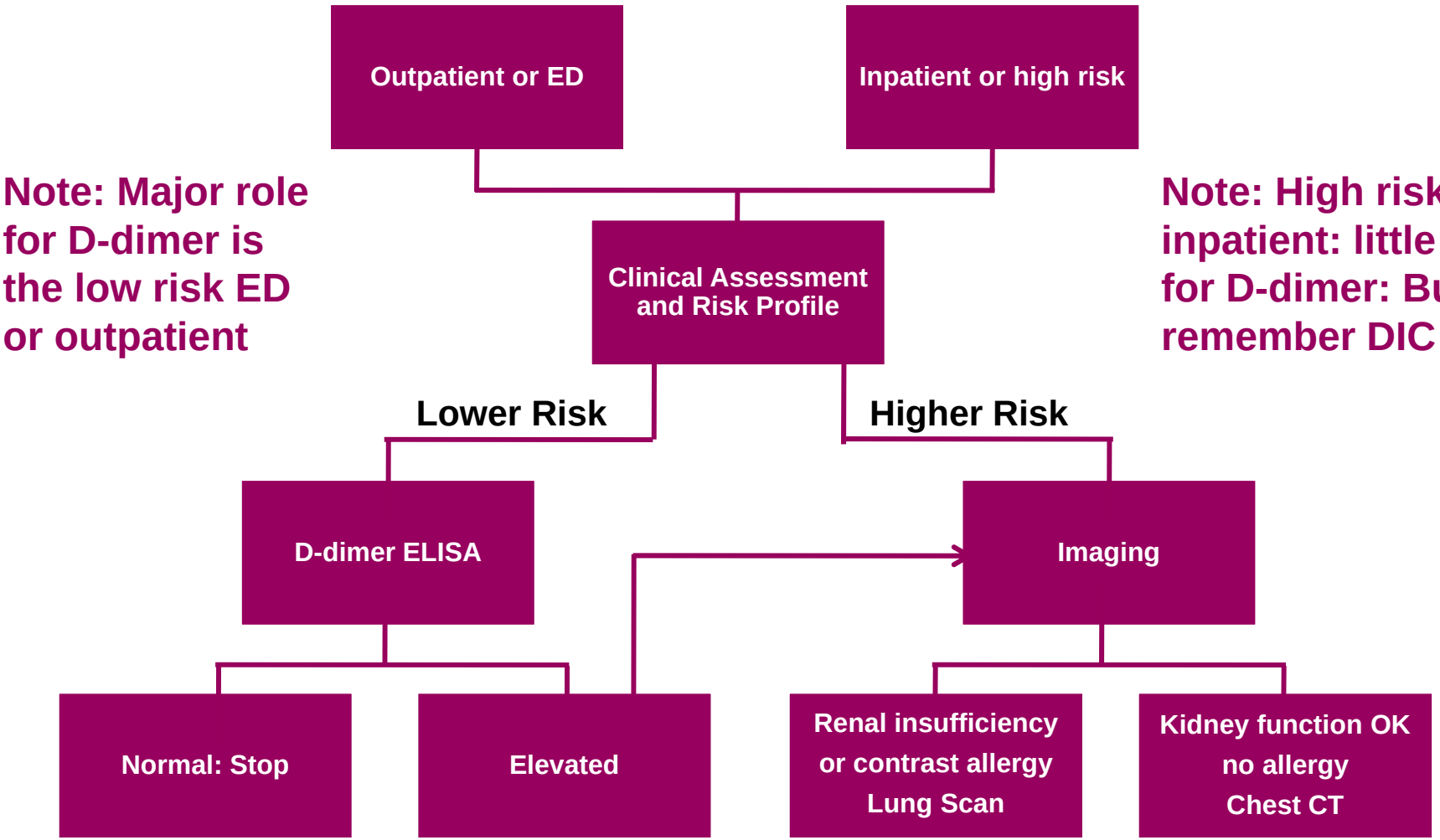
Clinical Characteristics	Score
Clinical signs and symptoms of DVT	3
PE likely or more likely than alternative diagnosis	3
Heart rate greater than 100 beats/min	1.5
Immobilization (bedrest ≥ 30 days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (Receiving treatment,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

In patients with low to moderate 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

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

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**

Impact of a Rapid Rule-Out Protocol for Pulmonary Embolism on the Rate of Screening, Missed Cases, and Pulmonary Vascular Imaging in an Urban US Emergency Department.

Kline JA, *et al*., Ann Emerg Med. 2004;44:490-502.

Rapid Rule-Out Study

- Study Objective
  - To evaluate a “rapid rule out” protocol for patients with suspected PE in the emergency department utilizing a point of care D-dimer
- Hypothesis
  - the accelerated screening protocol would result in
    - decreased length of stay
    - fewer than 1% of patients would have an adverse outcome
    - would not result in increased imaging

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Study Design/Methods

- Baseline study conducted to determine underlying utilization of imaging and length of stay
- No D-dimer used
- Intervention: “Rapid rule-out criteria” initiated
- Primary outcome= presence of adverse outcome within 90 days of ED visit, defined as new case of treated PE, DVT, or sudden unexpected death
- Secondary outcome= length of stay and absolute number of imaging studies performed

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Rapid Rule out Protocol for PE

Two key pieces of information:

Only low risk patients; as defined by the Charlotte Rule

Once eligible for the screening protocol, patients had point of care qualitative D-dimer and measurement of alveolar dead space prior to or in lieu of imaging

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Results

Before Protocol

61,322 total ED visits

453 evaluated for PE (0.74% of total); all 453 were imaged

5 false negatives in 90 d f/u period

FN rate 1.2%

After Protocol

102,848 total ED visits

1460 evaluated for PE (1.4%)

657 imaged (35%)

752 had a negative protocol

5 went on to have adverse event at 90 days for a FN rate of 0.66%

More positive scans:
657 scans to find 74 PE vs. 453 scans to find 37 PE
11% vs. 8% positivity rate --- P<0.001

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Length of Stay

Median LOS decreased by 25% overall from 385 minutes to 297 minutes. ($p<0.0001$).

For discharged patients, LOS improved by 127 minutes and by 38 minutes for admitted patients.($p<0.001$)

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Imaging

Total number of CT or V/Q scans did not increase

The percentage of patients imaged decreased as 100% of patients with suspected PE were imaged during the baseline period and 35% were imaged after protocol initiation

Screening for PE doubled with the adoption of the protocol without increasing the census-adjusted rate of pulmonary imaging (actually declined slightly)

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

Key points

POCT and the development of an accelerated protocol decreased ED LOS, decreased the number of patients requiring imaging, and resulted in less than 1% adverse outcomes

This was accomplished with a qualitative D-dimer

Kline JA, *et al.*, *Ann Emerg Med*. 2004;44:490-502.

Author Conclusions

Kline, Annals of Emergency Medicine

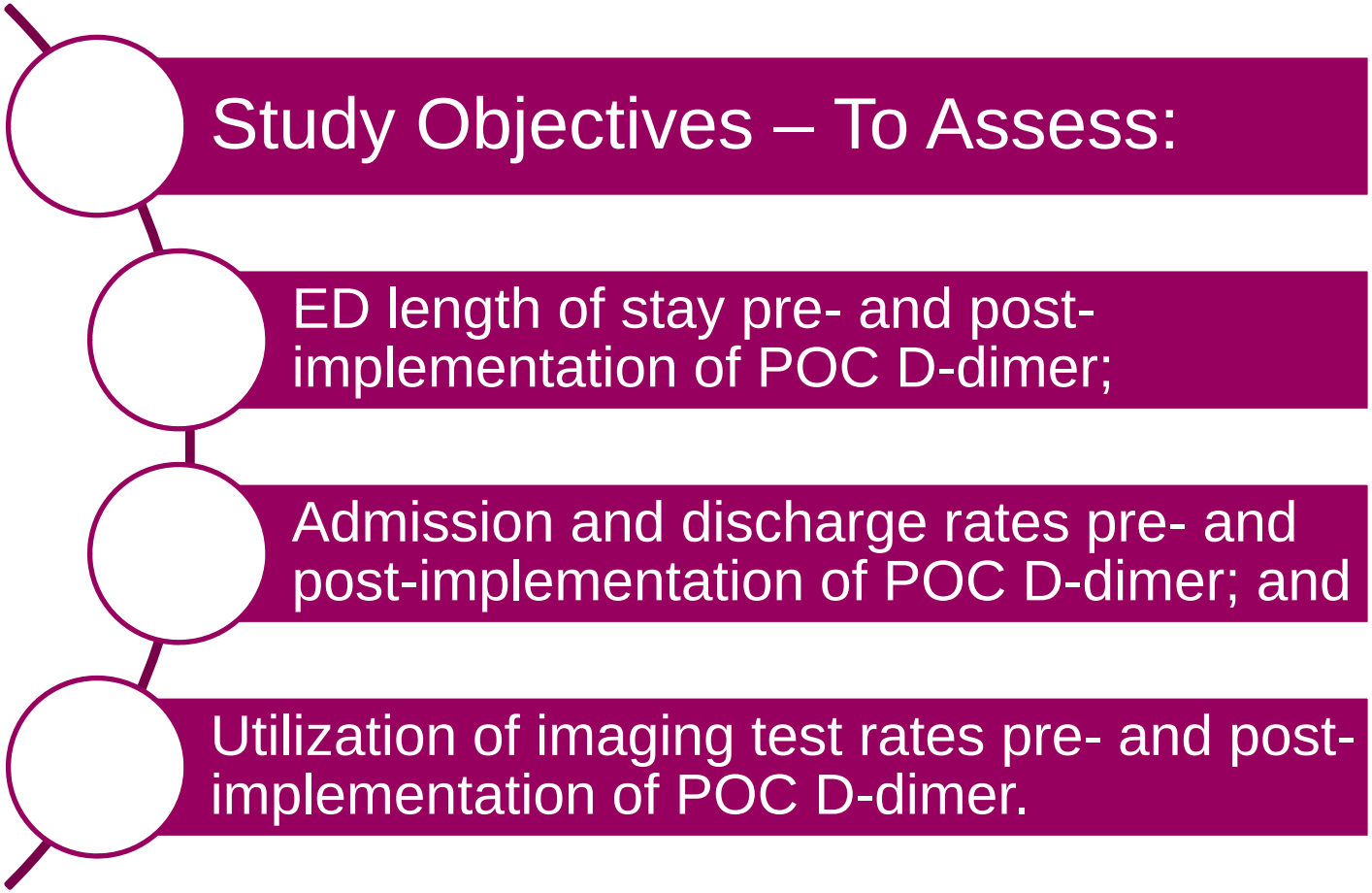
- “We considered using a quantitative d-dimer assay performed in the hospital laboratory…we believe that point-of-care testing is more efficient and more practical than quantitative d-dimer testing performed in a central hospital laboratory.”
- If they had the quantitative test available, they would not have used alveolar dead space measurements, which could have further improved turn around time

Kline JA, *et al., Ann Emerg Med*. 2004;44:490-502.

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



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; and
- 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.

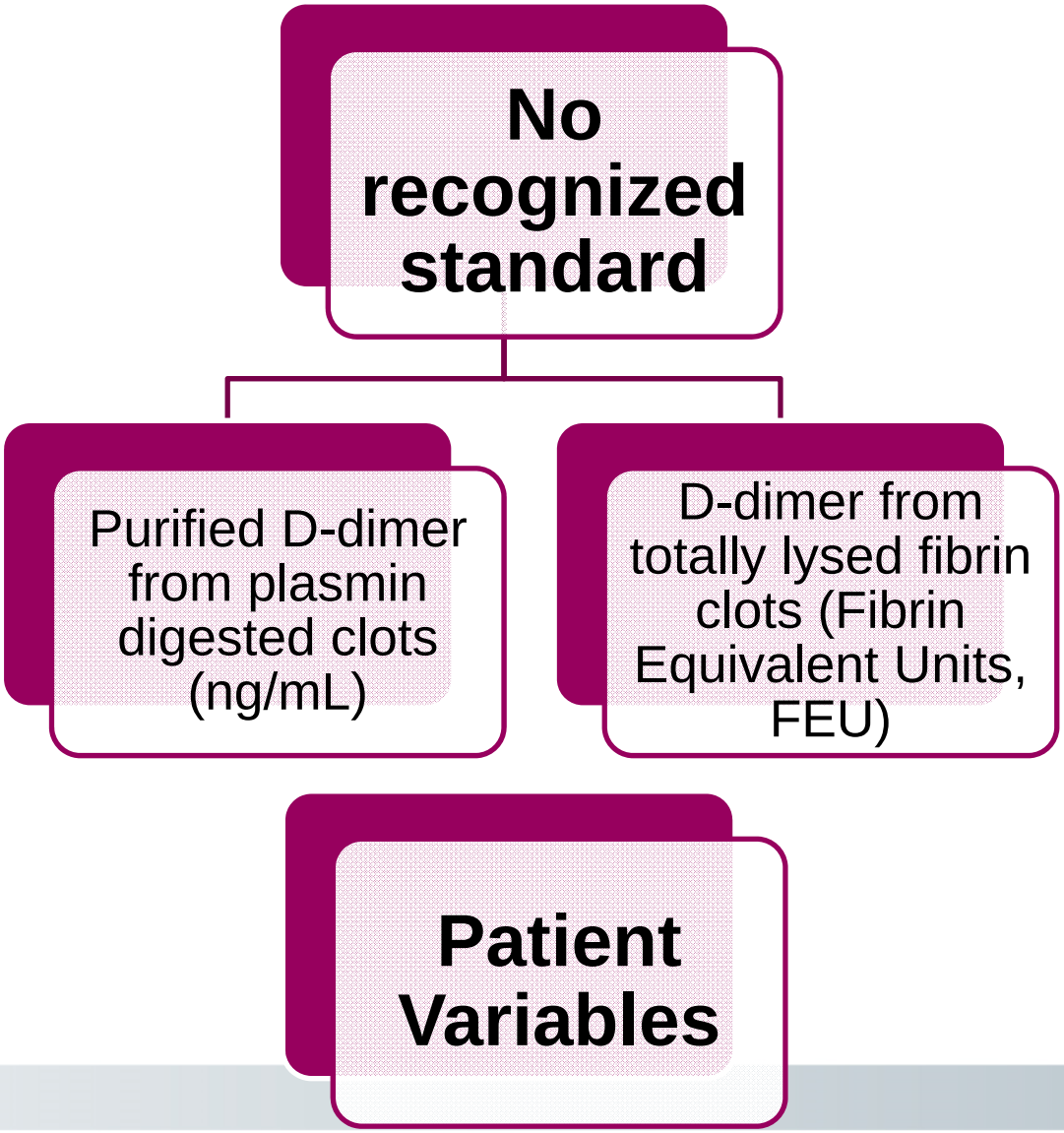
These changes should result in decreased costs.

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

D-dimer tests: Choices

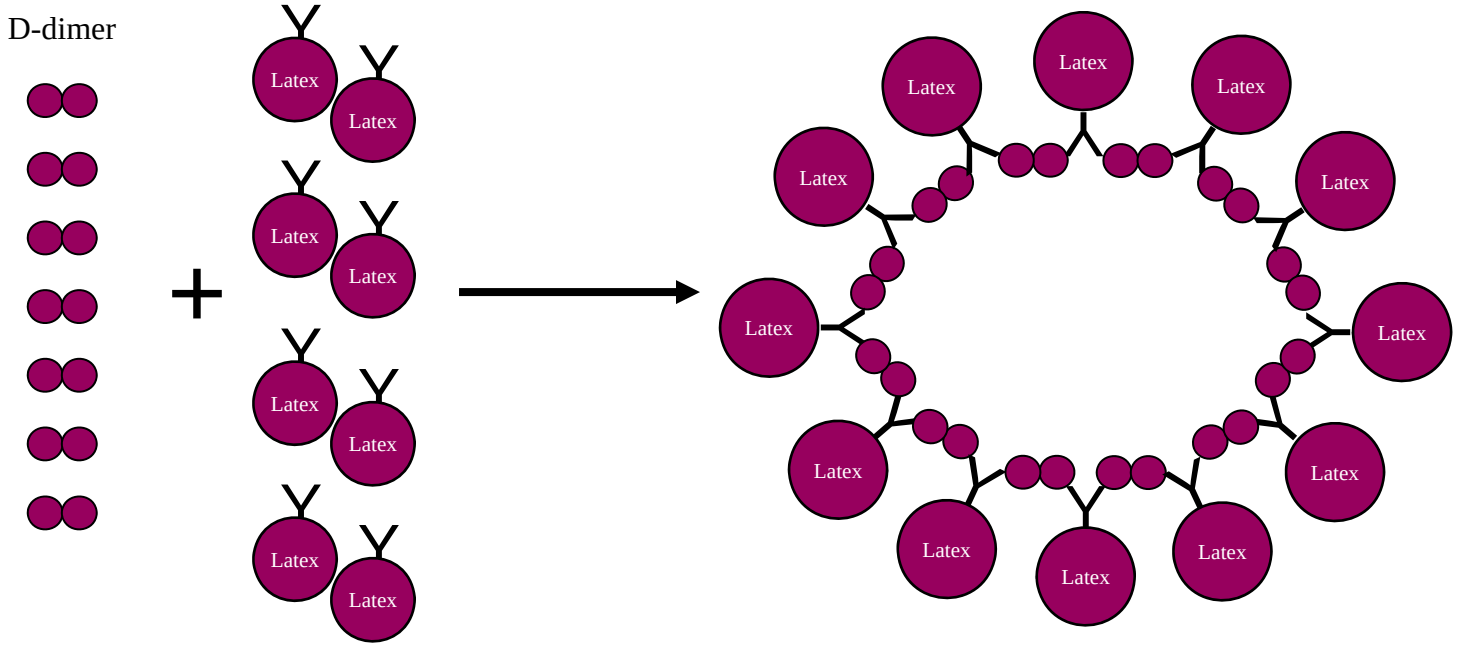
Latex Agglutination	• Qualitative or semi-quantitative • Relatively insensitive
Whole Blood Agglutination	• More sensitive than latex • Somewhat subjective
Turbidimetric	• Much less subjective
ELISA/ Immunoassay	• High analytical sensitivity • Historically laborious

D-dimer tests: Challenges



How Were D-Dimers Measured?

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



- Similar to the 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

Enzyme-Linked Immunosorbent Assay

Synonymous with Enzyme Immunoassay (EIA)

1st ELISAs were run in microtiter plates (aka ELISA plates)

Immunometric or Sandwich Assays

All involve capturing the analyte

All involve measuring captured analyte using a form of signal generator

Signal Generators

EIA uses an enzyme-labeled antibody to convert an “invisible” molecule into a “visible” molecule

FIA (Fluorescence immunoassays, or IFA, immunofluorometric assay) use a fluorescent-labeled antibody as the signal

ELFA-Enzyme linked fluorescent immunoassay

Barriers to POCT

Testing is usually not performed by laboratory personnel

Will the testing be too complicated for non-laboratory people?

- Will the nurses screw it up?

Will they forget to run controls?

Will they forget to document the testing

- Will all results get billed?

Will the testing be accurate and precise enough to be clinically useful?

Attributes of a Useful POC System

- Point of Care diagnostic systems should:
  - use small volumes of whole blood
  - be simple enough that any healthcare worker can be trained to run the test
  - require only a single step for completion
  - not require calibration
  - involve minimal use of external controls
  - have self-contained QC
  - provide quantitative, rapid (no more than 15-20 minutes), accurate results for a entire panel of markers simultaneously
  - allow for multiple patients to be assayed without sacrificing time to result
  - have a footprint no larger than a desktop phone
  - be capable of interfacing with the hospital's LIS

Who Does the Testing?

POCT can be performed in many different scenarios

Nursing

Laboratory

Phlebotomy

ED Stat Lab

EMT

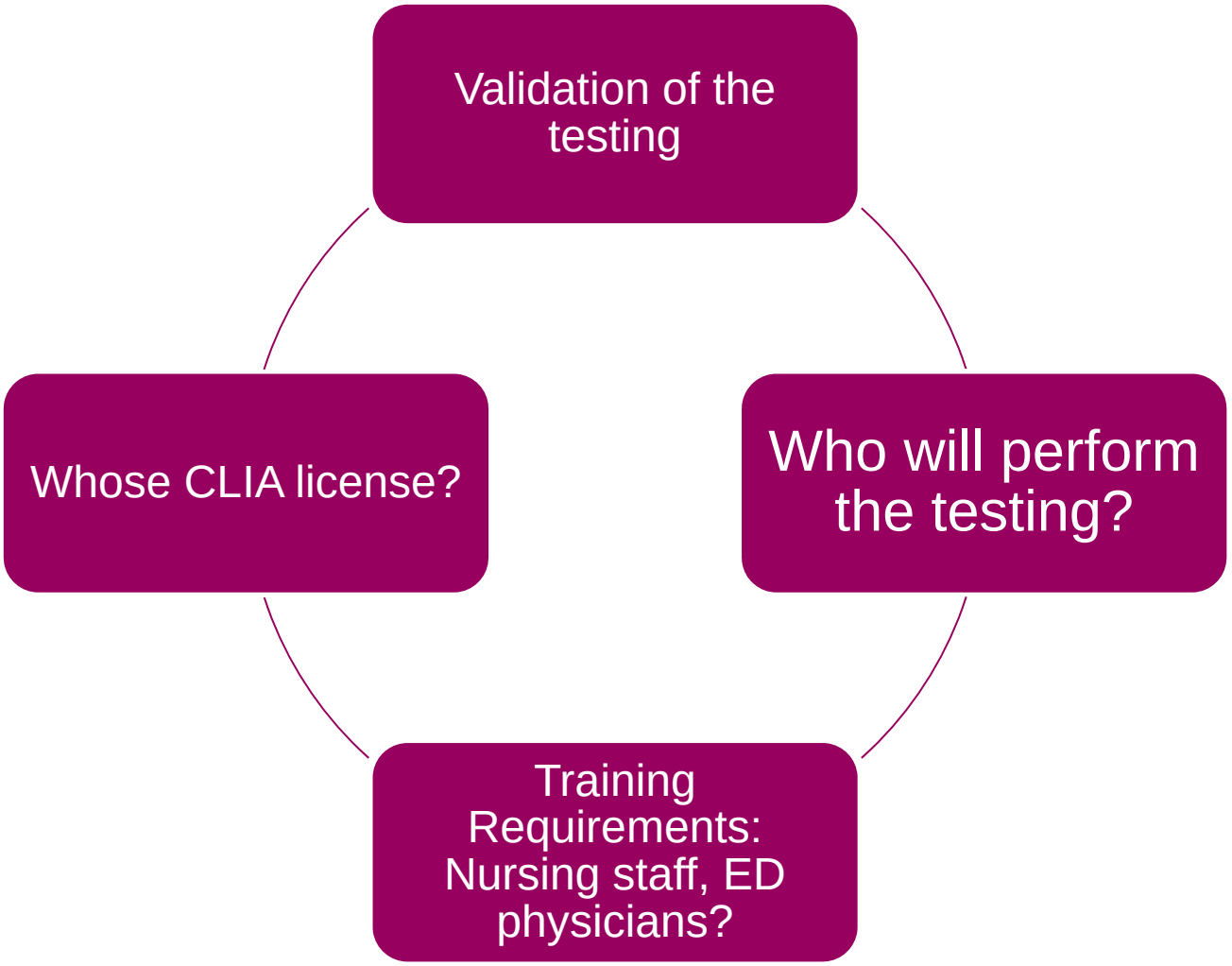
The best solution depends on the site

In all instances, the lab should have visibility and control over the testing

Instrument/Platform Considerations

- What is the volume of testing to be managed?
- What other tests might you want to run in the ED?
- Footprint – i.e. how much space is required?
- How complex is it to operate?
- Instrument daily/weekly/monthly maintenance?
- QC: How often and who will do the QC?
- Workflow: Throughput and how efficiency?
- What are the consumables and waste?

Quality Control and Training



Whose CLIA license?

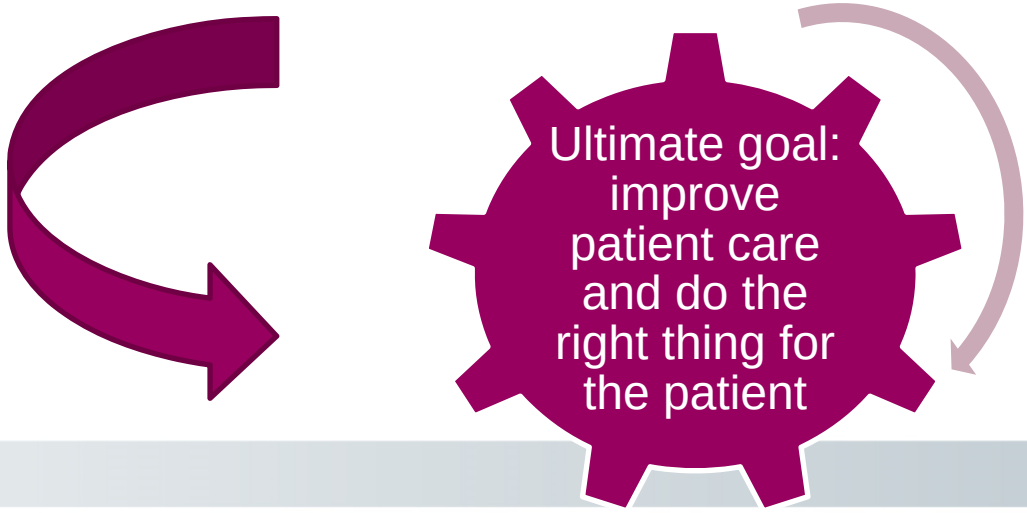
Separate POC certificate for test site?

Must assure that all requirements are met

Daily/weekly/monthly maintenance

Proficiency testing

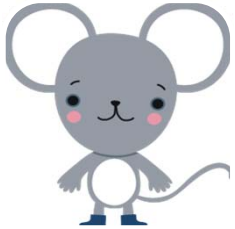
Inventory management



Connectivity is a Must

- Lab MUST have visibility to testing and testing results
- Connectivity is essential to the reduction of testing errors
- Good connectivity permits central monitoring of all devices in the facility
- Connectivity ensures billing for all billable tests
- All the reputable POC vendors provide connectivity to all major interfaces

Negative Control



Ideally the Negative Control should be comprised of a mixture of IgG from the animals producing the antibodies for the test.

If HAMA or heterophile antibodies persist in a sample after exposure to neutralizing antibodies, they will bind to the Negative control line

- Non-analyte derived signal at the Negative Control will invalidate the test

The Negative Control assures that positive results are due to analyte derived signal

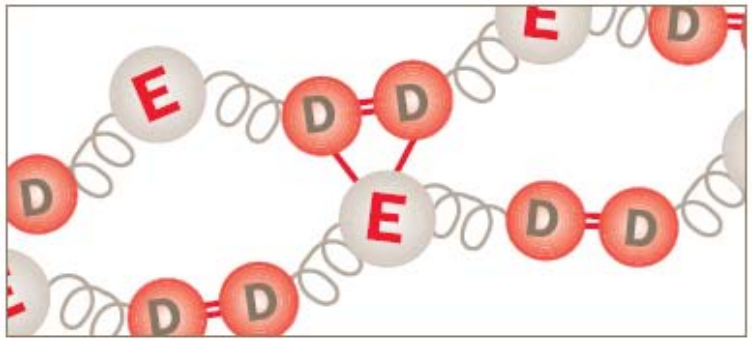
Positive (Immunoreactive) Controls

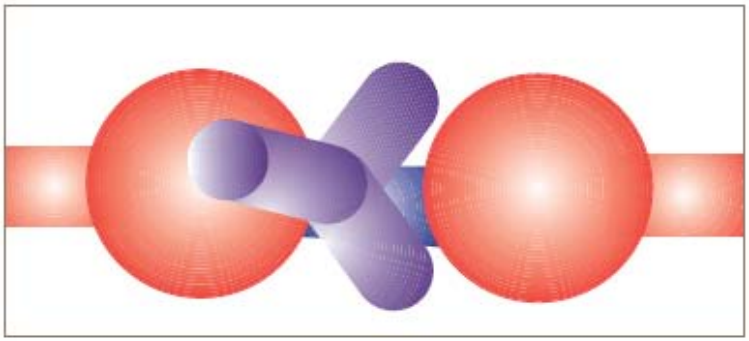
Ideally, the Positive Control should be an immunoassay that runs concurrently with the analyte immunoassay

The Positive Control assures that negative results are due to the absence of analyte, not to a failure of immunoreactive components of the test system

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

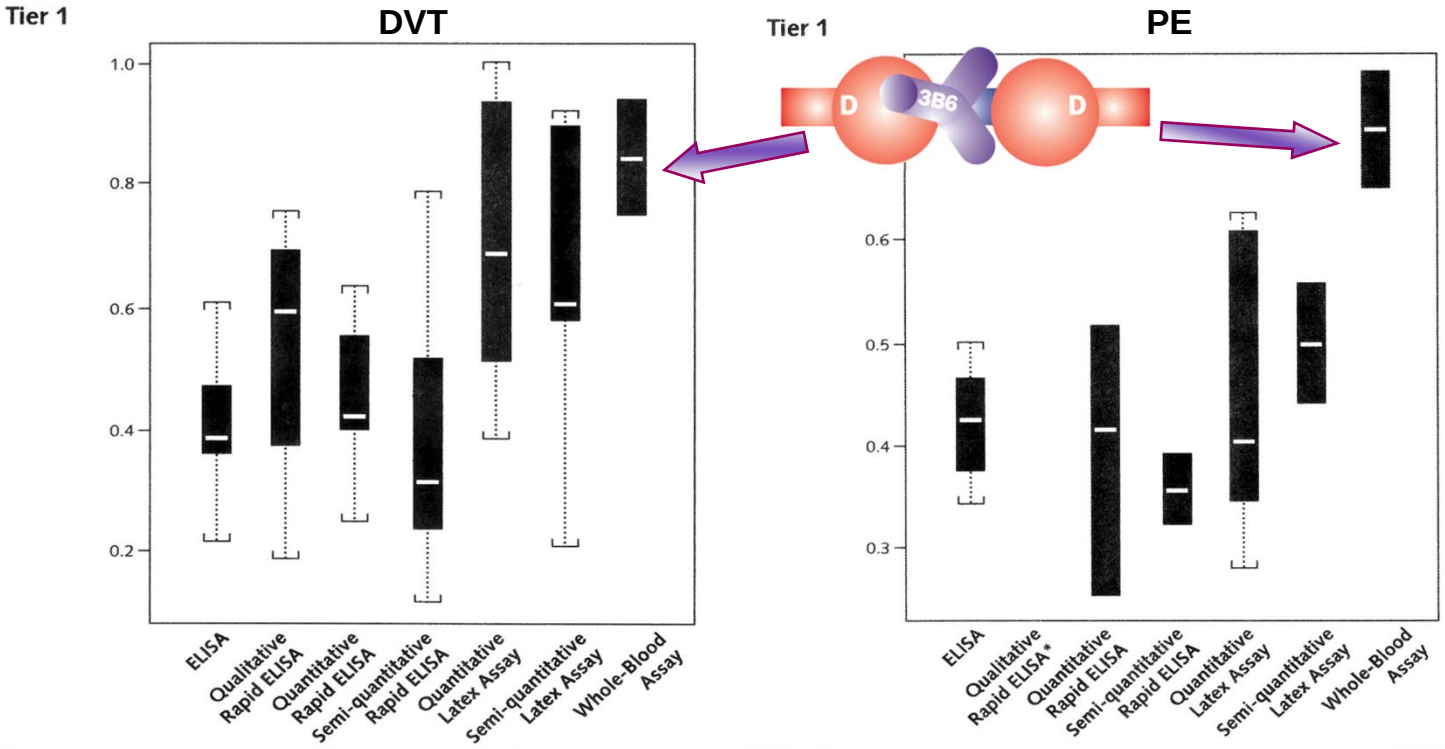




- The 3B6 monoclonal antibody offers high specificity due to its affinity to the cross-linking epitope (recognition site) of D-dimer

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.

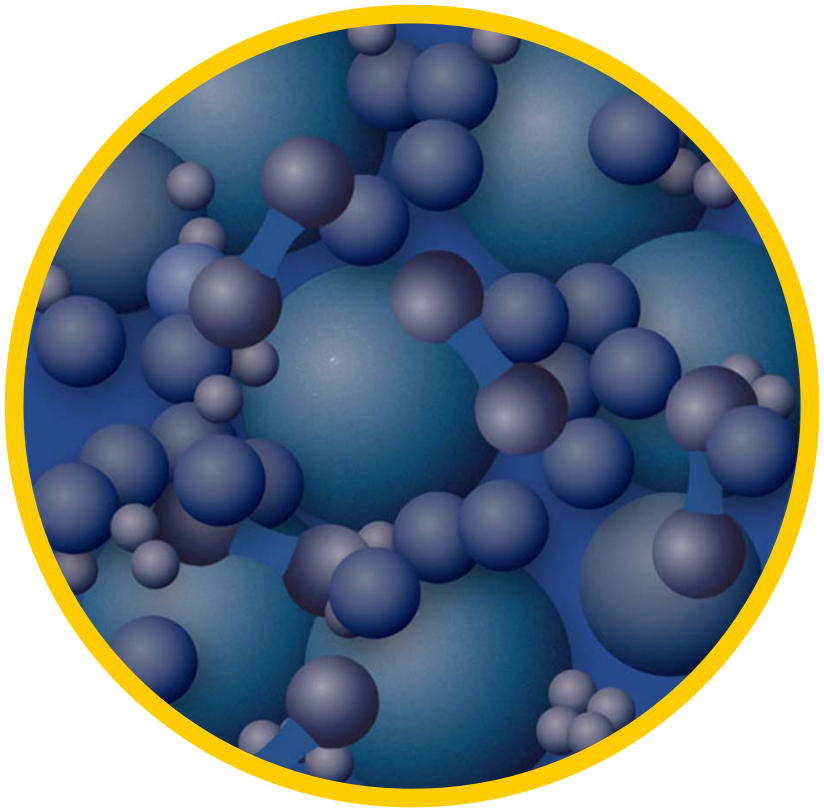
Fibrin Assay Comparison Trial (FACT)

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
- 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.

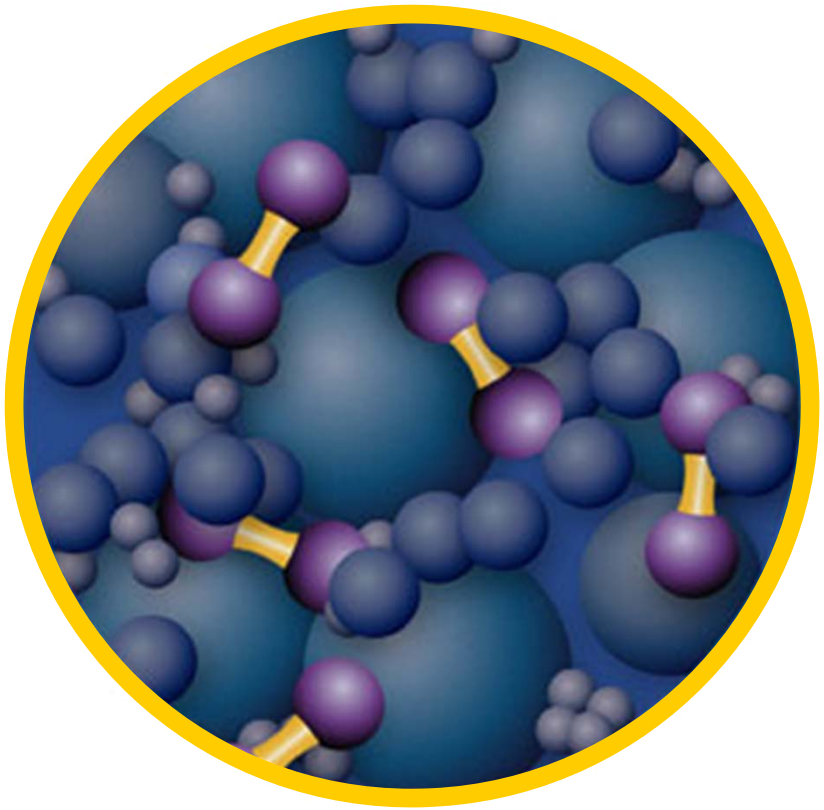
Distinguish from other FDPs



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

D-dimer, conclusions

- Most appropriate for ED patients as hospitalized patients 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.

Questions????