

## Pathophysiology and Diagnosis of Venous Thromboembolism (VTE)

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### Agenda

- Pathophysiology of Pulmonary Embolism
- Diagnosis
  - History & Physical examination
  - Noninvasive testing
  - Invasive testing
  - Lab work
- D-dimer Tests
  - Latex
  - Immunometric
  - Specificity
  - Point of Care

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### Venous Thromboembolism (VTE)

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

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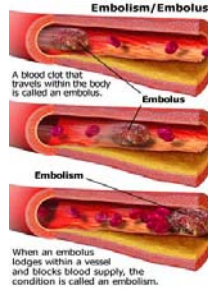
## Venous Thromboembolism

→ 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

→ Once dislodged, the clot becomes an embolism when it obstructs blood flow in the vessel. Potentially traveling to the lungs. (Pulmonary Embolism)



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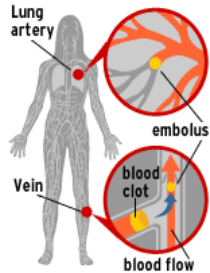
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## Physiology

→ Pulmonary Embolisms are clots that travel through inferior vena cava to reach and block a pulmonary vessel.

→ 90% of blood clots that cause PE form in the deep veins of the leg.



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## Pulmonary Embolus

- 600,000 episodes/year in the US
- 100,000 – 200,000 deaths/yr
- Mortality rates in patients with undiagnosed PE is 30%
- 10% die within the first hour
- Prognosis depends on underlying disease state & appropriate diagnosis and therapy

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### Risk Factors

- Age >40 yr
- History of VTE
- Surgery requiring >30 min of anesthesia
- Prolonged immobilization
- Congestive heart failure
- Fracture of pelvis, femur or tibia
- Cancer
- Obesity
- Pregnancy or recent delivery
- Estrogen therapy
- Genetic or acquired thrombophilia

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### Signs and Symptoms

- Shortness of breath
- Pleuritic CP
- Hemoptysis (blood tinged sputum)
- Increased heart rate
- Increased resp rate
- Cough
- Anxiety
- Syncope
- Fever
- Wheezing

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### Diagnosing PE

- ➔ History & Physical examination
- ➔ Noninvasive testing
- ➔ Invasive testing
- ➔ Lab work

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## Diagnosing PE

- DVT and PE
  - Non-Invasive scan methods
    - Not always available
    - Difficult to interpret
  - Invasive techniques
    - Often diagnostic and very specific
    - Involve a certain risk of morbidity and mortality
    - Not frequently performed
  - Laboratory tests
    - No single test provides ability to rule in PE
    - May be able to rule out PE

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## History & Physical

- Clinical or Pre-Test Probability
  - Physician assessment prior to obtaining other diagnostic tests
  - Risk factor point system for determining PE probability
    - Clinical signs/symptoms of DVT (dyspnea, chest pain, fever, patient history)
    - Alternate diagnosis deemed less likely than PE
    - HR >100 bpm
    - Immobilization or surgery in prior 4 weeks
    - Previous DVT or PE
    - Hemoptysis
    - Cancer; Receiving treatment or treatment < 6 mos.
  - Patient classified as Low, Medium or High risk (<10%, 10% - 70% and >70%, respectively, for prevalence of PE)

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## Diagnostic Testing

- Ultrasound (Duplex, Doppler or Compression)
  - Uses Doppler sound wave properties to visualize venous flow and direction
  - Most frequently used method for DVT
  - Used to aid in diagnosis of PE
    - Non-invasive
    - Excellent sensitivity in proximal vein thromboses, but poor in DVT
    - Negative result does not rule out VTE (Positive in only 50% of patients with embolism)
    - Reliability of the exam depends on:
      - Material quality
      - Operator competence
      - Patient profile (obesity, casts, unusual anatomy, etc.)

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## Diagnostic Testing

- Venography or Contrast Venography
  - Detects defects in venous system
  - Gold standard for DVT (only test to rule in)
  - Not commonly used
  - Requires injection of <sup>125</sup>I – radio-opaque dye
  - Typically performed in Radiology suite
    - Excellent sensitivity for all thrombosis
    - Requires skilled technicians and clinicians to perform and interpret results
    - Invasive technique
    - May result in DVT, allergic reactions, or mortality (0.5%)
    - More expensive than other radiographic methods

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## Diagnostic Testing

- Ventilation Perfusion Scan (V/Q Scan)
  - Used to observe ventilation and perfusion deficiencies
  - Most commonly used test for PE
  - Qualitative result for PE (normal to high probability)
  - Overall sensitivity and specificity of a high-probability V/Q scan are 41% and 97%
  - Typically performed in Radiology/Nuclear Medicine
    - Requires transport of potentially unstable patients outside ED
    - Requires injection of radioactive material and inhalation of radiographic gas
    - Has limited utility in patient with severe preexisting pulmonary diseases or history of PE
    - May require further diagnostic testing to confirm PE (70% are non-diagnostic)

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## Diagnostic Testing

- Computed Tomography (CT Scan) - Helical or Spiral
  - Advanced computerized x-ray technology
  - Performed in Radiology
    - Allows direct visualization of emboli
    - Sensitivity ranges from 57% to 100%, Specificity 78% - 100% (based on utilization of single or multiple sliced technology and location of emboli)
    - Requires transport of potentially unstable patients outside ED
    - Contrast medium poses risk to patients with renal insufficiency and diabetes
    - Requires high level of expertise to perform and interpret results
    - "Normal CT scan indicates reduced likelihood of PE, but cannot be used to rule out [PE] with the same degree of certainty that a negative V/Q scan provides."

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## Diagnostic Testing

- Magnetic Resonance Imaging (MRI)
  - Electronic imaging magnet
  - Not commonly used
  - Performed in stand alone area of hospital
    - Not readily available
    - Not used for emergency diagnosis
    - Very costly

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## Diagnostic Testing

- Pulmonary Angiogram or Angiography
  - Determines filling defects within pulmonary arterial tree
  - Not commonly performed
  - Gold standard for PE (the only rule in test)
  - Contrast medium injected into large vein
  - Performed in Radiology or Cath Lab
    - Excellent sensitivity for all thrombosis
    - Expensive method
    - Requires transport of potentially unstable patients outside ED
    - Invasive; may have major non-fatal implications (0.8%), rarely death (0.5%)
    - Requires technical expertise for performance and interpretation

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## Diagnostic Testing

- O<sub>2</sub> Sat and Arterial Blood Gas (ABG)
  - May be normal in 15% of patients
- Chest X-Ray
  - Identify areas of decreased perfusion
  - First imaging procedure obtained when one presents with dyspnea
    - Most are abnormal but remain non-diagnostic for PE
- EKG
  - Often not diagnostic

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## D-Dimer

- A specific fibrin degradation product released by a dissolving fibrin clot that can be measured in peripheral blood.
- ½ life of 6 hrs in population with normal renal function
- Non-invasive test
- Relatively low cost laboratory test vs imaging methods
- Aids in ruling out PE
  - high negative predictive value (95%-100%)
  - high sensitivity (90%-100%)
- Lacks standardization
- Not useful for in-patient VTE testing
- Subsequent testing is required to rule in or rule out other conditions

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## Other conditions elevating D-Dimer

- Age
- Coronary disease
- Pregnancy
- Peripheral arteriopathy
- Bleeding disorders
- Thrombolytic treatment
- Cancer
- Liver disease
- Infection
- Inflammation
- Hematoma

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## Medical Treatment

- Immediate full anticoagulation is mandatory
  - IV heparin
  - Oral coumadin: minimum of 6 months, indicated longer in patients with reoccurring VTE.
  
- Thrombolytics
  - Should be considered for patients who are hemodynamically unstable, patients who have right heart strain, and high risk patients with underlying poor cardiopulmonary reserve
  - Superior within first 24 hrs

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## Medical Treatment

- Surgical Intervention
  - Embolectomy: surgical removal of clot
    - Indicated for massive PE
    - Rarely performed
    - Mortality rate 25%
  - Inferior Vena Cava filter (Greenfield Filter)
    - Indicated for patients with acute VTE who have an absolute contraindication to anticoagulant therapy: recent surgery, hemorrhagic stroke, or recent/significant bleeding
    - Survival of massive PE where recurrent PE is inevitable
    - patients with recurrent VTE and not tolerating anticoagulant therapy

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## Summary

- PE is a very serious condition and major healthcare problem
- When presenting to the ED, physicians must quickly assess, diagnose and disposition a wide range of acute patients; AMI, CHF, PE or other diagnoses
- Multiple methodologies are utilized when attempting to rule in or rule out pulmonary embolism
- Pulmonary embolisms are treatable and preventable if diagnosed
- D-dimer alone is not a diagnostic test for PE
- D-dimer and traditional cardiac markers demonstrate prognostic and risk stratification value for PE
- A multi-marker strategy is needed to assist physicians with the diagnostic dilemma to appropriately disposition patients and determine level of intervention with AMI, CHF and PE.

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"Is Your Test an ELISA?"

(What is ELISA?)

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## ELISA / EIA

- **Enzyme-Linked Immunosorbent Assay**
  - Synonymous with Enzyme Immunoassay (EIA)
  - 1<sup>st</sup> 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 (or IFA, immunofluorometric assay) are similar to EIA except that they use a fluorescent-labeled antibody as the signal
  - FIA can be just as sensitive as EIA (e.g., TnI or BNP)

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"Is Your Test an ELISA?"

Interpretation:  
We Don't Want Agglutination!

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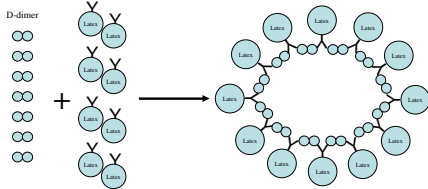
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## How Were D-Dimers Measured?

### → Latex Agglutination:

- Big clumps that are visible to the naked eye



### → Turbidimetric:

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

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## Testing Methods

- Latex Agglutination:
  - Poor Negative Predictive Value
    - ~ 52 – 57%
  - Subjective
  - Lower sensitivity
    - ~ 61%
- Turbidimetric systems
  - Automated agglutination method
  - Less precise

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## Turbidimetric Assays

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



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## POC Immunometric Assay Technology

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## Assay Procedure - What the User Sees

### Step 1



Add whole blood to protein chip

### Step 2



Insert protein chip into instrument

### Step 3



Read results

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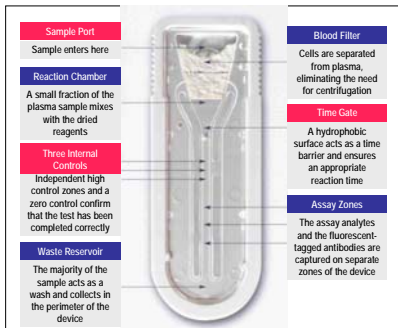
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## Microfluidics of the Test Device – What the user doesn't see




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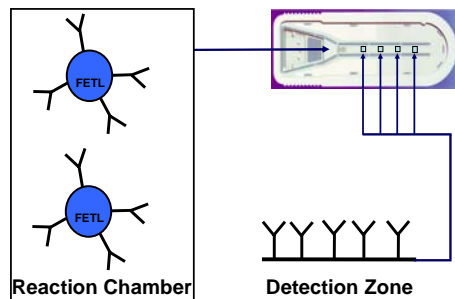
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## Test Device Components




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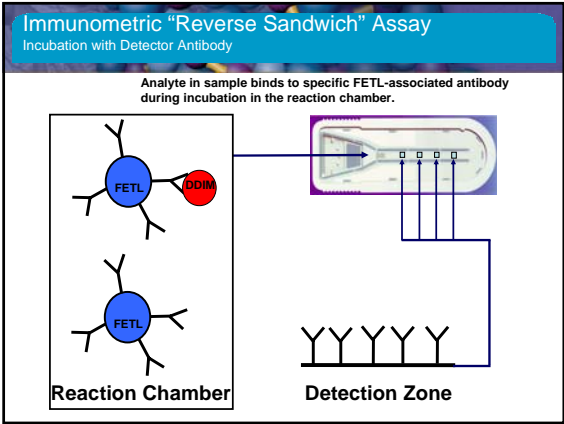
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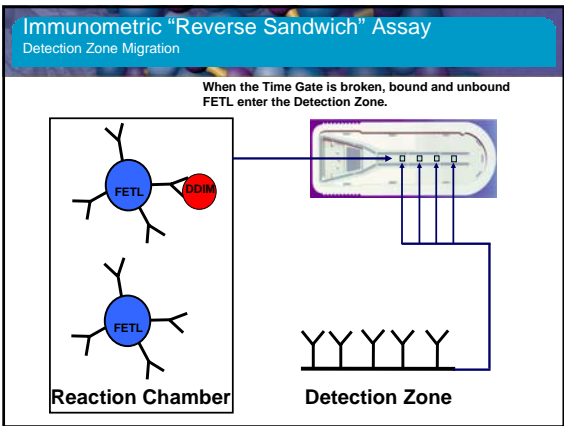
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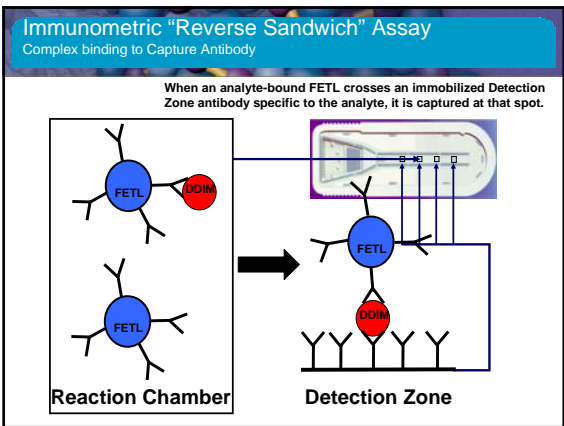
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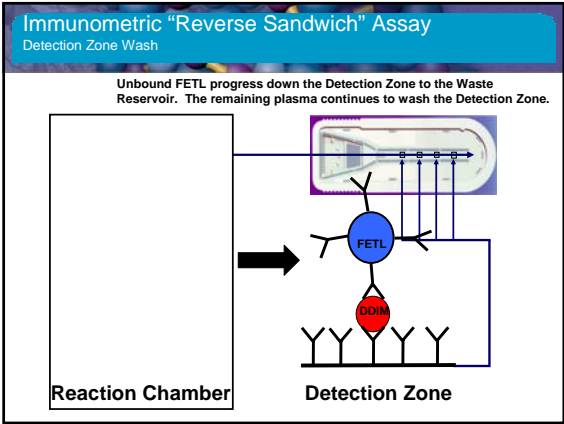
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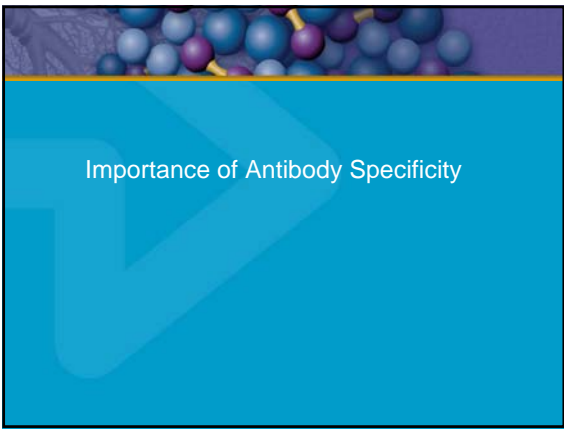
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### Value of D-dimer Antibody Specificity

- 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

Stein PD, Hull RD, Patel KC, et al. D-Dimer for the Exclusion of Acute Venous Thrombosis and Pulmonary Embolism: a Systematic Review. Ann Intern Med. 2004; 140:589-602.

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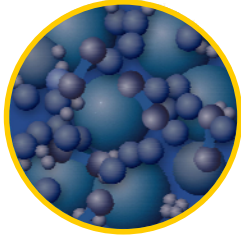
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### The Ability to Distinguish from other FDPs



- 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

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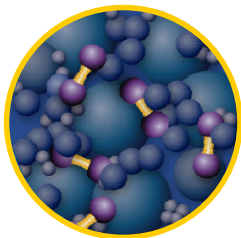
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### The Ability to Distinguish from other FDPs



- D-dimer

The 3B6 antibody detects only cross-linked FDPs (D-dimer) for accurate measurement of the sample

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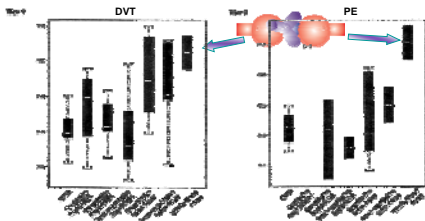
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### Review of 78 DVT/PE Studies

- 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, Hull RD, Patel KC, et al. D-Dimer for the Exclusion of Acute Venous Thrombosis and Pulmonary Embolism: a Systematic Review. *Ann Intern Med.* 2004; 140:589-602.

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## 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 report falsely high values
  - 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, Zepf S, Ergul H, et al. The Fibrin Assay Comparison Trial (FACT). Thrombo Haemost. 2001;86:671-8.

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## Impact of Rapid Rule Out Protocol for PE in the ED

Rate of Screening, Missed Cases and Pulmonary Vascular Imaging

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## Kline et al., Annals of Emergency Medicine, Nov 2004

### → 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

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## 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

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## Rapid Rule out Protocol for Suspected PE

- Two key pieces:
  - 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

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## Results

- Baseline period (no D-dimer): 61,322 total ED visits, 453 evaluated for PE (0.74% of total); 37 actual PE's, 5 false negatives in 90 d f/u period, FN rate 1.2%
- Intervention: 102,848 patients seen, 1460 evaluated for PE, 1368 entered into study (92 missed study due to MD not informed of protocol); 1200 met rapid protocol criteria

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## Results

- 1460 evaluated, only 657 imaged, or 35%
- 74 PE's diagnosed
- 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 dx 74 PE vs. 453 scans to dx 37 during the baseline period (11% vs. 8% positive rate)—P<0.001

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## 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)

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## 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 the intervention; census-adjusted rate of pulmonary imaging did not increase (actually declined slightly)
- Screening for PE doubled with the adoption of the protocol without increasing the use of imaging

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### 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

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### 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

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### Can a negative D-dimer exclude PE? 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  $\leq 2$

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## A Quantitative POC D-dimer Test Compared to Lab Analyzer Tests

Comparisons to Vidas, Stratus CS, and  
HemosIL (ACL Advance)

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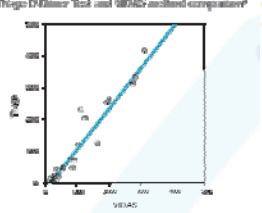
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### Analytical Comparison to VIDAS (Mass General)

**Triage D-dimer Test and VIDAS method comparison**




→ Highly correlated with VIDAS ( $r = 0.962$ )

→ According to the authors -

- In conclusion this study demonstrates that the Triage D-dimer assay using a cutoff of less than 400 ng/mL compares favorably with the VIDAS D-dimer assay using a cutoff of less than 500 ng/mL.

Stat	Parameter Value	Correlation Coefficient
Slope	1.320	$r=0.962$
Intercept	-24.36	

Lai-Leung-Chow et al. Evaluation of the Biotrace Triage® quantitative whole blood D-dimer assay and comparison with the bioMérieux VIDAS® D-dimer exclusion test... *Point of Care* 2009;4:133-137




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### Wheaton Franciscan Study Statistics

	Sensitivity/ NPV	Specificity	PPV
Triage	100%	48.9%	14.7%
Vidas	100%	41.5%	11.3%
Stratus	100%	53.7%	13.9%
ACL	100%	47.8%	14.4%

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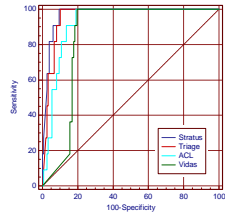
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## Comparative ROC Curves



	AUC	SE	95% CI
Stratus	0.951	0.026	0.931 to 0.973
Triage	0.957	0.025	0.913 to 0.983
ACL	0.854	0.056	0.870 to 0.965
Vista	0.845	0.078	0.770 to 0.889

Manuscript in preparation

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## D-dimer, conclusions

- Most appropriate for ED patients as in patients will usually have elevated levels
- Highly sensitive, not very specific
- Is a screening test with great potential to reduce imaging, cost, and length of stay, particularly when used at the point of care

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Questions?

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