


Generate Knowledge



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

Paul Riley, PhD, MBA

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Disclosures

- Salaried employee of Diagnostica Stago, Inc.

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Learning Objectives

- Define and differentiate DVT, PE and VTE
- Learn PE prevalence, risk factors, mechanism of disease, symptoms, and clinical decision rules for risk stratification
- Explain the role of clinical decision rules and D-dimer in the diagnostic algorithm and their impact on imaging utilization

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Presentation Outline

- **Overview of Venous Thromboembolism (VTE)**
 - Define deep venous thrombosis (DVT) and Pulmonary Embolism (PE)
 - Prevalence, risk factors, and treatment
 - Post-thrombotic syndrome
- **Clinical decision rules**
 - PERC Score
 - Wells Score
- **Diagnostic algorithm (including use of D-dimer)**
- **Case studies**
- **Use of D-dimer vs. imaging techniques**
- **Recent clinical studies of different D-dimer assays; extending utility of the assay**
 - Age adjusted cutoffs
 - Prospective use of the D-dimer

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Overview of Venous Thromboembolism (VTE)

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Venous Thromboembolism (VTE)

- **VTE is one disease entity with two patterns of clinical presentation:**
 - Deep Vein Thrombosis (DVT) is blood clot in leg veins
 - Pulmonary Embolism (PE) involves clot migrating from leg veins to the lung, associated with significant morbidity & mortality
- **VTE affects 300,000 to 600,000 Americans annually, results in ~100,000 deaths**
- **~30% of patients presenting with suspected VTE have PE, with 20 - 25% presenting as sudden death, diagnosed at autopsy (27,000 people)**
- **PE is the leading cause of preventable hospital death and maternal mortality in the US**
- **Treat with anticoagulation for customized length depending on patient needs, family history, comorbidities, bleeding risk, other medications, etc.**

Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4 Suppl):S495-501.

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Women's Health Initiative Data 1993-2012

In a study of women's health based on Medicare claims, VTE rates are different between ethnic groups along with associated clinical factors

Predisposing Conditions	All	White	Black/African American	Hispanic/Latino	Asian/Pacific Islander
Total participants	71,267	61,230	5,514	17,959	1,819
Total number of VTE	2,881	2,249	215	32	117
Mean follow-up in years	6.37	6.46	6.75	5.89	7.46
VTE incidence ^a	4.06	3.68	3.93	0.18	6.40
Adjusted rate ratio (95% CI)	-	1.00 ^b	0.78 (1.28, 1.36)	0.76 (0.35, 1.11)	0.20 (0.22, 0.36)
95% CI	-	-	0.68	0.16	0.09

^a Adjusted for 12 cardiovascular risk factors, VTE, venous thromboembolism, ^b Adjusted rate ratio (95% CI)

^c Reference group

^d Includes other race and ethnicity categories

Burven DR, Wu C, Cirillo D, Rossouw JE, Margolis KL, Limacher M, et al. Venous thromboembolism incidence, recurrence, and mortality based on Women's Health Initiative data and Medicare claims. *Thromb Res.* 2017; 150: 78-85.

PE Incidence US vs. Outside US (Europe + Canada)

Due to difference in clinician practices, there is a much higher number of patients suspected of PE in the US and prescribed imaging to confirm PE compared to outside US suggesting the higher rates of unnecessary imaging procedures in the US compared to Europe and Canada

	US	OUS (Europe + Canada)	US + Canada	Europe (w/o Canada)
PE Prevalence (%)	2.5	10.7	3.7	10.9
Negative DD (%)	76	68.8	75.1	68.8

	OUS	US	p
Negative DD with Low PTP	20/405 (4.9%)	48/227 (20.3%)	p < 0.001
Negative DD with moderate PTP	15/78 (19.2%)	20/45 (44.4%)	P = 0.01

Perrot G, Caterino J, Maignan M, Tissier C, Kassis J, Lazarchick J, et al. D-Dimer Use and Pulmonary Embolism Diagnosis in Emergency Units: Why Is There Such a Difference in Pulmonary Embolism Prevalence between the United States of America and Countries Outside USA? *PLoS One.* 2017 Jan 13;12(1):e0169268.

Signs and Symptoms are Nonspecific

- DVT**
 - Pain tenderness and/or swelling in the calf or leg
 - Discoloration of the calf that can extend to the foot
 - Symptoms of PE
- PE**
 - Difficulty breathing
 - Sharp chest pain worsened by taking a deep breath
 - Blood in the sputum
 - Rapid heart rate

www.emedicinehealth.com/slideshow_pictures_deep_vein_thrombosis_dvt/article_em.htm
accessed Aug 28, 2017

Anatomy of a Clot

http://www.rdist.com/blood_clots/page8.htm, accessed Aug 28, 2017

<https://www.thrombosisadvisor.com/images-library-about-venous-arterial-thrombosis/>, accessed Aug 28, 2017

Pulmonary Embolism

<https://www.thrombosisadvisor.com/images-library-about-venous-arterial-thrombosis/>
accessed Aug 28, 2017

Risk Factors for DVT and PE

HYPERCOAGULABLE STATE

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

VASCULAR WALL INJURY

- Trauma or surgery
- Inteepuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

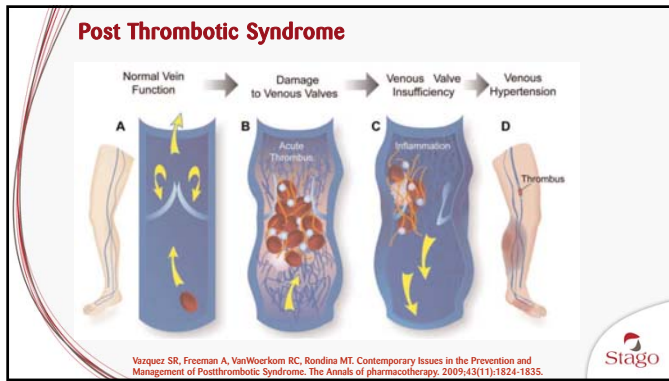
CIRCULATORY STASIS

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

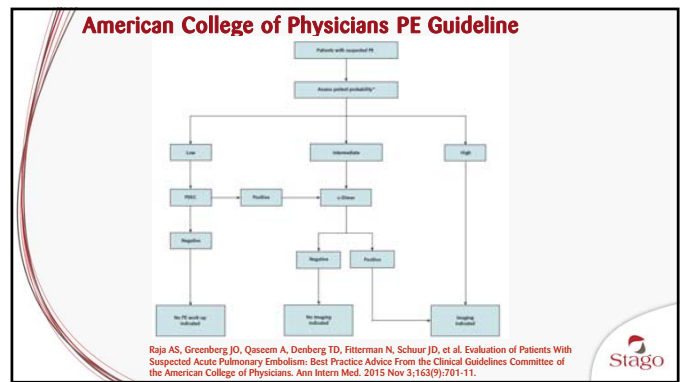
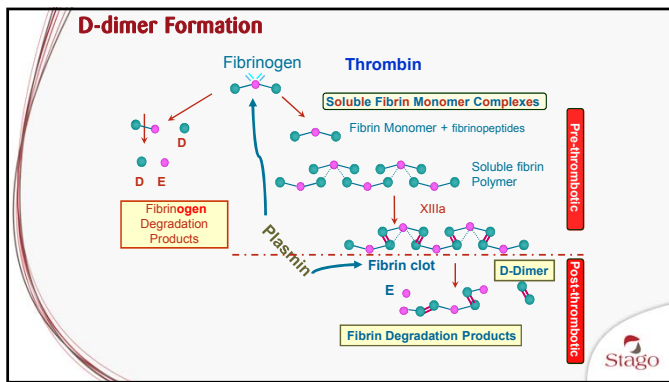
Virchow's Triad

- Stasis of blood flow
- Hypercoagulability
- Endothelial injury

<https://www.thrombosisadvisor.com/images-library-about-venous-arterial-thrombosis/>
accessed Aug 28, 2017



VTE Diagnostic Strategies and Scoring Algorithms



Well's Pre-Test Probability for DVT and PE

Well's Pre-Test Probability for DVT		Well's Pre-Test Probability for PE	
Clinical Feature	Points	Clinical Feature	Points
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1	Suspected DVT	3
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1	Alternate diagnosis is less likely than PE	3
Recently bedridden for > 3 days or major surgery within 4 weeks	1	Heart Rate > 100 beats/min	1.5
Localized tenderness along the distribution of the deep venous system	1	Immobilization or surgery in the previous 4 weeks	1.5
ENTERS leg swollen	1	Previous DVT/PE	1.5
Calf swelling > 3 cm when compared with the asymptomatic leg	1	Hemoptysis (coughing up blood)	1
Pitting edema (greater in the symptomatic leg)	1	Malignancy (on treatment, treated in past 6 months, or palliative)	1
Collateral superficial veins (non-varicose)	1		
Alternative diagnosis as likely as or greater than that of DVT	-2	Total	

High pretest probability ≥3 points
Moderate pretest probability 2-2 points
Low pretest probability zero or negative points

High pretest probability ≥6 points
Moderate pretest probability 2-6 points
Low pretest probability <2 points

CLSI. Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline. CLSI document H59-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.


PE Rule Out Criteria (PERC) Score

Clinical Characteristic	Meets Criterion	Does Not Meet Criterion
Age < 50 y	0	1
Initial heart rate < 100 beats/min	0	1
Initial oxygen saturation > 94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 wk	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1
	Pretest probability with score of 0 is < 1%	

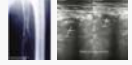
Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD, et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2015 Nov 3;163(9):701-11.

D-dimer is Sensitive but Not Specific for PE

- **Non-VTE causes of elevated D-dimer**
 - Cancer
 - Rheumatoid arthritis
 - Conditions requiring intensive care
 - Advanced age (>65 years)
 - Developing DIC
 - Sepsis
 - Inflammation
 - Pregnancy
- **The greatest utility of D-dimer is its negative predictive value**




Diagnosis of DVT



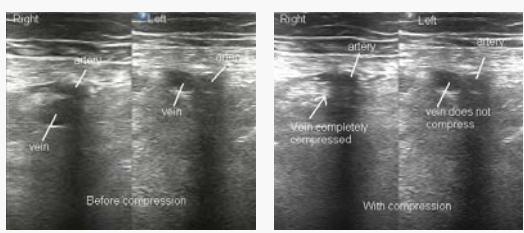
- **Difficult diagnosis as clinical symptoms (leg pain, etc.) are nonspecific**
- **Imaging diagnostic methods:**

Test	Description	Disadvantages
Contrast venography	"Gold standard"	Invasive, equipment, rare serious side effects
Impedance Plethysmography	Non invasive	Inadequate specificity and sensitivity
Compression Ultrasound	Non invasive	Not accurate for all DVT


20



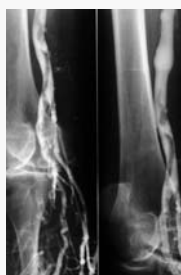
Compression Ultrasound




<http://emedicine.medscape.com/article/1362989-overview>; accessed Aug 28, 2017




Venography – Femoral Vein



<https://www.thrombosisadvisor.com/image-library/about-venous-arterial-thrombosis/>; accessed Aug 28, 2017



Diagnosis of PE




- **Difficult diagnosis as clinical symptoms (cough, dyspnea, etc.) are nonspecific**
- **Non specific tests (EEC, blood gas)**
- **Imaging diagnostic methods:**

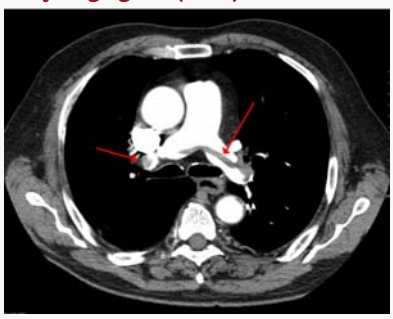
Test	Description	Disadvantages
Pulmonary Angiography	"Gold standard"	Invasive, equipment, rare serious side effects
Spiral Computed Tomography	Non invasive	Sensitivity low overall
Perfusion scanning	Non invasive	Many scans non diagnostic

Imaging methods are considered the gold standard for DVT and PE diagnosis, but expose the patient to high amounts of radiation, are expensive, and only available in limited times and centers as they require specialized equipment and expertise to operate and interpret results.


23



CT Pulmonary Angiogram (CTPA)



Source: James Hollman, MD March 2011



Case Studies

DVT Case - Presentation

- 52 year old man presents in ER with dyspnea (shortness of breath), wheezing and chest tightness.
- Blood pressure is 145/88 mmHg, pulse rate >110 bpm and respiratory rate >30/min. Blood gas results reveal hypoxia (low oxygen) and cardiac exam found tachycardia (rapid heart rate).
- Clinical history includes long history of seasonal allergy and bone fracture 1 month prior with 3 weeks immobilization. A diagnostic workup is prescribed.

TEST	RESULT	REFERENCE RANGE
D-dimer (STA-Liatest D-Di)	0.38 µg/mL FEU	< 0.50 µg/mL FEU

DVT Case – Lab Testing

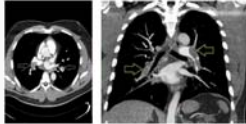
➤ Additional testing is performed:

TEST	RESULT	REFERENCE RANGE
Erythrocytes (RBC)	6.01 x 10 ¹² /L	4.32-5.72 x 10 ¹² /L
Leucocytes (WBC)	11.7 x 10 ⁹ /L	3.5-10.5 x 10 ⁹ /L
Eosinophiles	> 400 cells/µL	30-350 cells/µL
Platelet count	220 x 10 ⁹ /L	150-450 x 10 ⁹ /L
Hb	15.5g/dL	13.4-19.9 g/dL
MCHC	34g/dL	31-37 g/dL
MCV	99 fL	88-123 fL
D-dimer (STA-Liatest D-Di)	0.38 µg/mL FEU	< 0.50 µg/mL FEU
Ig E (serum)	185 IU	100 IU
Erythrocyte sedimentation rate (ESR)	27.8 mm/hr	0-22 mm/hr (men)

PE Case

- 39 year-old male with sickle cell trait presented to hospital with shortness of breath and pleuritic chest pain following flight from Trinidad to Jamaica via Miami
- Blood pressure was 135/79 mm Hg, pulse was 92 beats/min, respiratory rate was 24/min, O₂ saturation was 85%, BMI 34 kg/m²
- Wells score was calculated as 3 (moderate risk for PE), D-Dimer test was >10,000 µg/L (normal < 500)
- Diagnosed with bilateral PE, subQ enoxaparin started followed by rivaroxaban

CTPA showed large filling defect in left and right pulmonary arteries (axial view, left, coronal, right)



Abdool K, Ramcharan K, Reyes AJ, Lutchman N, Alexander A. Bilateral Pulmonary Embolism after a Short-Haul Flight in a Man with Multiple Risk Factors including Sickle Cell Trait. Case Reports in Emergency Medicine. 2017;2017:4316928.

D-dimer vs. Imaging for VTE Diagnosis

CTPA Overuse Study – Patients

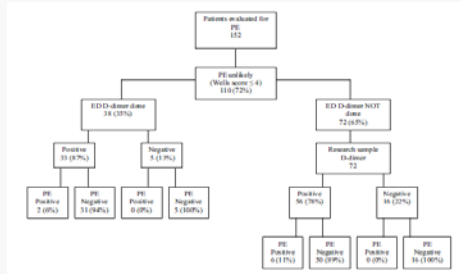
Most Common Signs and Symptoms	Prevalence (%)
Shortness of breath	77.0%
Chest Pain	74.3%
Lower extremity pain or swelling	44.1%

- Patients were predominantly middle-aged females
- Risk factors included
 - History of prior VTE
 - Active malignancy
 - Recent surgery or trauma
 - Exogenous estrogen use (BCP, HRT)

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

Crichlow A, Coker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.

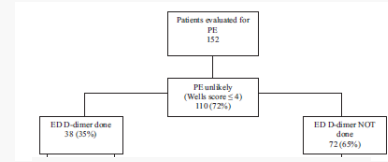
CTPA Overuse Study – Results of Wells/D-dimer



Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



CTPA Overuse Study - Results

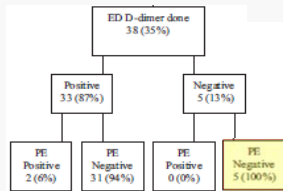


Of the 110 (72%) patients with Wells score indicating PE is unlikely, only 35% had a D-dimer result. Why?

Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



CTPA Overuse Study - Results – PE Negative Patients

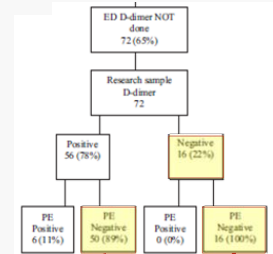


13.8% of the "D-dimer" patients were found to be PE negative upon follow-up and did not require CT-PA

Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



CTPA Overuse Study - False Positives / True Negatives



False Positives (pointing to C2) True Negatives (pointing to D2)

Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



Results – Likelihood Ratio (LR) Analysis

	Sensitivity	Specificity	PPV	NPV	+LR	-LR
PERC	1.00 (0.78-1.00)	0.10 (0.06-0.17)	0.13 (0.08-0.20)	1.00 (0.73-1.00)	1.12 (1.05-1.18)	0
Wells/D-dimer	1.00 (0.78-1.00)	0.16 (0.10-0.23)	0.14 (0.09-0.21)	1.00 (0.81-1.00)	1.19 (1.10-1.28)	0

+LR = positive likelihood ratio; -LR = negative likelihood ratio; NPV = negative predictive value; PERC = pulmonary embolism rule-out criteria; PPV = positive predictive value.
95% CIs are shown in parentheses.

Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



Results of CT-PA time & ED Length of Stay (LOS)

- **CT-PA accounted for more than 1/2 of the ED LOS**
 - Median time for a CT-PA is 160 minutes (2hrs 40 min.)
 - Median ED LOS was 295 minutes (4 hrs 55 min.)
 - Without an appropriate comparison group, impact of LOS by avoidance of CT-PA cannot be determined
- **Time waiting for potentially unnecessary imaging may contribute to ED crowding**
 - Associated with poor care in the ED
 - Delays in medications
 - Increased mortality rates
 - Increased healthcare cost

Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2012 Nov;19(11):1219-26.



Supporting Studies

- CT-PA requests had increased 56% between 2000 and 2005 w/o significant increase of PE positive rate (3.1%)
 - Inappropriate use of CT-PA was suggested
- Guidelines using the Wells/D-dimer were placed in the order entry menu of a VA hospital
- Over 24 months on 252 patients (57% inpatient/43% outpatients) were enrolled (mostly men)
- PE prevalence was 19%
- Detection rate increased from 3.1% to 16.5% w/ CT-PA
- In patients with suspected PE, implementation of a clinical decision rule (Wells/D-dimer) significantly increased the yield of PE using CT-PA and improved its utilization

Soo Hoo GW, Wu CC, Vazirani S et al. Does a Clinical Decision Rule Using D-dimer Level Improve the Yield of Pulmonary CT Angiography? AJR. 2011; 196: 1059-64.



Supporting Studies

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



Figure 1. Preferred diagnostic algorithm for clinically suspected acute PE. CDR, clinical decision rule; HS, highly sensitive.

Huisman MV, Klok FA. How I Diagnose Acute Pulmonary Embolism. Blood. 2013; 121: 4443 - 8.



Recent Clinical Studies Featuring D-dimer; Extending the Utility of the Assay

Exclusion of PE – Large Management Trial

- A large trial of 1,141 patients from 9 centers in Europe and North America was conducted to evaluate performance of the STA Liatest D-di for exclusion of PE

	STA Liatest D-Di (%)	Requirements	
		CLS (%)	FDA (%)
Sensitivity		≥97	≥95
Point estimate	97.8	≥99	≥99
95% lower limit of CI	97.7	NA	NA
95% upper limit of CI	99.7	NA	NA
NPV		≥98	≥97
Point estimate	99.7	≥99	≥99
95% lower limit of CI	99.0	NA	NA
95% upper limit of CI	100.0	NA	NA

CI, confidence interval; CLS, Clinical and Laboratory Standard Institute; FDA, Food and Drug Administration; NA, not applicable; NPV, negative predictive value.

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

Pernod G, Wu H, de Maistre E, Lazarchick J, Kassis J, Aguilarr C, et al. Validation of STA-Liatest D-Di assay for exclusion of pulmonary embolism according to the latest Clinical and Laboratory Standard Institute/Food and Drug Administration guideline. Results of a multicenter management study. Blood Coagul Fibrinolysis. 2017 Apr;28(3):254-260.



CAP and Age Adjusted D-dimer Cutoffs (AADD)

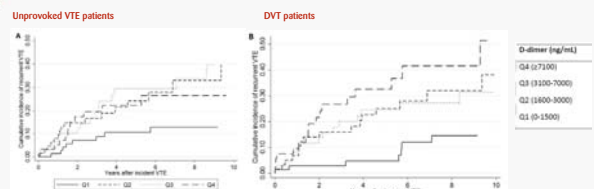
Study, Year	D-Dimer Assay	Method	Unit	Baseline Cutoff in the Study	Manufacturer Cutoff for VTE With Unit	Low- and Intermediate-Risk Patients, n	Total Patients With Pulmonary Embolism, n	Negative Predictive Value for Pulmonary Embolism, %	Negative Likelihood Ratio
Sharp et al. 2016[1]	STA-Liatest D-Dimer (Stago)	Latex-enhanced immunoturbidimetric immunoassay	FEU	500 ng/mL	Yes	31 094	527	99.8	-
Righini et al. 2014[5]	STA-Liatest D-Dimer (Stago)	Latex-enhanced immunoturbidimetric immunoassay	FEU	500 ng/mL	Yes	389	0	100.0	-
Peralta et al. 2012[1]	STA-Liatest D-Dimer (Stago)	Latex-enhanced immunoturbidimetric immunoassay	FEU	500 ng/mL	Yes	1783	NR	-	0.09
Woller et al. 2014[6]	STA-Liatest D-Dimer (Stago)	Latex-enhanced immunoturbidimetric immunoassay	FEU	500 ng/mL	Yes	1745	86	98.5	-

If a lab is interested in reporting AADD (age x 10 ng/mL FEU), they should know whether the assay used in the lab has been reported used in larger trials reporting AADD and should clarify the units reported (DDU or FEU) both for AADD and regular use

Goodwin AJ, Higgins RA, Moser KA, Smock KJ, Chandler WL, Kottke-Marchant K, et al. Issues Surrounding Age-Adjusted D-Dimer Cutoffs That Practicing Physicians Need to Know When Evaluating Patients With Suspected Pulmonary Embolism. Ann Intern Med. 2017 Mar 7;166(5):361-363.



Baseline D-dimer and Recurrence Risk



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

Bjorn E, Johnsen HS, Hansen JB, Braekken SK. D-dimer at venous thrombosis diagnosis is associated with risk of recurrence. J Thromb Haemost. 2017 May;15(5):917-924.



Using D-dimer Prospectively - MAGELLAN

Patients with elevated baseline D-dimer have higher rates of VTE whether patient is taking rivaroxaban or enoxaparin; shows which patients would benefit most from receiving extended duration anticoagulation

Cohen AT, Spiro TE, Spyropoulos AC, Desantis YH, Homering M, Büller HR, et al. D-dimer as a predictor of venous thromboembolism in acutely ill, hospitalized patients: a subanalysis of the randomized controlled MAGELLAN trial. J Thromb Haemost. 2014 Apr;12(4):479-87.

Conclusions

- VTE/PE/DVT are a significant public health issues
- D-dimer assays are most useful when demonstrated to have high sensitivity and specificity
- Specificity saves healthcare dollars by preventing false positives
- Last, D-dimer assays with high negative predictive value (NPV) demonstrate the ability of the test to identify disease-free individuals
- D-dimer assay continues to be a mainstay of the clinical laboratory

Stago 24/7 Educational Webinar Sites

- www.stago-edvantage.com
 - US based speakers
 - 1 hour; PACE accredited
 - Accessible from mobile devices
 - Virtual exhibit hall
- www.stagoweinars.com
 - Mostly European speakers
 - 30 - 45 min including 15 min discussion
 - Accessible from mobile devices

Stago Educational Apps

- **Haemoscore**
 - Clinical scoring algorithms
 - Apple and Android
 - Tablet or phone
- **iHemostasis**
 - Coagulation diagrams
 - Case studies
 - Apple & Android
 - Tablet only

