The Role Of D-Dimer In Venous Thromboembolic Disease And Disseminated Intravascular Coagulation

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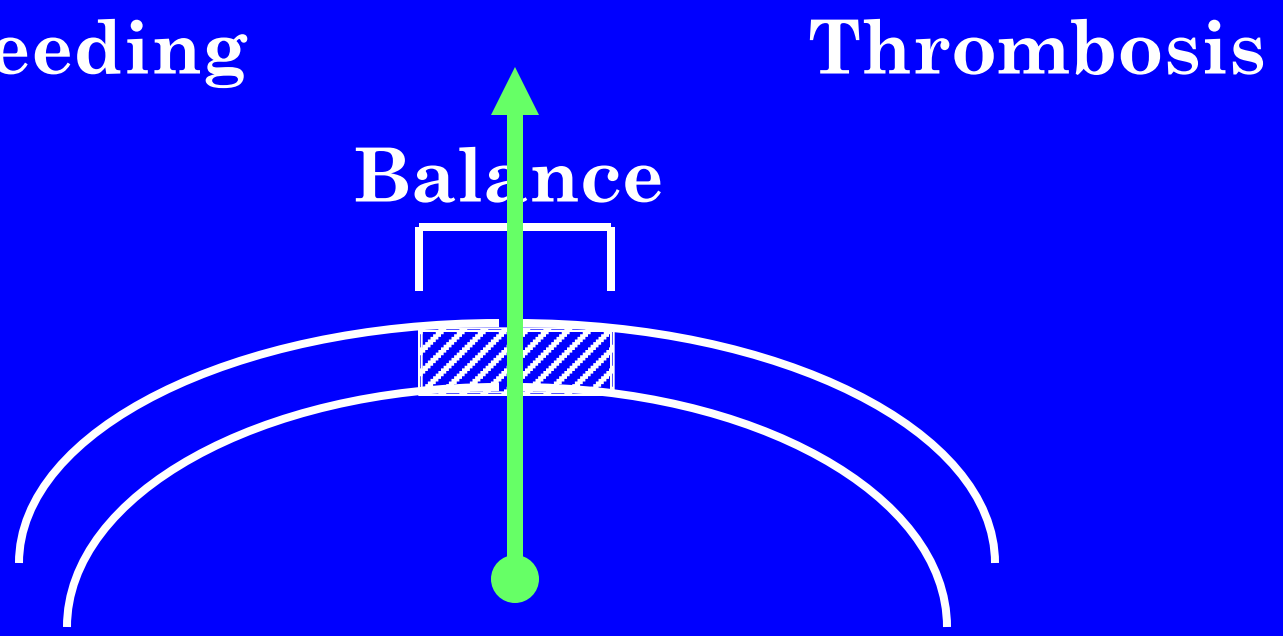
Selected slides courtesy Mike Laposata MD, PhD

Statement On Conflicts Of Interest

- The speaker has no conflicts of interest to declare and will receive no remuneration for this presentation

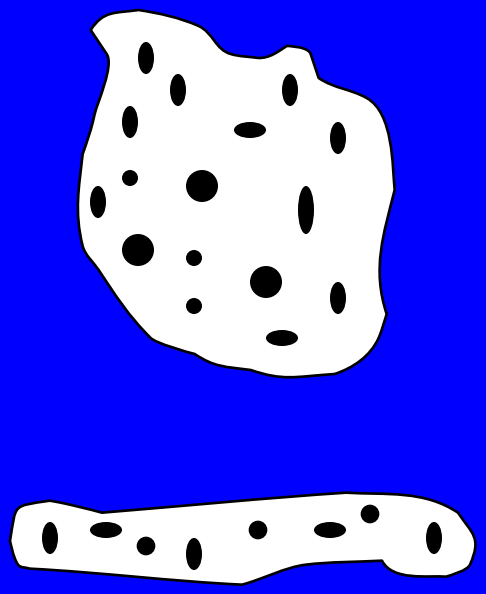
D-dimer

The Appropriate Level of Hemostasis



The Elements Of Hemostasis

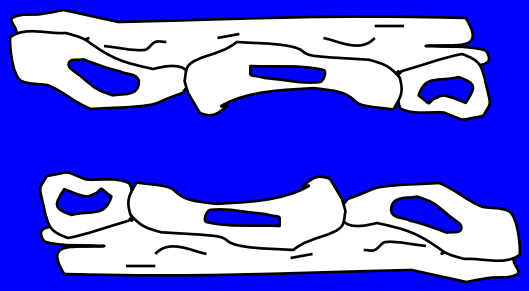
Platelets



Coagulation Factors

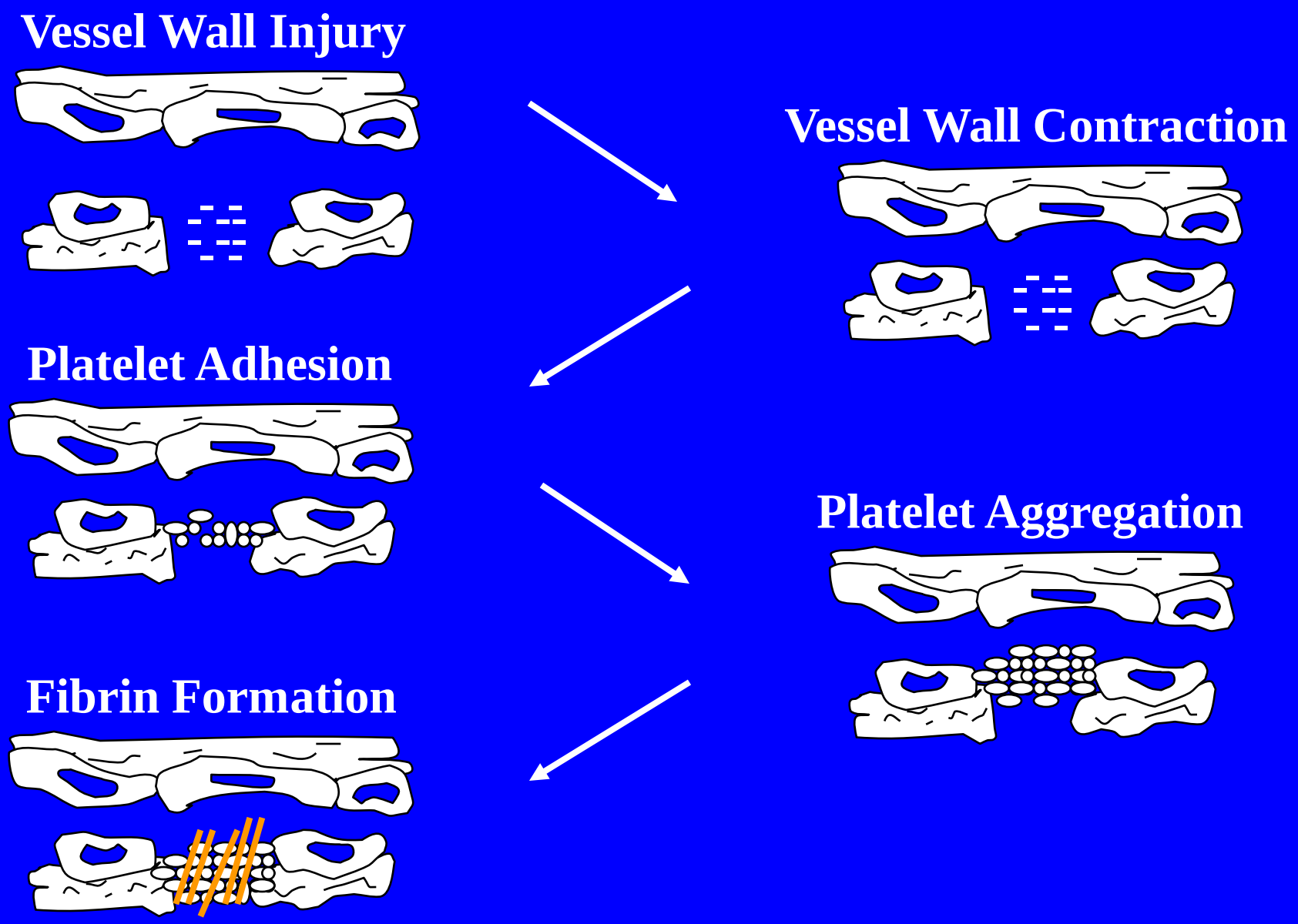
Fibrinogen
Factor II
Tissue Factor
Factor V
Factor VII
Factor VIII
Von Willebrand Factor
Factor IX
Factor X
Factor XI
Factor XII
Factor XIII

Blood Vessels

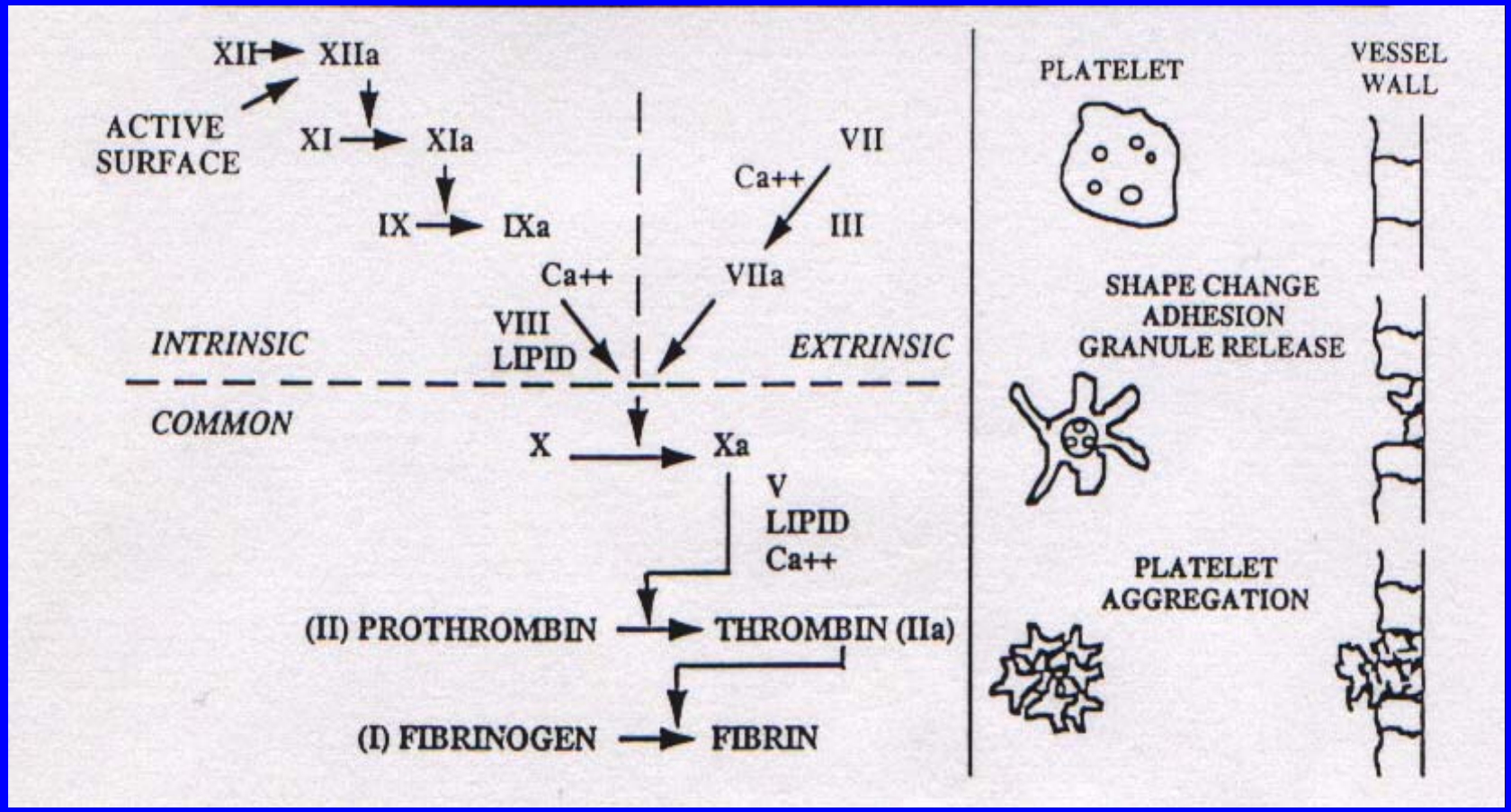


Goal: Form Clot And Plug Vascular Leaks

Clot Formation



Coagulation Factors
Why Have A Cascade of Multiple Factors

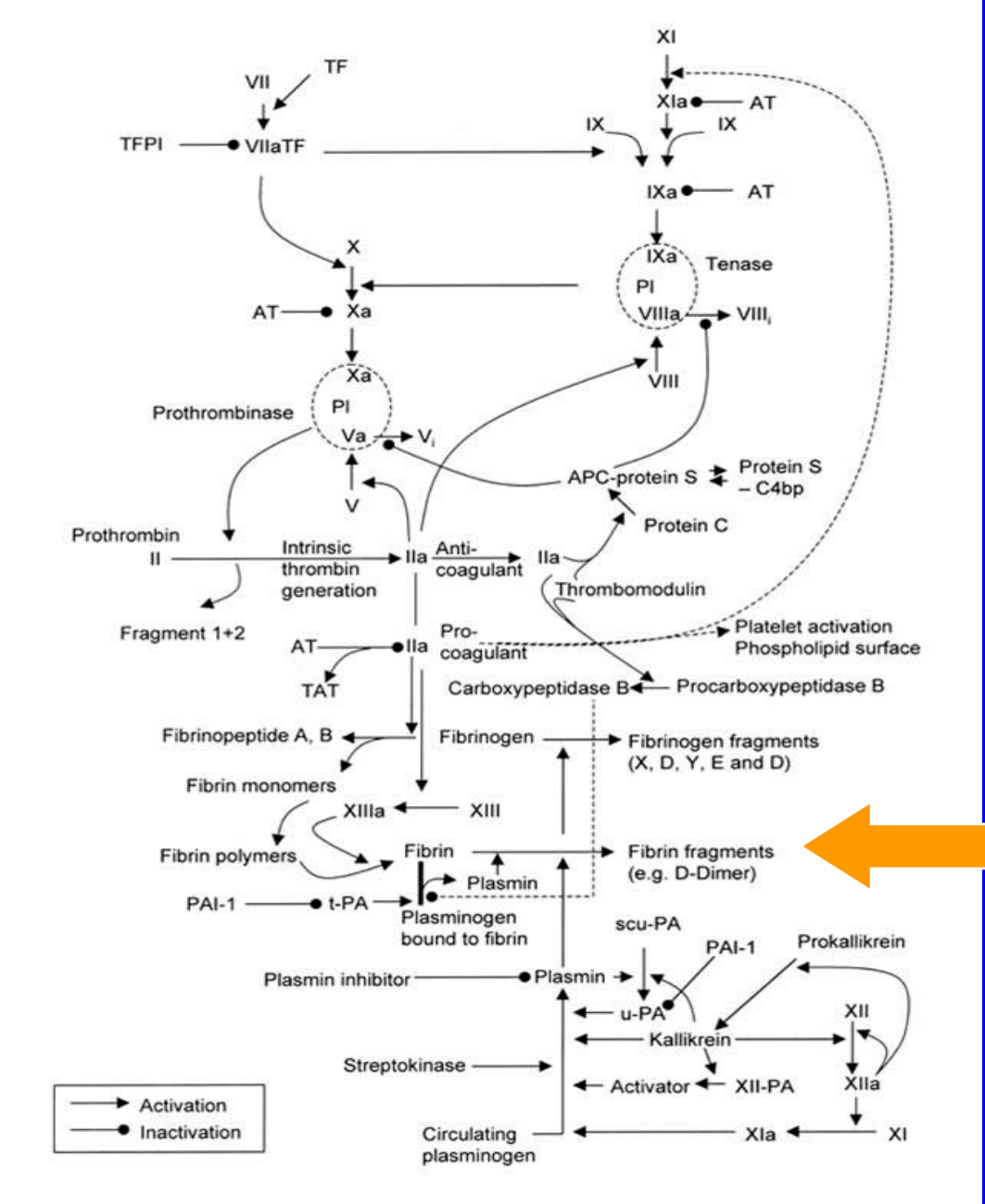


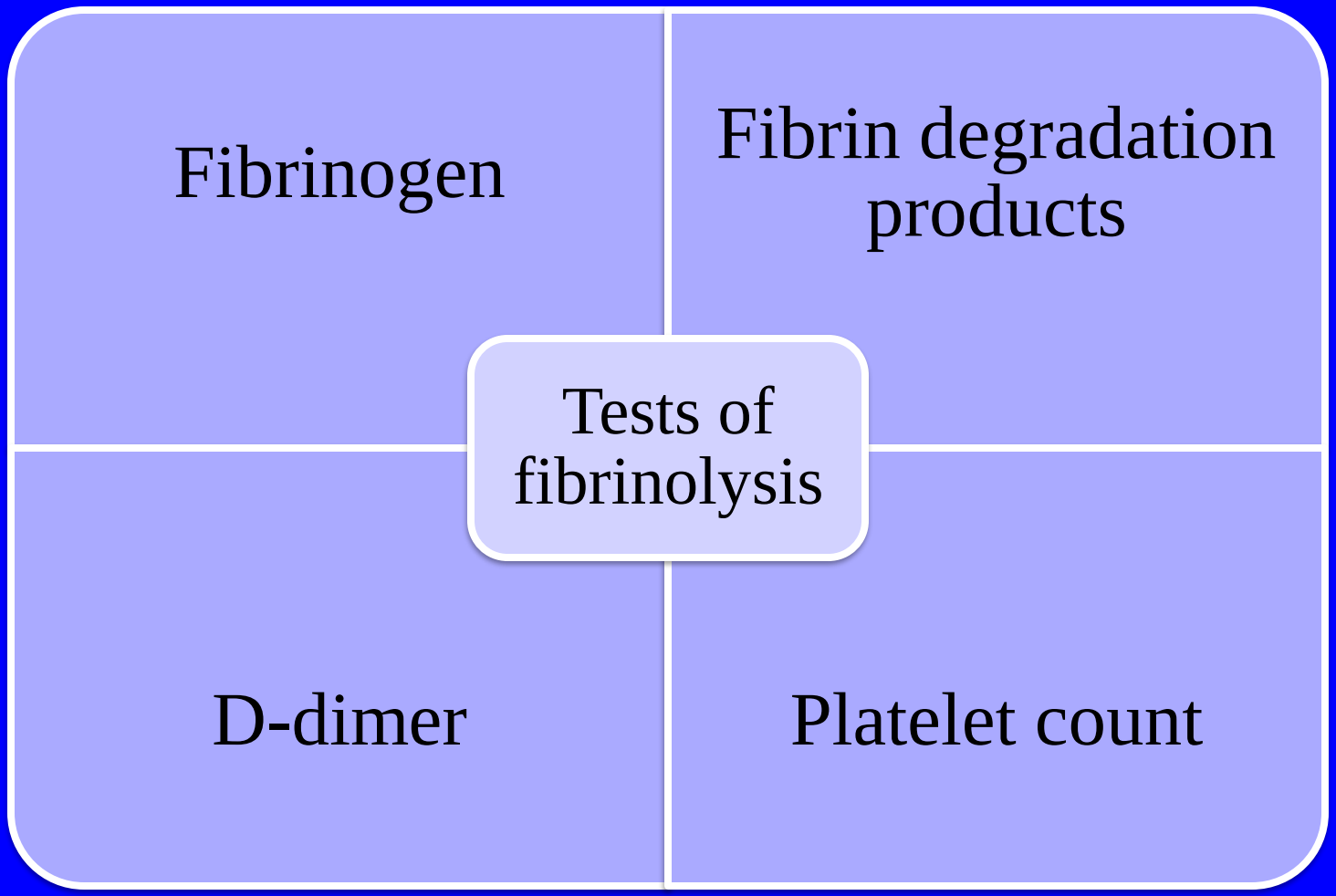
Fibrinolysis

Very Complex Process

Final Stage: Degradation Of Fibrin Clot By Plasmin

Creates FDP including D-Dimer





Only D-dimer is useful for DVT and PE

Deep Vein Thrombosis (DVT)

- DVT is a blood clot (called “thrombus”)
- It occurs in major veins, usually in the legs
- More than two million Americans develop DVT each year

Ileo-femoral DVT

Picture from US National Library Of Medicine MedlinePlus

Venous Blood Clot

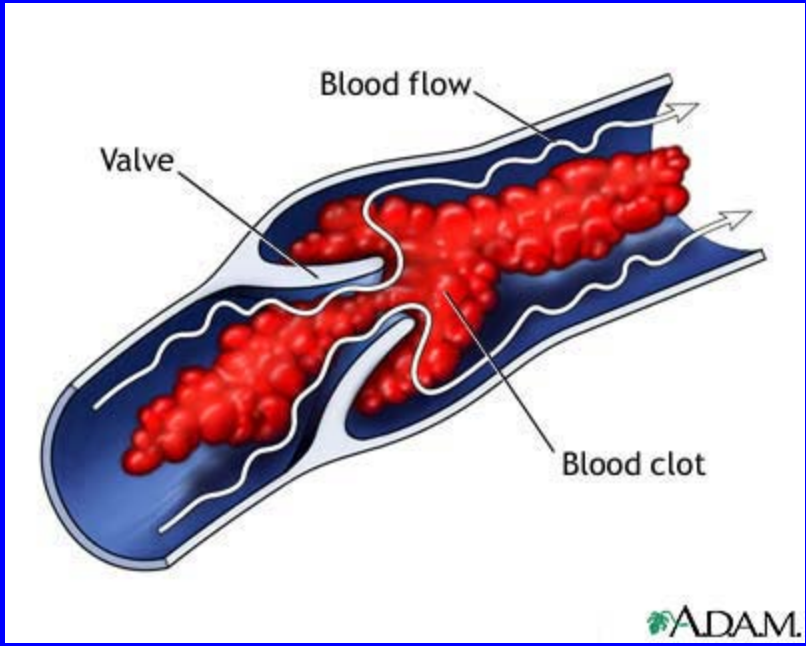
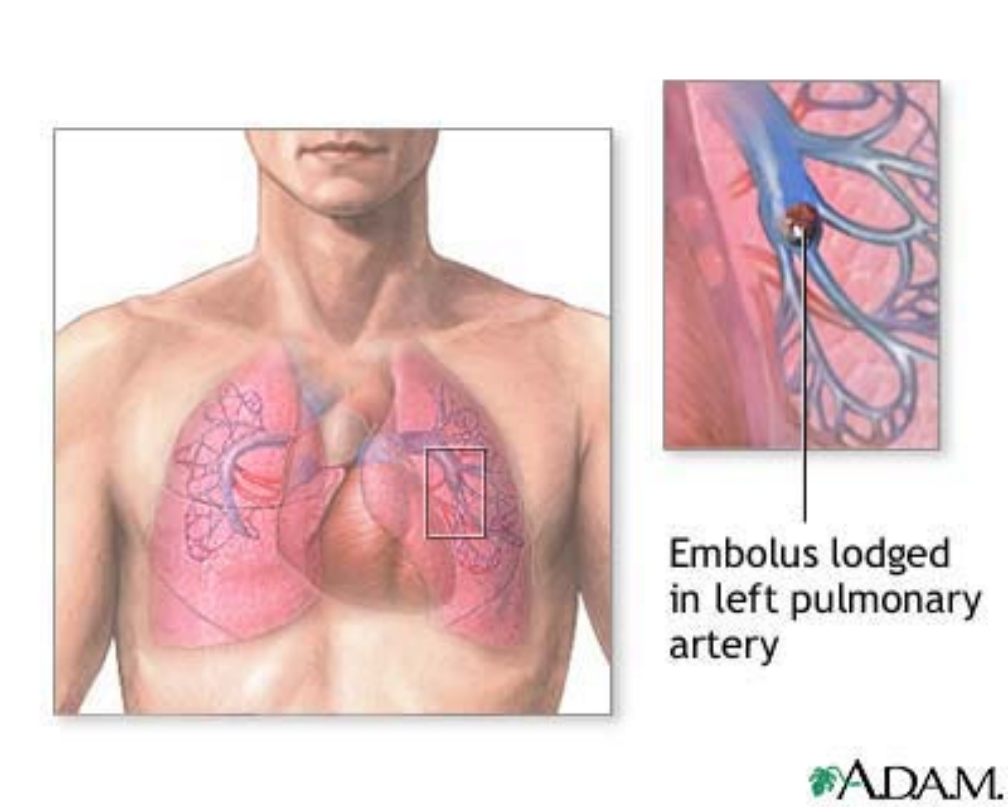


Image from National Library of Medicine

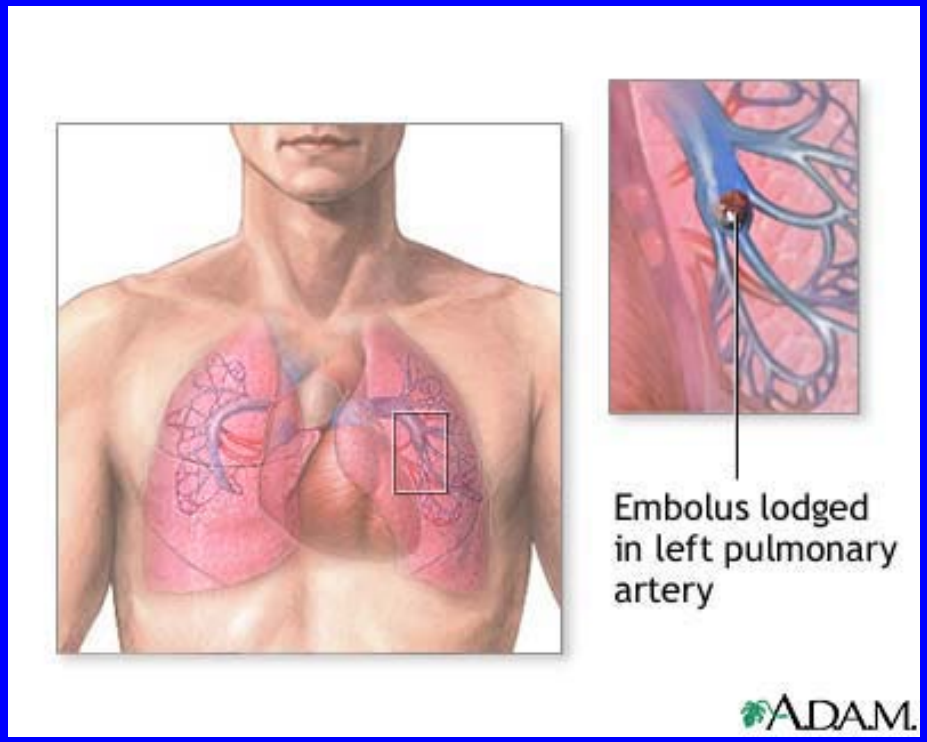
Pulmonary Embolism (PE)

- If a clot reaches the pulmonary artery and lung, blood circulation and gas exchange are impaired
- In the US each year 600,000 people develop PE
- Mortality = 10%



Picture from National Library of Medicine

Deep venous thrombosis (DVT) and pulmonary embolism (PE) collectively called venous thromboembolic disease (VTE)



Clinical appearance
Symptoms of DVT and PE

DVT

- Pain, swelling and redness of the leg

PE

- Shortness of breath
- Chest Pain
- Cough
- Hemoptysis (coughing up blood

So What's The Problem?

The clinical presentation of both DVT and PE may be subtle or asymptomatic

Radiologic studies are expensive and not always readily available

Need a simple, fast, inexpensive test that is highly sensitive and preferably specific

Who Gets DVT and PE

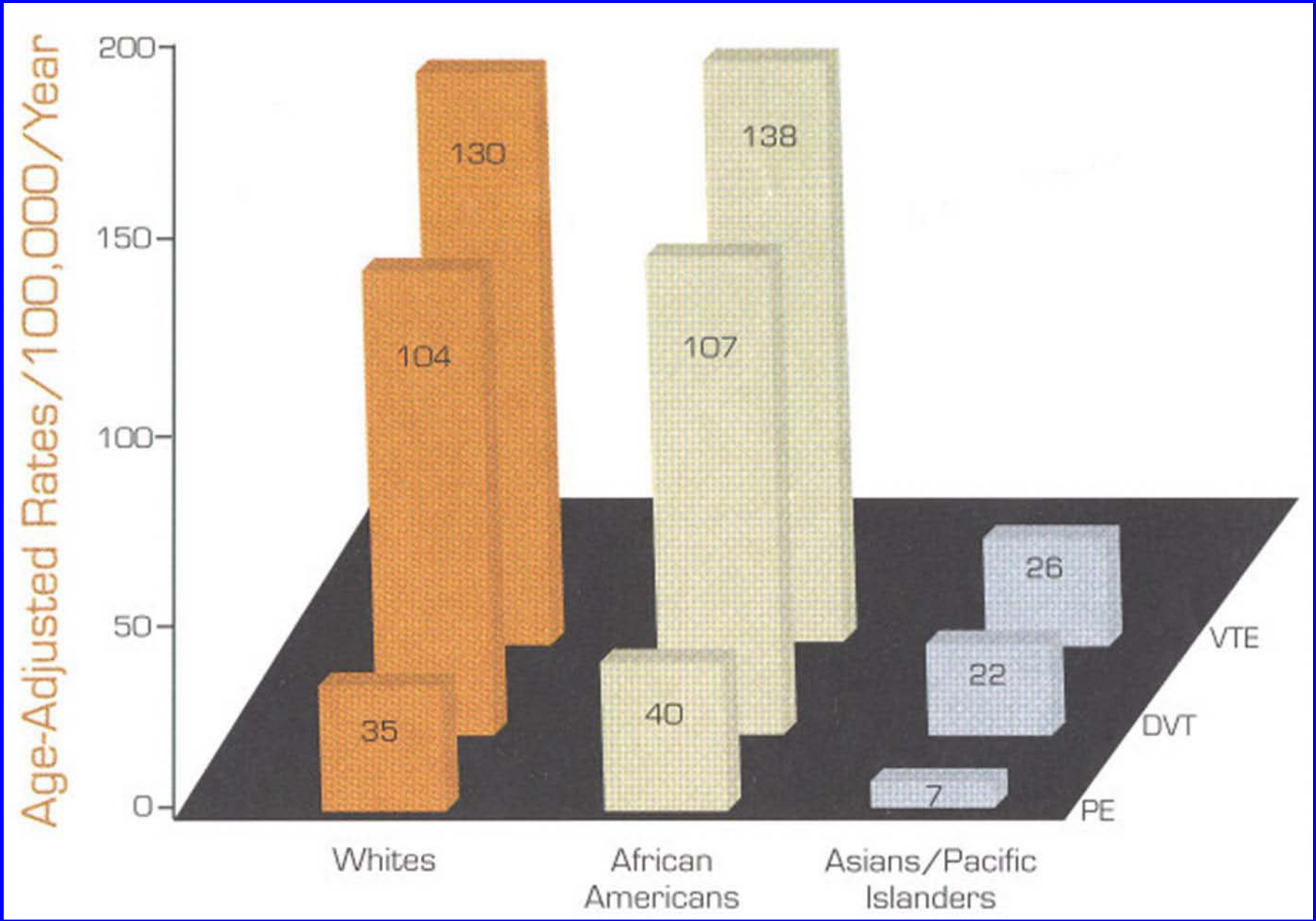
Hereditary causes Acquired causes

The common elements:

Stasis

Vascular injury

Hypercoagulable states



Am J Med 2004; 116:435-442

The Acquired Risk Factors

- Surgery / Trauma
- Immobilization
- Malignancy
- Pregnancy
- Oral Contraceptives/ ERT
- Lupus Anticoagulant
- IgG (or IgM?) Anticardiolipin Antibody
- Obesity
- Nephrotic Syndrome
- Polycythemia Vera
- Smoking

The Hereditary Risk Factors

Activated protein C resistance	• Nearly always the factor V Leiden mutation • May be heterozygous or homozygous
Prothrombin G20210A mutation	• May be heterozygous or homozygous
Hyperhomocysteinemia	• Acquired form: From decreased intake of folate, vitamin B6 and/or vitamin B12 • Congenital form: From enzyme deficiencies in homocysteine degredative pathways

Diagnosis Of DVT and PE
Utility Of The D-dimer Assay

Diagnostic Modalities: DVT

Physical exam and history

- Unreliable

D-dimer

- Sensitive but not specific

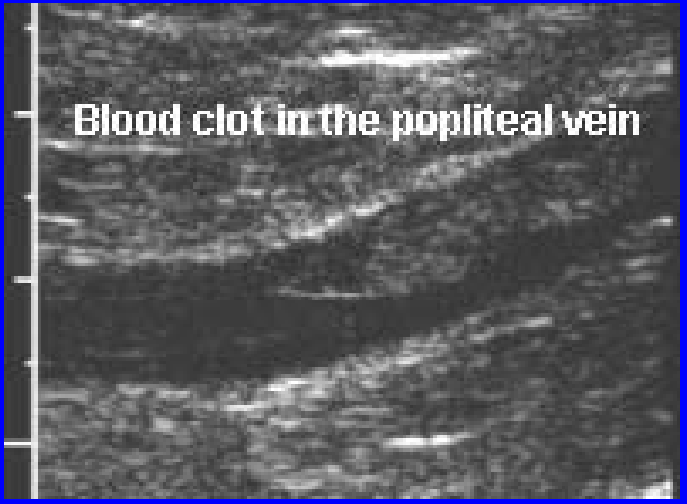
Duplex venous ultrasonography

- Most used test.
- Sensitivity 95% for proximal DVT and 75% for symptomatic calf vein thrombosis

MRI

- Most useful for vena cava and pelvic TE
- Venography: Invasive and requires dye injection

Ultrasound: The most common test for the diagnosis of DVT



Diagnostic Modalities: Pulmonary Embolism

Physical exam and history

- Unreliable

D-dimer

- Sensitive but not specific. Hence limited role in patients already hospitalized

ECG

- Right ventricular strain

Venous ultrasound

- Confirmed DVT is surrogate for PE

Chest CT

- Superceding lung scanning

Lung scanning

- Radiolablelled albumin aggregates injected IV----Filling defect

MRI

- Gadolinium contrast agent

Pulmonary venography

Radiologic Diagnosis Of PE

Computed tomography
- non-invasive
- high sensitivity
- Time consuming
- Expensive
- Requires expert interpretation

Lung Scan (V-Q Scan)

Angiography

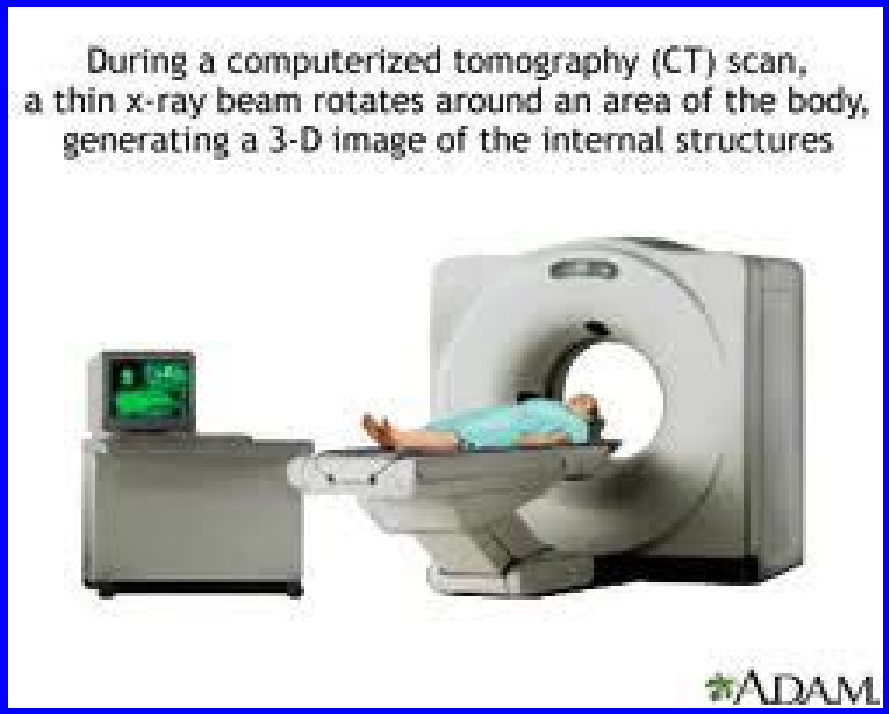
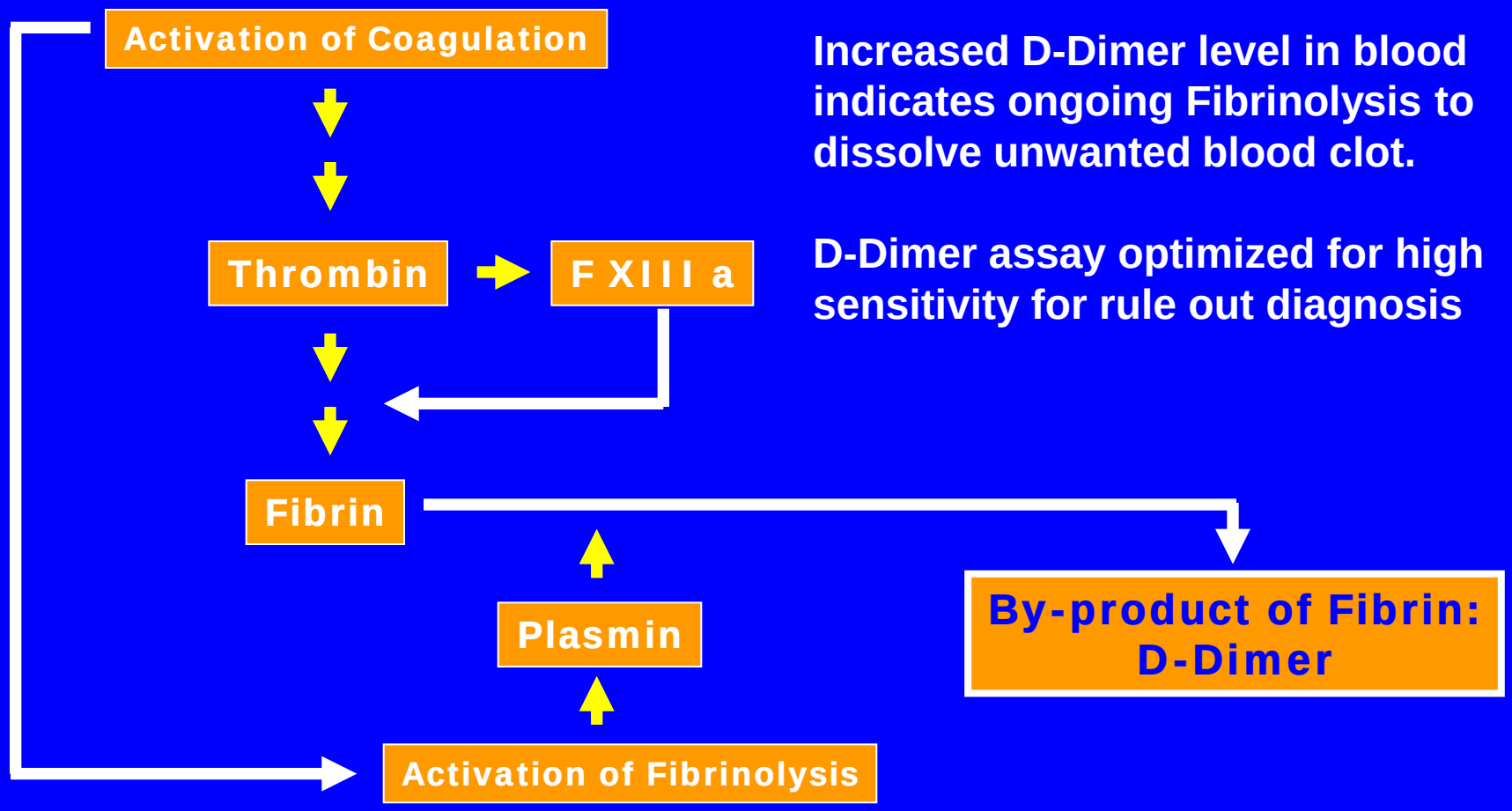


Image from National Library of Medicine

General disadvantage: Instrument and skilled staff have to be available

What is D-Dimer?



Increased D-Dimer level in blood indicates ongoing Fibrinolysis to dissolve unwanted blood clot.

D-Dimer assay optimized for high sensitivity for rule out diagnosis

But Remember: D-dimer may be positive in other conditions

For example, disseminated intravascular coagulation, liver disease, surgery, etc

Hence a positive test does not prove the existance of DVT/PE

Risk Stratification For DVT: Pre-test Probability: The Wells Score

Symptom	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of DVT	2

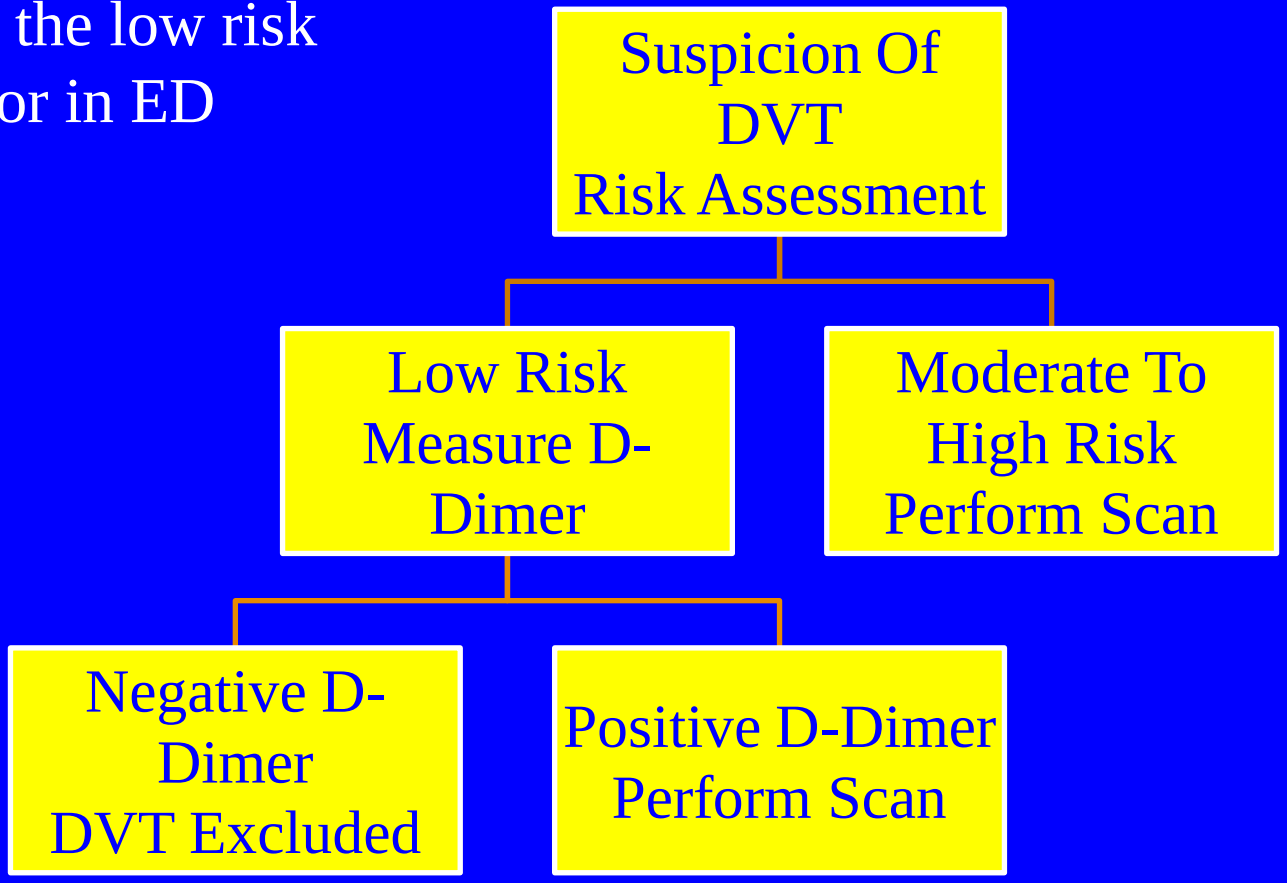
0 = low risk of DVT

1 – 2 = medium risk of DVT

≥ 3 = high risk of DVT

Evaluation Of DVT

Note: The major role for D-dimer is the low risk outpatient or in ED

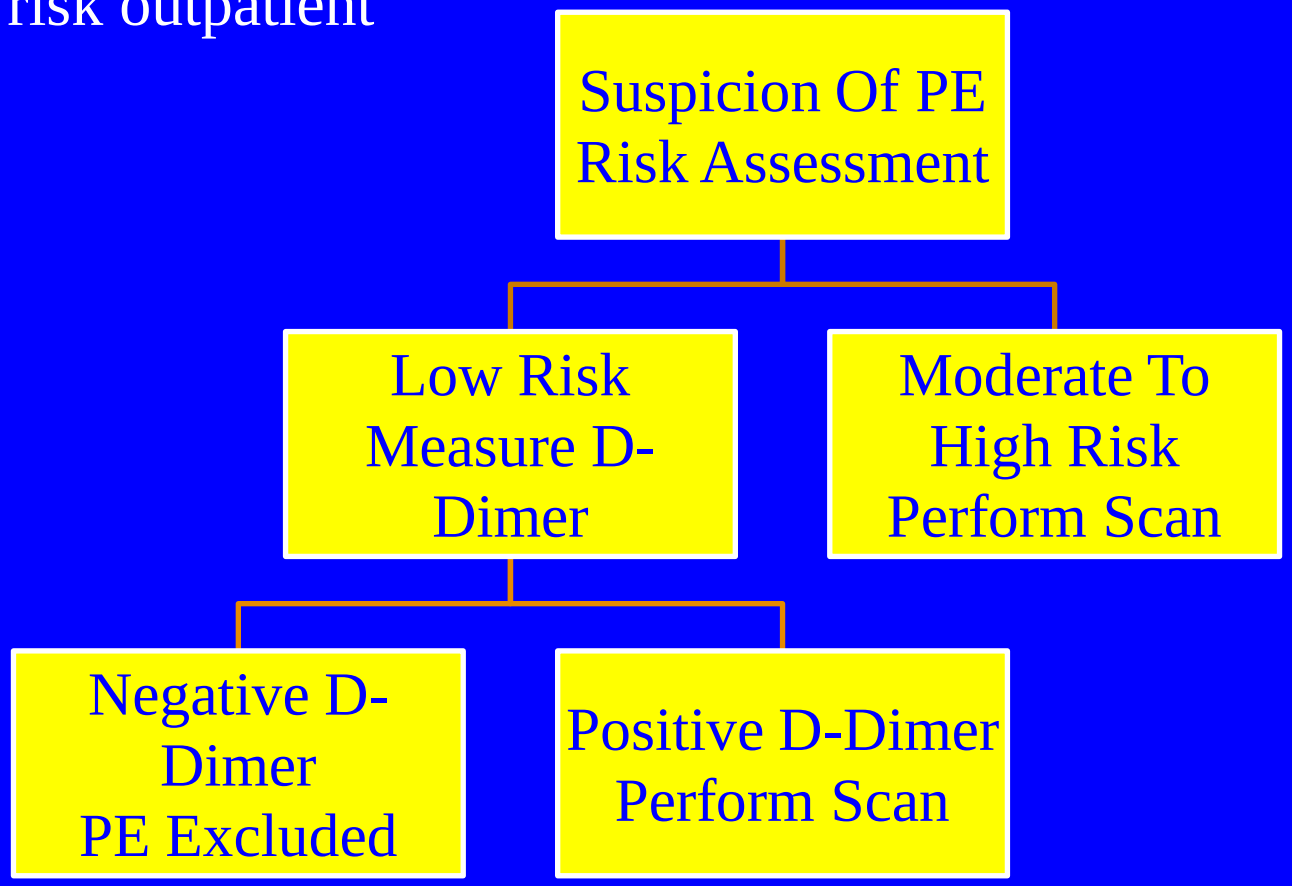


Well's Criteria for Pulmonary Embolism

Criteria	Points
PE more likely than alternatives	3
Suspected PE	3
Tachycardia (pulse >100 beats per minute)	1.5
Surgery or immobilization in last 4 weeks	1.5
Prior DVT or pulmonary embolism	1.5
Hemoptysis	1
Active malignancy	1
Score	**Probability**
0-2 points	Low (3.6% risk)
3-6 points	Moderate (20.5% risk)
>6 points	High (66.7% risk)

Strategy For Diagnosis Of PE

Note major role for D-dimer is the low risk outpatient or in ED



But Wait A Minute

Not all D-dimer assays are the same

1. Qualitative or quantitative
2. Citrate vs Whole blood EDTA
3. Cutoff
4. Assay turnaround time
5. Analytical range
6. Sensitivity and specificity

In the past there were a number of poor performing D-dimer assays

The Historical Gold Standard

VIDAS® D-dimer Exclusion Test

FDA approved for the rule out of both DVT and PE in low risk patients

In recent years a number of new D-Dimer tests have come on the market with excellent sensitivity

High Sensitivity Is The Major Consideration

Test Results	Diseased	Non-Diseased
≥ Cutoff	A (True-Positives)	C (False-Positives)
< Cutoff	B (False-Negatives)	D (True-Negatives)

Sensitivity = A / (A+B)

Specificity = D / (C+D)

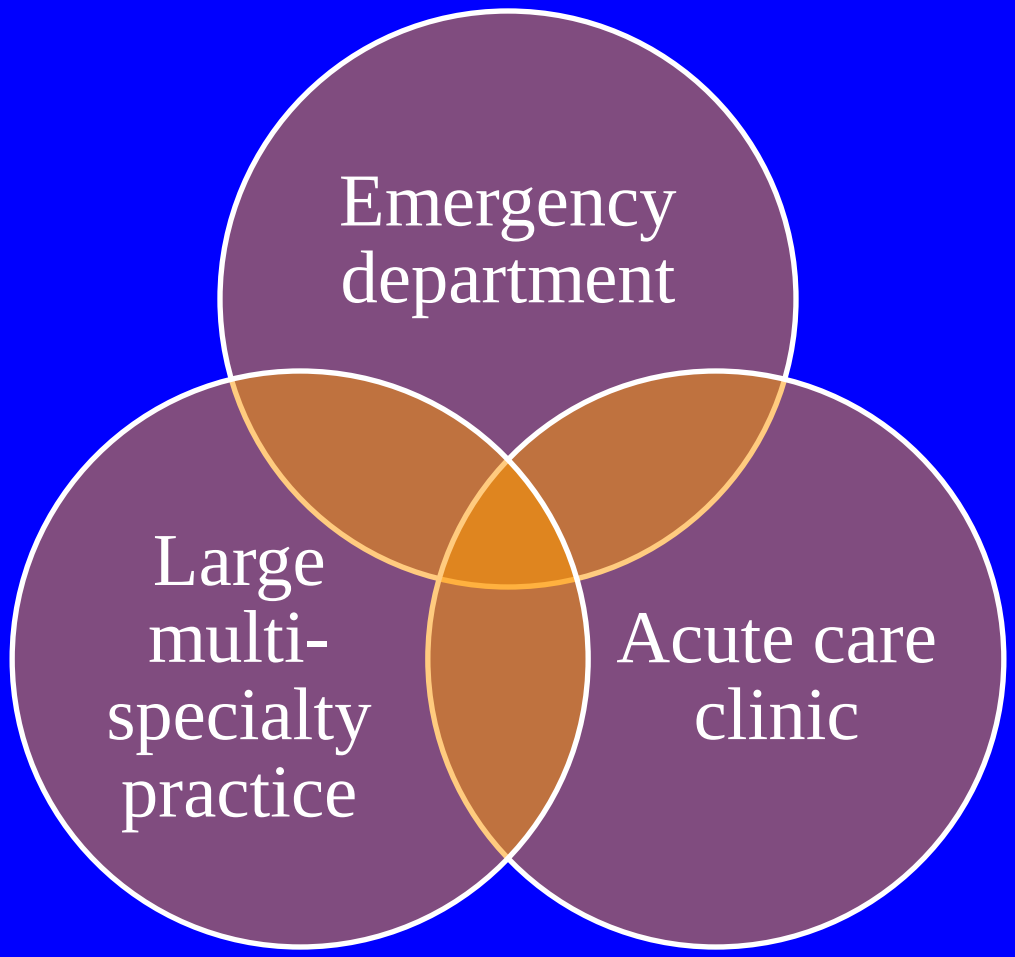
NPV = D / (B+D)

PPV = A / (A+C)

D-Dimer Assay Should Have A Minimum Number Of False Negative Results

What Are The Advantages Of A Point-Of-Care D-Dimer

D-Dimer is used for rule out of low risk patients



Point-Of-Care: ED Length Of Stay (Hours) For Patients Tested For D-Dimer Before and After POCT

	Before POCT D-Dimer	After POCT D-Dimer
Mean LOS	8.46	7.14 p=0.016
Median LOS	6.20	5.88 p=0.026

Rate (percent) 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

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

Issues Concerning Cutoff Values

- Many laboratory tests have established cutoff values (e.g troponin, D-dimer, et al)
- Cutoff values are set to achieve a balance between a desired sensitivity and specificity
- Virtually never are both 100%
- In the case of D-dimer the cutoff should be optimized to maximize sensitivity without excessive loss of specificity
- You do not want to miss a VTE and will therefore accept a certain percentage of false positives

Issues Concerning Cutoff Values

- For an assay that yields continuous quantitative values over a linear range there is rarely an absolute “cutoff” value
- Thus virtually all assays will have some false positive and false negative results
- Example troponin I cutoff set at the 99th percentile of the normal range
- By definition 1% of normals will be positive and some patients with myocardial infarction will fall below the cutoff

Possible Solutions

1. Optimize the cutoff to balance sensitivity and specificity
2. Utilize a borderline range such that values are either negative, borderline or positive

MGH reporting of D-dimer values

< 350: Negative

350-400: Borderline

>400: Positive

- How did we arrive at this: Internal study of hundreds of cases and literature review

Issues Concerning Exclusion Claims For D-dimer

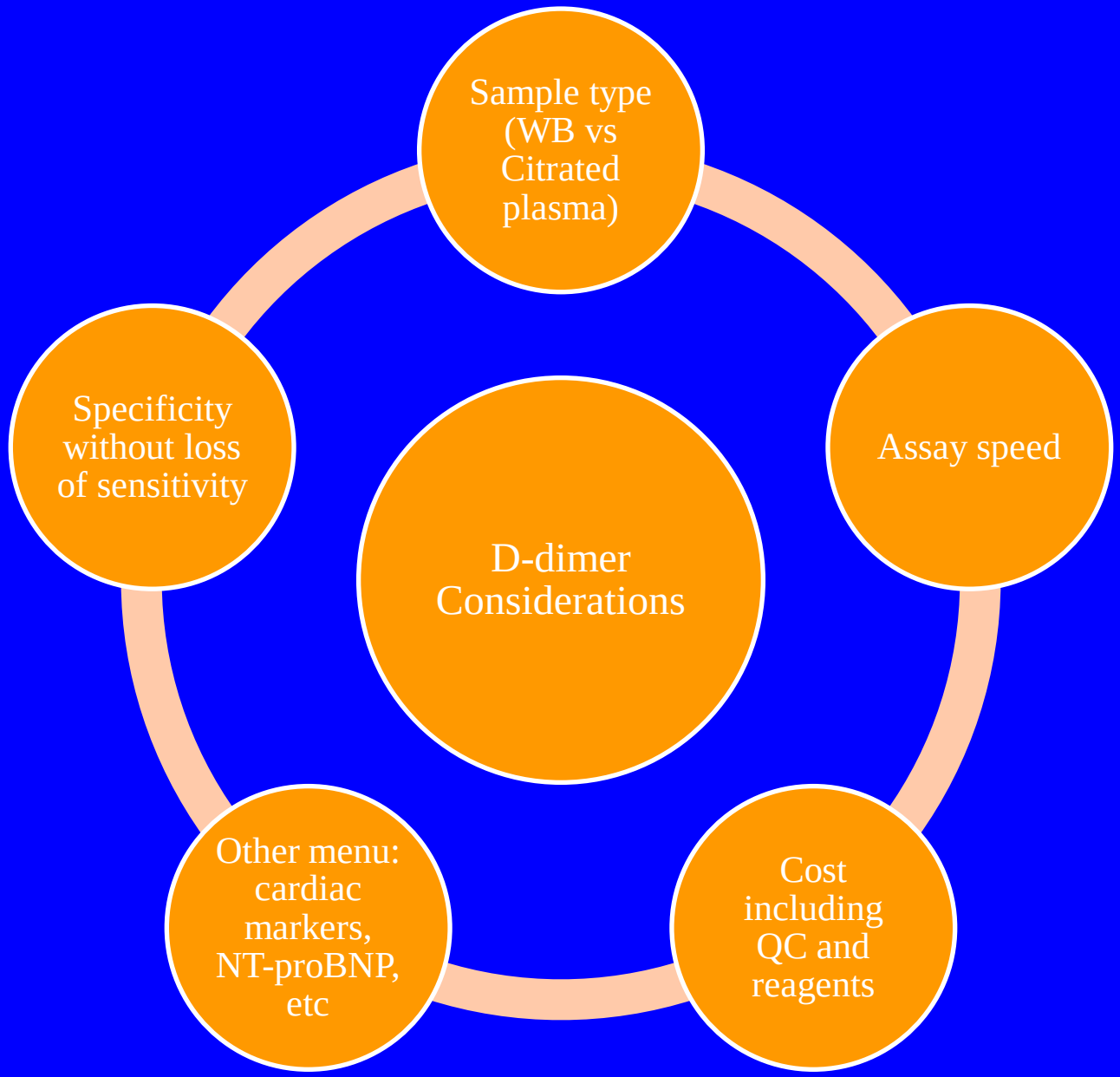
- In the past there were a number of poor quality D-dimer tests on the market
- The Vidas D-dimer was the first assay to achieve an exclusion claim for DVT/PE and was the best assay on the market
- A negative Vidas D-dimer could be used to exclude DVT/PE with a relatively high degree of certainty in LOW RISK PATIENTS
- Today there are other D-dimer assays with an exclusion claim and other good assays without the claim

What Does An Exclusion Claim Mean

- To have an exclusion claim the company must perform a large and very expensive clinical study that is submitted to the FDA
- Assays without exclusion claims may work just as well (or even better)
- Using an assay without an exclusion claim may require literature review, internal data and/or consultation with peer hospitals to establish the assay's performance

Conclusion

D-dimer tests that are equivalent in performance to the Vidas are acceptable and may be preferable in terms of:



One MGH Study Of Triage Versus Vidas D-dimer

- 211 patients evaluated in emergency department for DVT/PE
- Assays agreed on classification in 200 cases (94.5%)
- 11 discrepant results
  All were Vidas positive, Triage negative
  All were ruled out for DVT/PE
- In this study Triage was equally sensitive but more specific

	Sensitivity	Specificity
Vidas	100%	67.9%
Triage	100%	73.3%

Caveat: In reality no assay is 100% sensitive

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

Disseminated Intravascular Coagulation (DIC)

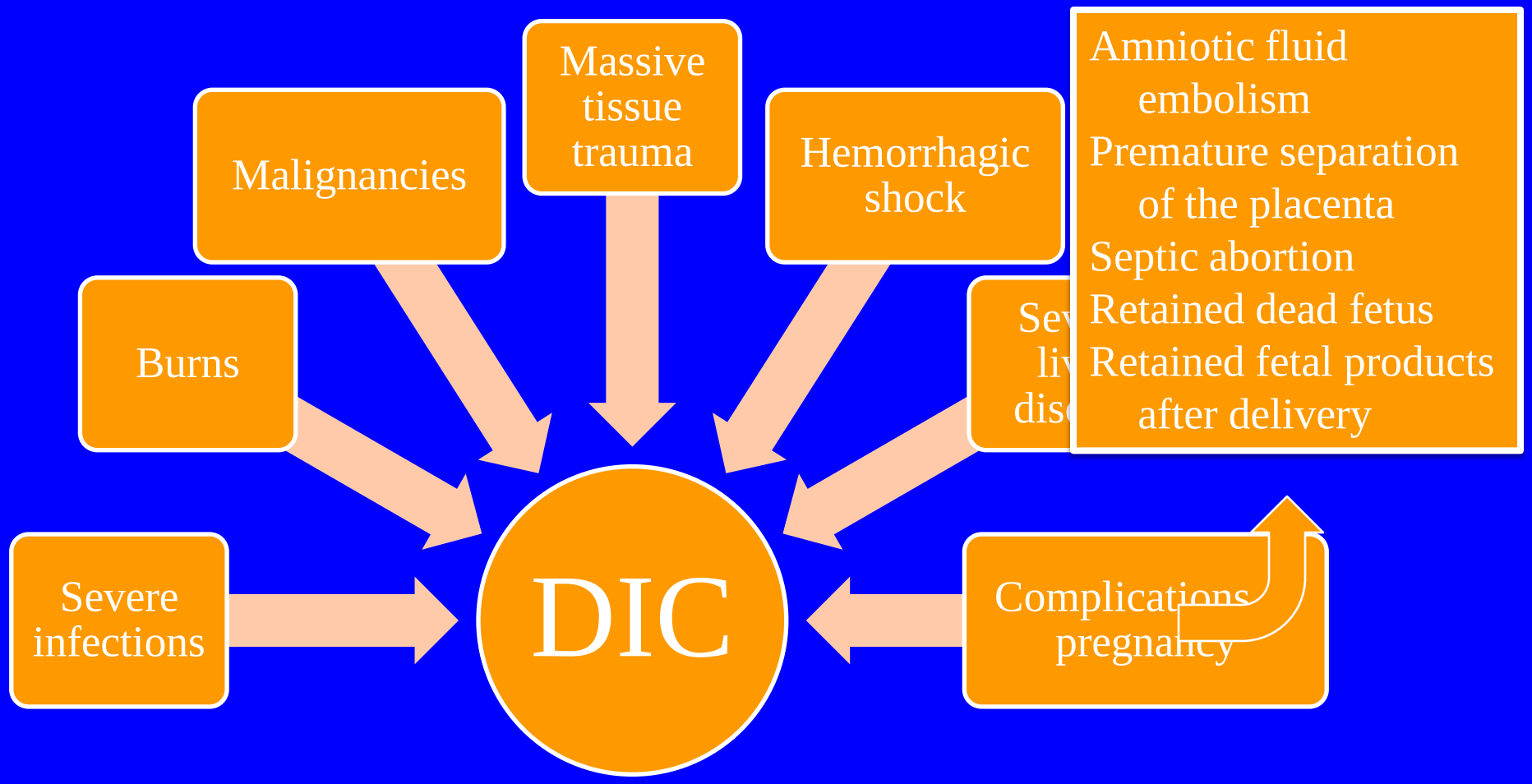
DIC is always a response to an underlying process

Patients exhibit a consumptive coagulopathy where they are both clotting and bleeding due to consumption of coagulation factors

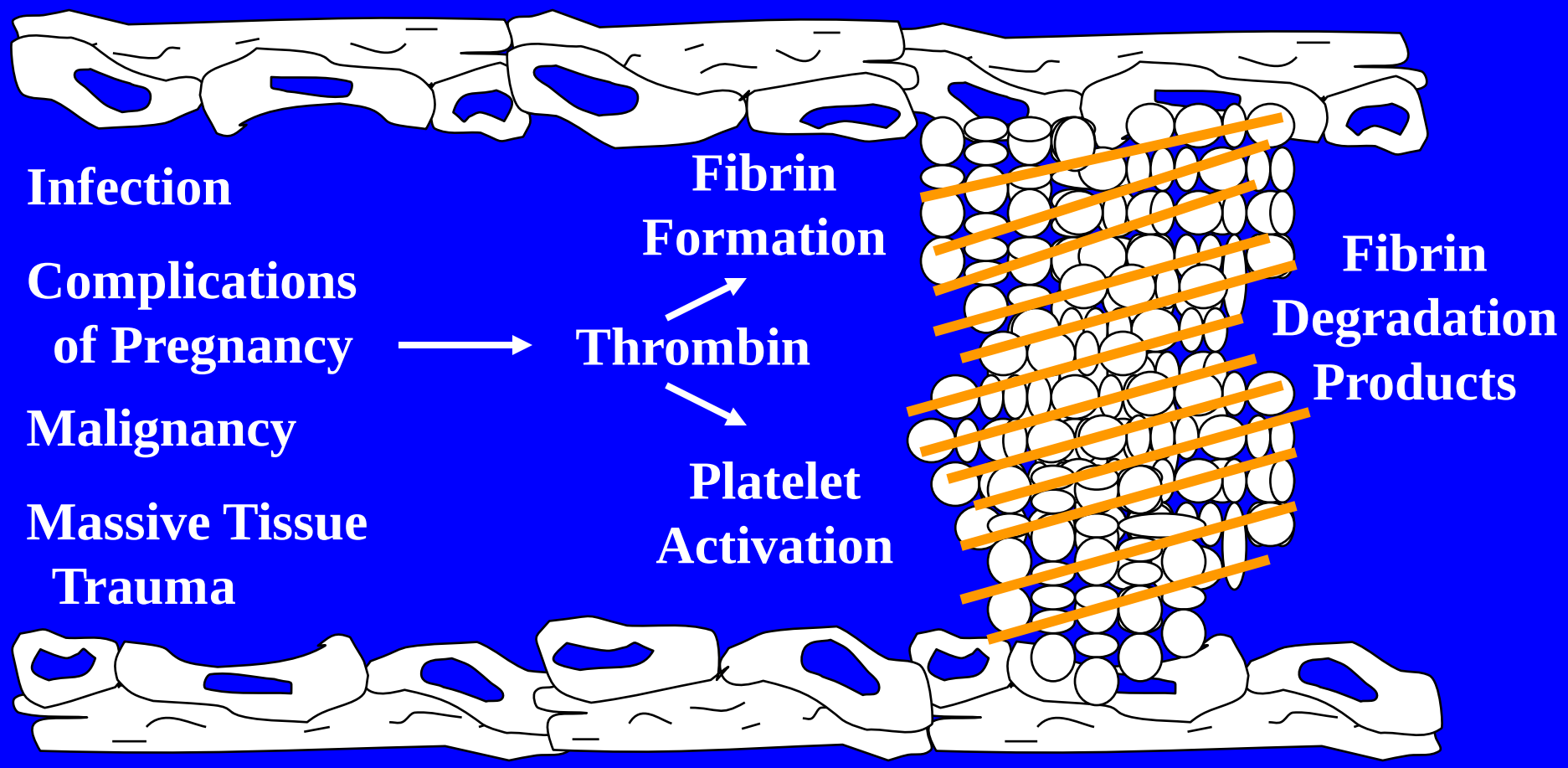
It results in a generalized activation of hemostatic mechanism

The mortality in DIC is related to the underlying disease

Conditions Associated with the Development of DIC



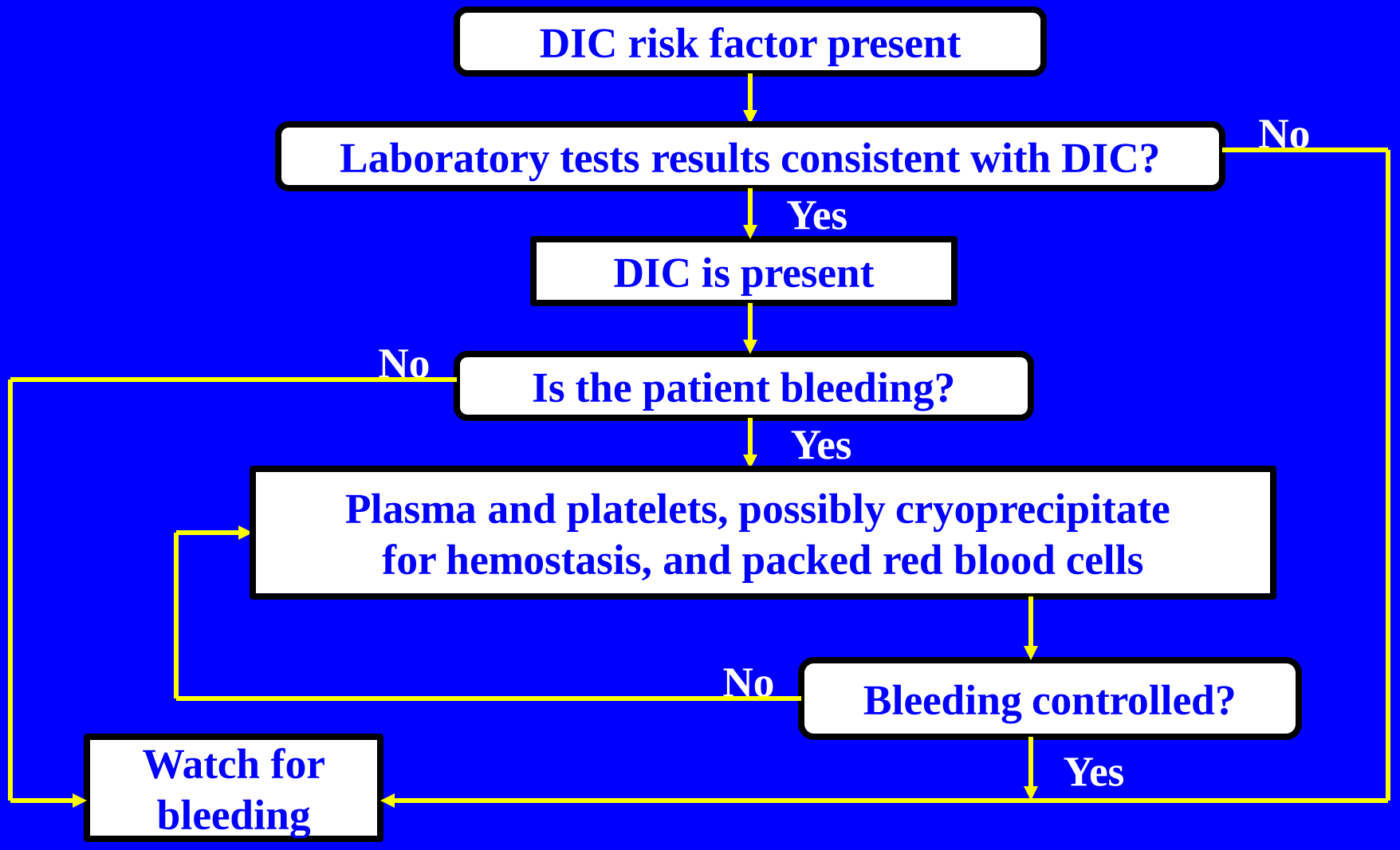
Disseminated Intravascular Coagulation (DIC)



Practical Laboratory Evaluation for DIC

	Changes in DIC
Platelets	Low or decreasing
Fibrinogen	Low or decreasing
FDP or D-Dimer	Increased
PT	Increased

Diagnostic and Therapeutic Approach to DIC



Case 1

Case 1:

65 y/o man in intensive care unit with bleeding from multiple sites and respiratory failure

Any role for D-Dimer ?

Laboratory Evaluation for DIC

	Changes in DIC
Platelets	Low or decreasing
Fibrinogen	Low or decreasing
FDP or D-Dimer	Increased
PT	Increased

Case 2

Case 2:

25 year old woman in good health presents to ED with mild bilateral swelling in her legs following a 4 hour car ride

Role for D-dimer?

Risk Stratification The Wells - Score

Symptom	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of DVT	2

0 = low risk of DVT

1 – 2 = medium risk of DVT

≥ 3 = high risk of DVT

This patient is a low risk rule out

Case 3

Case 3:

37 y/o woman, obese and heavy smoker presents to ED with acute shortness of breath and a painful edematous right leg. She has a history of 2 prior DVT's

Role for D-dimer

Case 3

Case 3:

Sounds high risk but criteria are not clear

Sounds like DVT and PE

D-dimer may be useful but ultrasound/ chest CT inevitable

Note 3rd DVT … Think hypercoagulable state

Case 4

Case 4:

35 y/o man presents to 24 hour clinic with right lower leg pain. There is no swelling

What to do ?

Case 4

<u>Case 4:</u>

D-dimer useful but will take 2 days to get back from reference lab
Ultrasound not available on site

Sure would be nice to have a rapid rule out test here

Case 5

Case 5:

57 y/o man presents with chest pain and shortness of breath. He is a heavy smoker.

Role for D-dimer

Case 5

<u>Case 5:</u>

Considerations
PE
Acute coronary syndrome
Congestive heart failure
COPD exacerbation

Ideally want Tn, natriuretic peptide, D-dimer