D-Dimer

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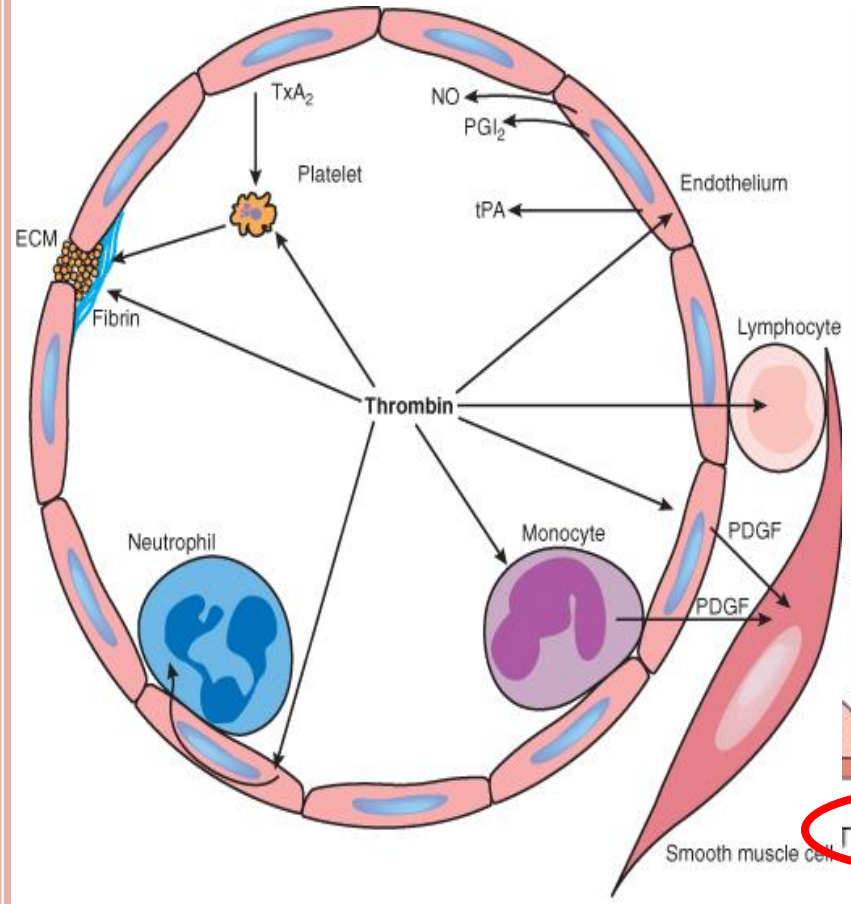
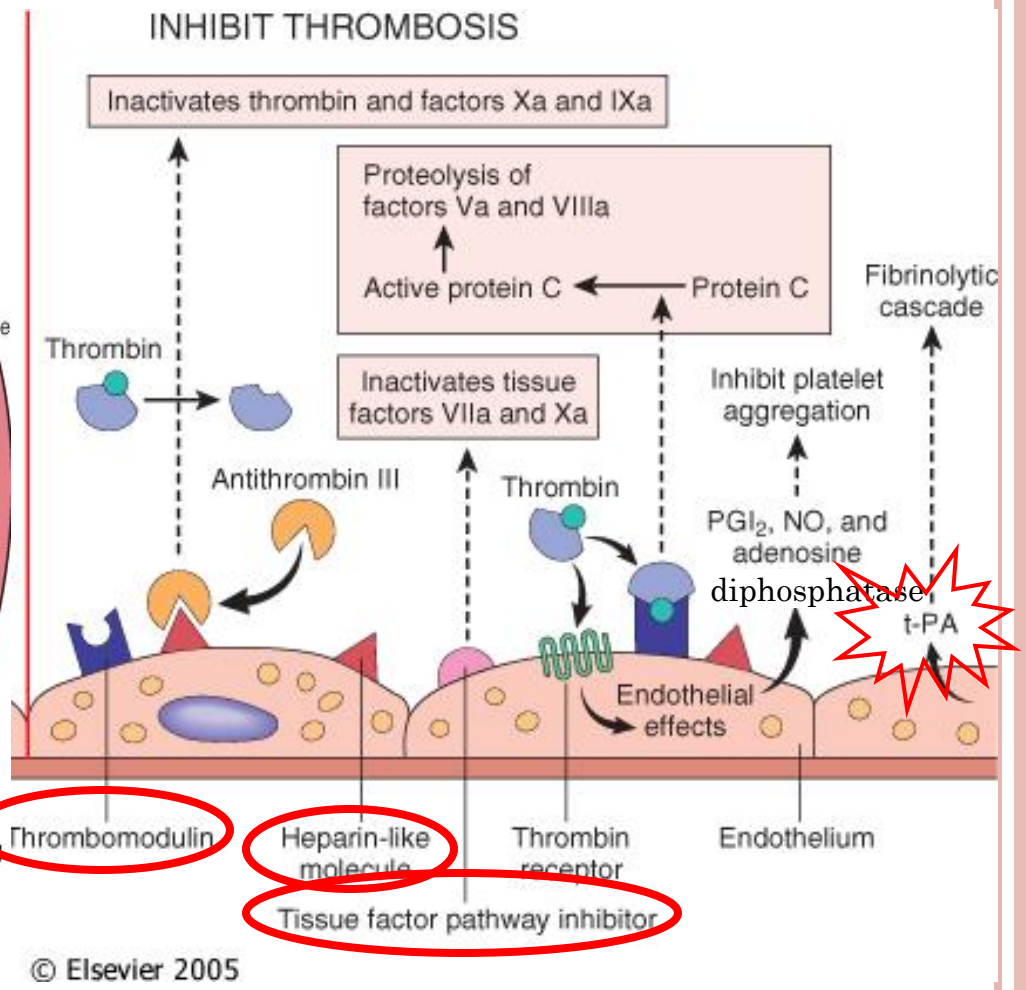
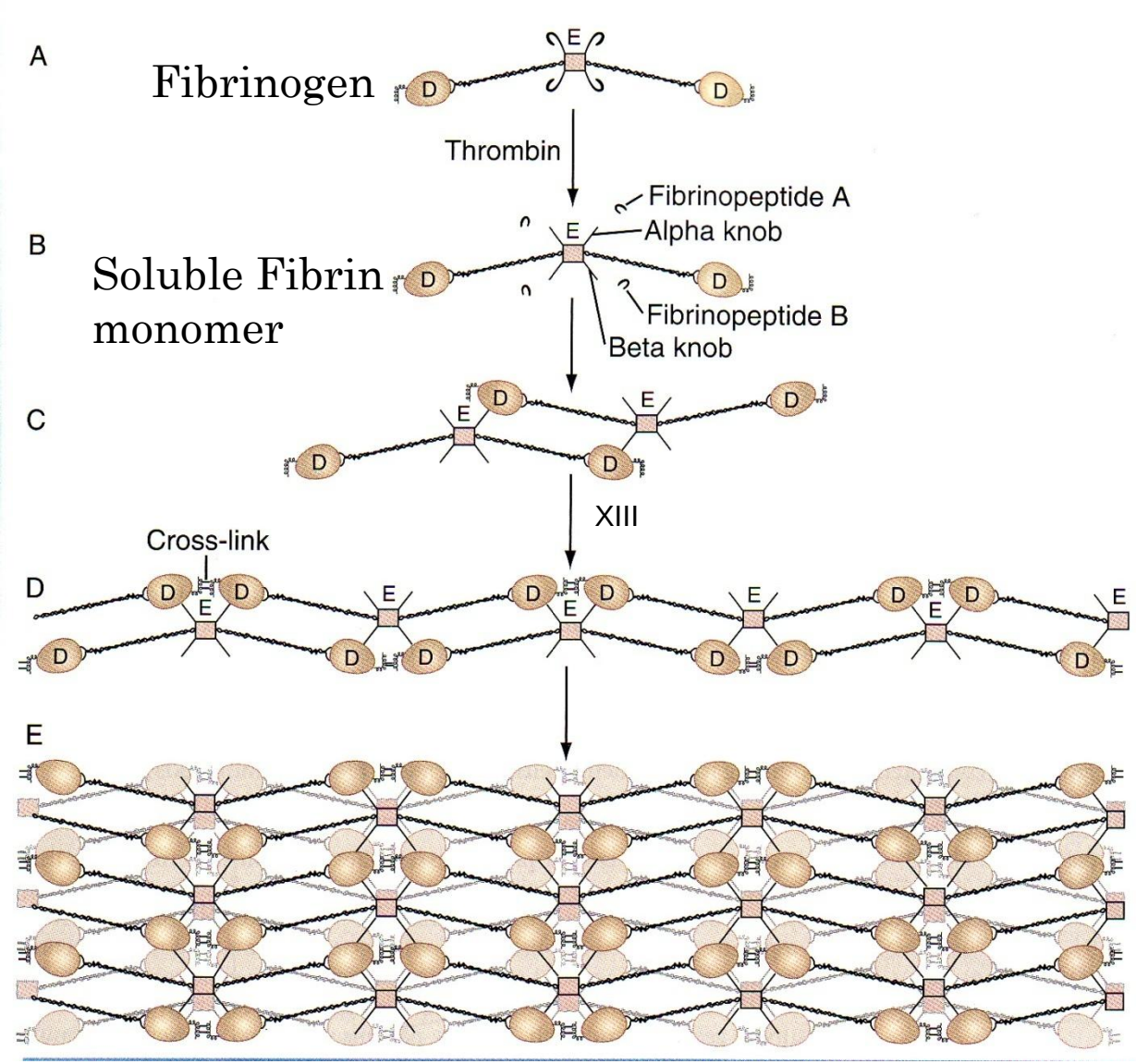
Anticoagulation and fibrinolytic system

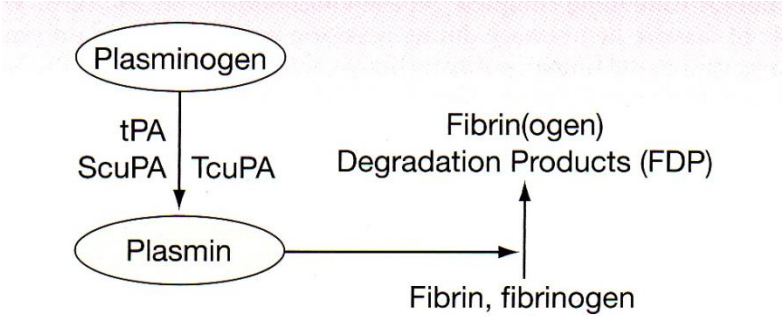


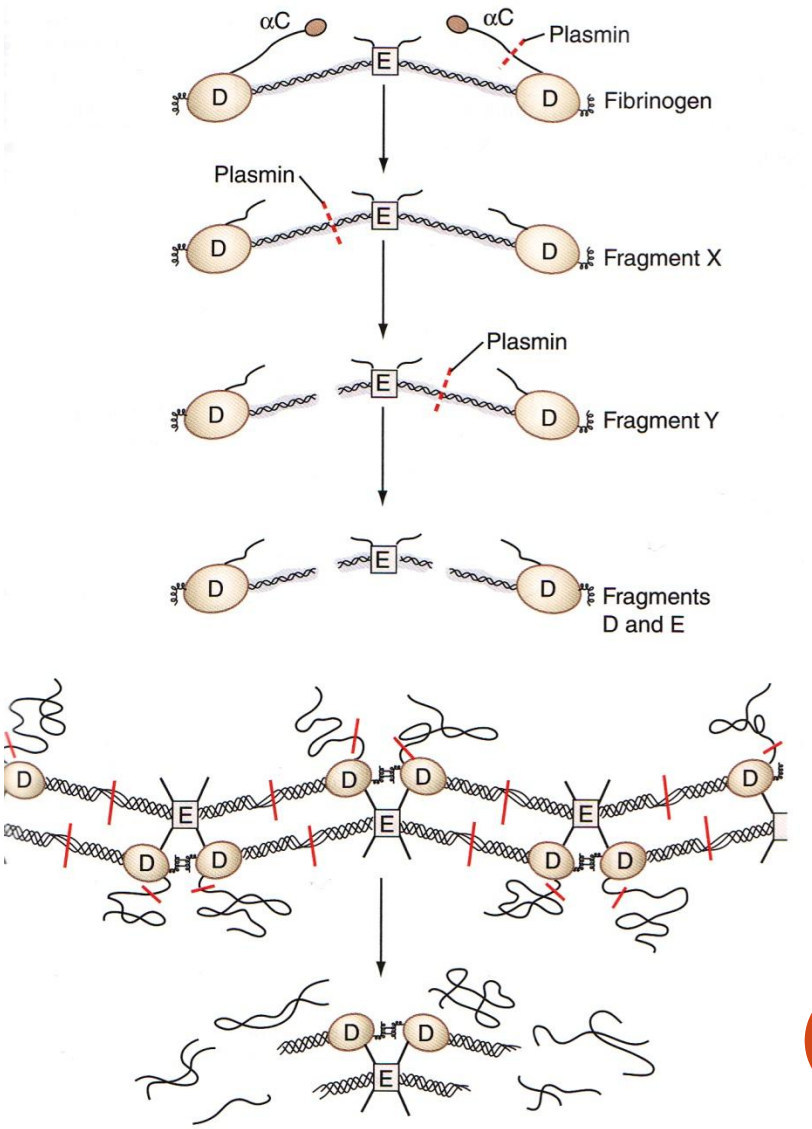


Formation of fibrin



Fibrinolytic system





- Activators:
  - Tissue plasminogen activator (tPA)
  - Urokinase plasminogen activator (uPA)
- Inhibitors:
  - Plasminogen activator inhibitor-1 (PAI-1)
  - α2-antiplamin

D-dimer

- Fibrin is formed as the end result of coagulation cascade activation
- Fibrinolysis causes cleavage of fibrinogen, fibrin, and fibrin clot, yields FSP (FDP)
- Only cleavage of fibrin clot (crosslinked fibrin) yields D-dimer

Conditions with elevated D-dimer

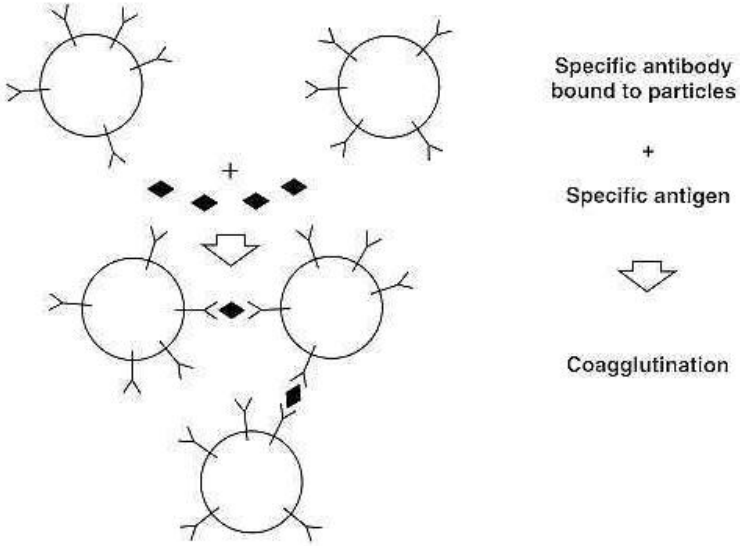
- DIC
- Thrombosis
- Significant bleeding
- Cirrhosis
- Tumors (mucinous secreting adenocarcinomas)

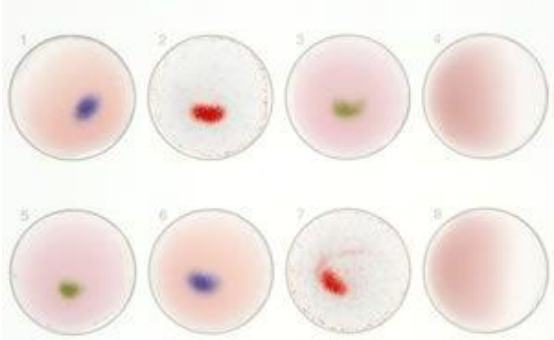
Current available tests

- Semi-quantitative FSP
- Qualitative D-dimer
- Semi-quantitative D-dimer
- Quantitative D-dimer

Semi-quantitative FSP

- The first test developed (in the early 70's)
- Latex agglutination, FSP antibodies are bound on latex beads, if sample contains FSP, agglutination can be detected
- Semi-quantitation:
  - Serial dilution of sample (1: 20 through 1:640)
  - A positive result at 1:20 corresponds to 20 µg/mL of fibrinogen equivalent units (FEU)





Semi-quantitative FSP

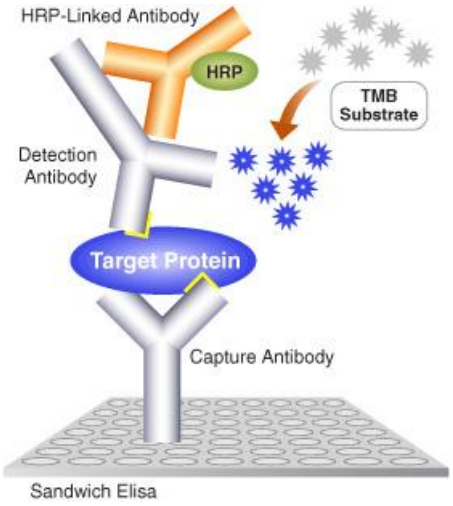
- Early generation FSP polyclonal antibodies cross-react with fibrinogen
  - Must use serum or plasma in tubes with bovine thrombin (consumes fibrinogen)
- Current FSP monoclonal antibodies do not cross react with fibrinogen
  - Can use plasma or serum
  - False-positive result with rheumatoid factor
- Clinical application: DIC, hyperfibrinolysis

Qualitative D-dimer

- Monoclonal antibodies directed against D-dimer domain
  - More specific for in-vivo fibrin clot formation
- Manual latex agglutination technique (as for FSP), plasma or serum sample:
  - Cut-off value: 0.5 µg/mL FEU
  - Semi-quantitative format: dilutions 1:2 through 1:16
- Abnormal result in DIC
- Normal result in primary fibrinolysis
- False-positive result by rheumatoid factor
- Sensitivity and specificity not significantly different from those of FSP for diagnosis of DIC

Quantitative D-dimer

- Automated ELISA, immuno-turbidimetry
- Increased in DIC (>0.66 µg/mL)
- High negative predictive value for venous thromboembolism (VTE including DVT, PE):
  - <0.4 µg/mL, VTE can be ruled out
  - Very sensitive but not specific: high NPV/low PPV



DIC

- Concurrent activation of the coagulation (thrombin) and fibrinolysis (plasmin) with consumption of both factors and inhibitors
- Secondary to sepsis, malignancy, obstetrical complications and massive tissue injury
- Hyperfibrinolytic state: ↑ PT & PTT, thrombocytopenia, ↓ fibrinogen
- Prothrombotic state: nl PT & PTT, nl/↑ fibrinogen, mild thrombocytopenia

DIC

- Semi-quantitative FSP: does not indicate clot formation
- Qualitative and semi-quantitative D-dimer
  - May also be increased in resolving large vessel thrombosis, hematomas
- Other tests: fibrinopeptide A, antithrombin and prothrombin fragment 1+2 (fibrinopeptide/prothrombin are normal in TTP)
- Treatment:
  - Treat underlying conditions
  - Fulminant DIC: antithrombin concentrates
  - RBC, platelet concentrate
  - Fibrinogen<100mg/dL
    - FFP (15-20 mL/kg) and or cryoprecipitate (1 U/10kg)

Venous Thromboembolism (VTE): DVT & PE

- Venous thrombosis in the legs (DVT): swollen, painful legs, pitting edema (can be subtle)
- Major complication of DVT: PE: chest pain, dyspnea, anxiety, cyanosis, hemoptysis (2/3 of patients with PE are asymptomatic)
- DVT: 48-182/100,000/year
  PE: 69-205/100,000/year
- Risk of VTE: 0.5% by 50 y/o, 10.7% by 80 y/o
- PE accounts for 5-10% of hospital deaths, mortality: 30% (untreated) and 8% (treated)

VTE

- Deep calf vein thrombosis: small thrombi, lower risk for serious PE
- Proximal vein thrombosis (popliteal, femoral, and iliac): more serious risk for PE
- 50% of patients with DVT have PE
- 70% of patients with PE have DVT
- ~30% of patients with suspected VTE are diagnosed with DVT and/or PE
- Etiologies of VTE
  - Inherited: Factor V Leiden, prothrombin variant 20210, APS (ACA/LAC), ATIII deficiency, protein C/S deficiency
  - Acquired: Immobilization, trauma, pregnancy
- Treatment:
  - Heparin, coumadin
  - Thrombolytics only for massive PE

Pathologies	No. of Patients	Negative Predictive Value (NPV) %	References
PE and DVT	918	99.3	Perrier A, et al., Lancet, 1999, 353: 190-5
PE and DVT	100	100	Freyburger G, et al. Thromb. Haemost. 1998, 79: 32-7
DVT	132	100	Jansen MCH, et al. Thromb. Haemost. 1997, 77: 262-6
DVT	103	98	D'Angelo A, et al. Thromb. Haemost. 1996, 75: 412-16
PE	195	100	De Moerloose P, et al. Thromb. Haemost. 1996, 75: 11-13
PE	965		Perrier A, et al. Amer J of Med. 2004, 116: 291-299
PE and DVT			Stein PD, et al. Annals of Int. Med.
DVT	302	100	De Moerloose P, Thromb. Haemost. 2001, 85: 185-186

Table 8. Diagnostic accuracy indices of D-dimer assays for VTE.

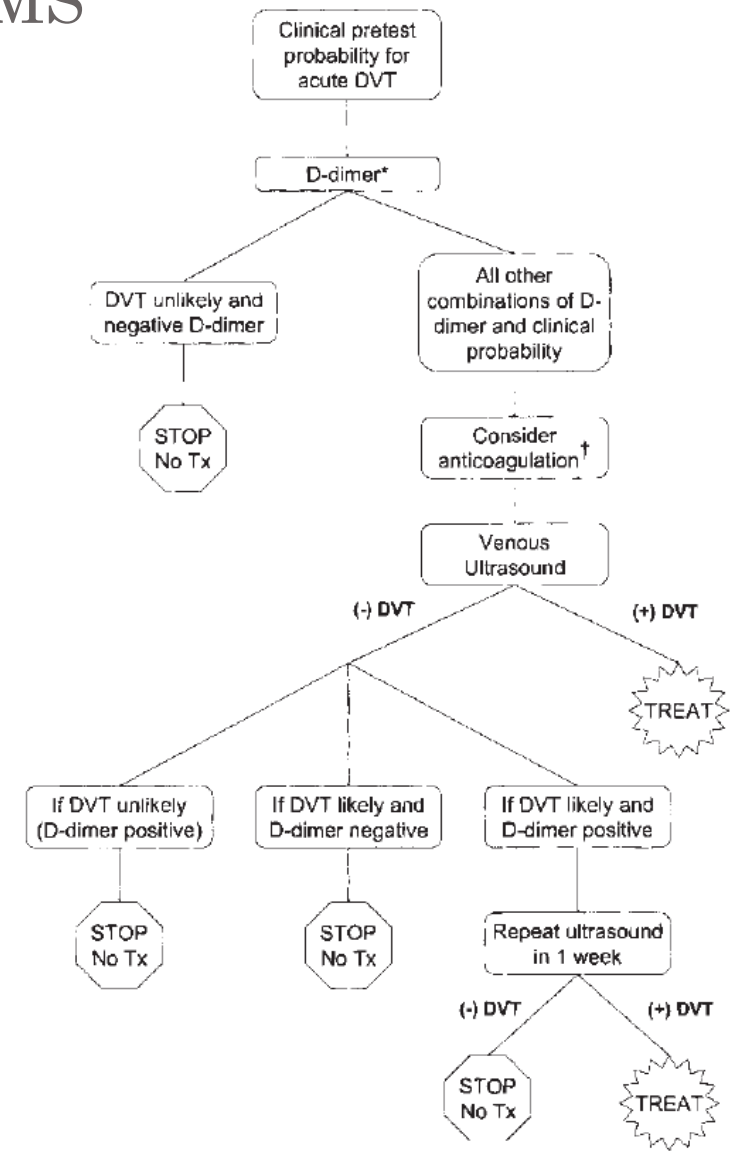
Assay Type	Studies (N)	Patients (N) - VTE + VTE	VTE Prevalence (%)	Sens (%)	Spec (%)	NPV (%)	PPV (%)
Manual Latex	27	3352 1255	37 (32-43)	82 (77-87)	61 (53-68)	83 (79-88)	62 (55-68)
Immuno-filtration	18	2665 1079	40 (35-46)	92 (90-95)	45 (34-56)	88 (84-92)	56 (49-64)
SimpliRED; whole blood agglutination	11	2734 646	24 (13-34)	88 (81-95)	69 (64-74)	91 (83-99)	54 (42-62)
Elisa	37	4783 1833	38 (34-42)	96 (95-98)	43 (37-49)	95 (93-97)	54 (50-58)
VIDAS; automated Elisa	9	1043 454	44 (35-52)	97 (96-99)	44 (33-55)	96 (94-98)	57 (47-67)
Immuno-turbidimetric	17	3401 1225	36 (28-44)	96 (95-98)	46 (40-53)	96 (94-98)	54 (46-62)

DVT: Clinical Prediction Rules & diagnostic algorithms

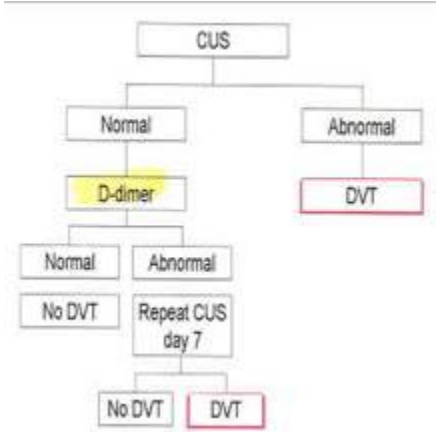
Table 1 Wells' Clinical Prediction Model for Suspected Deep Vein Thrombosis (≥2 DVT Likely, ≤1 DVT Unlikely)*

Clinical Finding	Points
Active malignancy (ongoing treatment, or within the last 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for ≥3 days, or major surgery within the last 12 weeks using general or regional anesthesia	1
Local lower extremity tenderness along the deep venous system	1
Swollen thigh and calf	1
Calf swelling ≥3 cm larger than asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Unilateral pitting edema of the symptomatic leg	1
Unilateral dilated superficial veins (nonvaricose) of the symptomatic leg	1
Previously documented DVT	1
Alternative diagnosis at least or more likely than DVT	–2

*Alternatively, <1 low probability of DVT, 1 or 2 moderate probability, >2 high probability.
Adapted from Wells et al 2003[22] and Wells et al 1995.[23]
DVT, deep vein thrombosis.



DVT: Testing advantages/disadvantages



- Venography: sensitive, but invasive and time-consuming, only 25-35% of cases show DVT
- Ultrasound: non-invasive, readily available, but not sensitive: requires repeated testing in 1 week
- Quantitative D-dimer: sensitive, not specific
  - Insufficient specificity in the elderly (>80 years) or hospitalized patients
  - Taken separately, a low Wells score or a negative D dimer is insufficient to rule out DVT (4-5% with DVT)
  - A negative D-dimer test in conjunction with low clinical probability may effectively exclude DVT (0.4% with DVT) without the need for compression ultrasound

PE: Clinical Prediction Rules & diagnostic algorithms

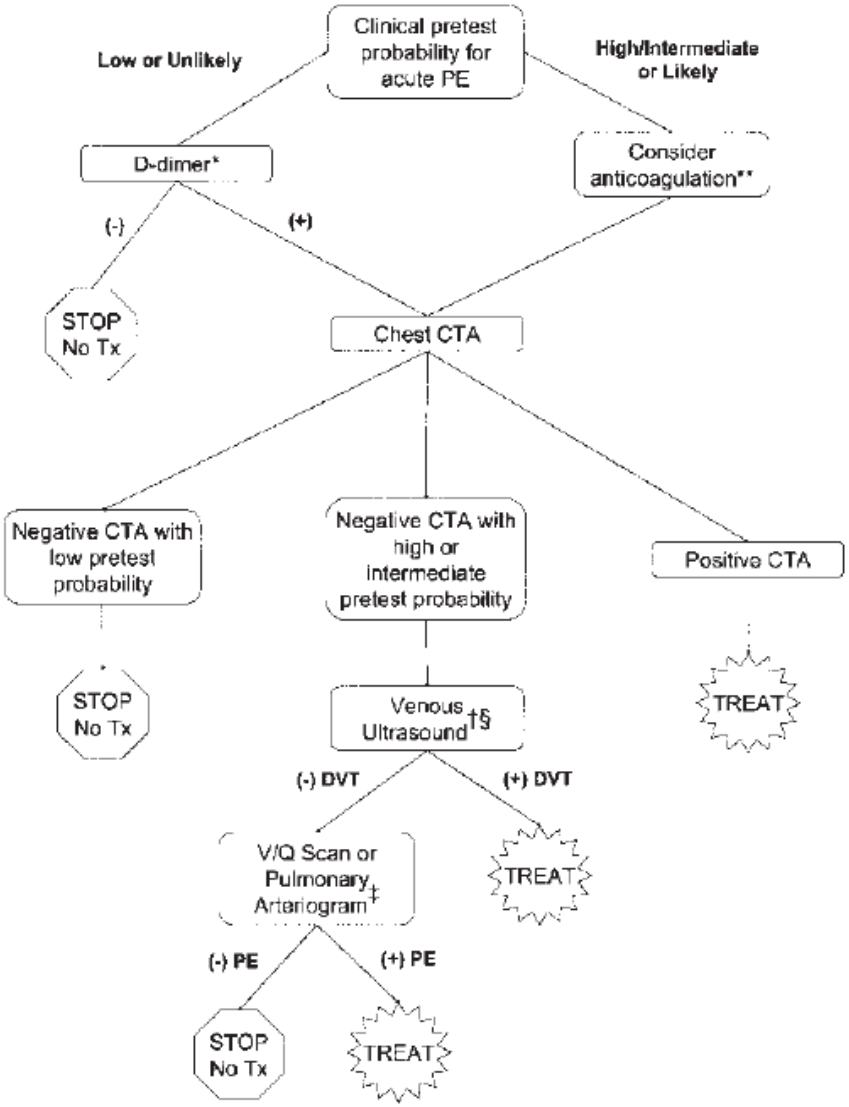


Table 2 Wells' Simplified Clinical Prediction Model (Canadian Scoring System) for Suspected Pulmonary Embolism (>4 PE Likely, ≤4 PE Unlikely)*

Clinical Finding	Points
Clinical signs and symptoms of DVT (at least local lower extremity tenderness along the deep venous system and swollen lower extremity)	3.0
No alternative diagnosis greater than or equal to the likelihood of PE.	3.0
Heart rate > 100 beats/min	1.5
Immobilization or surgery within the last 4 weeks	1.5
History of prior VTE	1.5
Hemoptysis	1.0
Active malignancy (ongoing treatment, or within the last 6 months, or palliative)	1.0

*Alternatively, < 2 low probability of PE, 2–6 moderate probability, > 6 high probability.
Adapted from Wells et al 2000.[40]
PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

PE: Testing advantages/ disadvantages

- Pulmonary angiography: sensitive, but invasive and time-consuming; positive in 25% of cases
- Ventilation-perfusion (V/Q) scan: less invasive, but not sensitive (60-70% of cases non-diagnostic)
- Quantitative D-dimer: sensitive
  - In cases of low clinical probability or if PE is unlikely, D dimer should be the next test because it may help guide the need for diagnostic imaging