Venous thromboembolism

Pusan National University Hospital
Department of Hematology-oncology
Hojin Shin, MD, PhD

Introduction

- Thromboembolism = thrombus + embolism
- Venous thrombosis
  - Blood clot or thrombus that forms within a vein
- Thromboembolism
  - Thrombus occludes a blood vessel
- VTE
  - DVT
  - PE

DVT

Incidence

- 1-2/1000 people each year, usually as DVT of leg or PE

- 900,000/yr in USA
- 1.1 million/yr in Europe

- < 40 yrs: 1/10,000

Annual incidence of VTE in Korean population

Table 1 Annual incidence of VTE, DVT and PE in the Korean population

	Annual incidence														
	2004			2005			2006			2007			2008		
Year	VTE	DVT	PE	VTE	DVT	PE	VTE	DVT	PE	VTE	DVT	PE	VTE	DVT	PE
Age group															
Male populations															
0–9	0.19	0.10	0.00	0.00	0.00	0.00	0.07	0.07	0.00	0.07	0.00	0.07	0.30	0.23	0.00
[illegible]															
54	20–29	3.50	1.71	1.24	2.82	1.33	1.03	4.38	2.11	1.50	4.17	1.97	1.24	5.09	1.86	2.
26	30–39	5.86	2.71	2.02	5.89	2.95	2.01	6.56	3.20	2.12	7.[illegible]	[illegible]	2.36	7.86	3.40	3.
[illegible]	40–49	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	50–59	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
41	60–69	31.46	11.00	16.36	25.[illegible]	9.[illegible]	16.36	29.42	14.02	14.[illegible]	35.[illegible]	16.[illegible]	15.[illegible]	38.[illegible]	14.[illegible]	15.
50	70–79	32.36	15.25	21.64	41.[illegible]	14.[illegible]	22.[illegible]	60.[illegible]	26.[illegible]	28.04	6[illegible]	25.[illegible]	35.[illegible]	76.[illegible]	31.[illegible]	47.
[illegible]	80–	69.86	26.26	35.[illegible]	65.05	25.[illegible]	[illegible]	90.[illegible]	29.[illegible]	49.46	10.[illegible]	31.[illegible]	67.[illegible]	108.[illegible]	33.[illegible]	64.
[illegible]	Subtotal	7.27	3.72	3.01	8.[illegible]	3.[illegible]	3.[illegible]	9.99	4.[illegible]	3.79	11.29	5.[illegible]	4.[illegible]	12.[illegible]	4.90	5.
Female populations															
[illegible]	0–9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	10–19	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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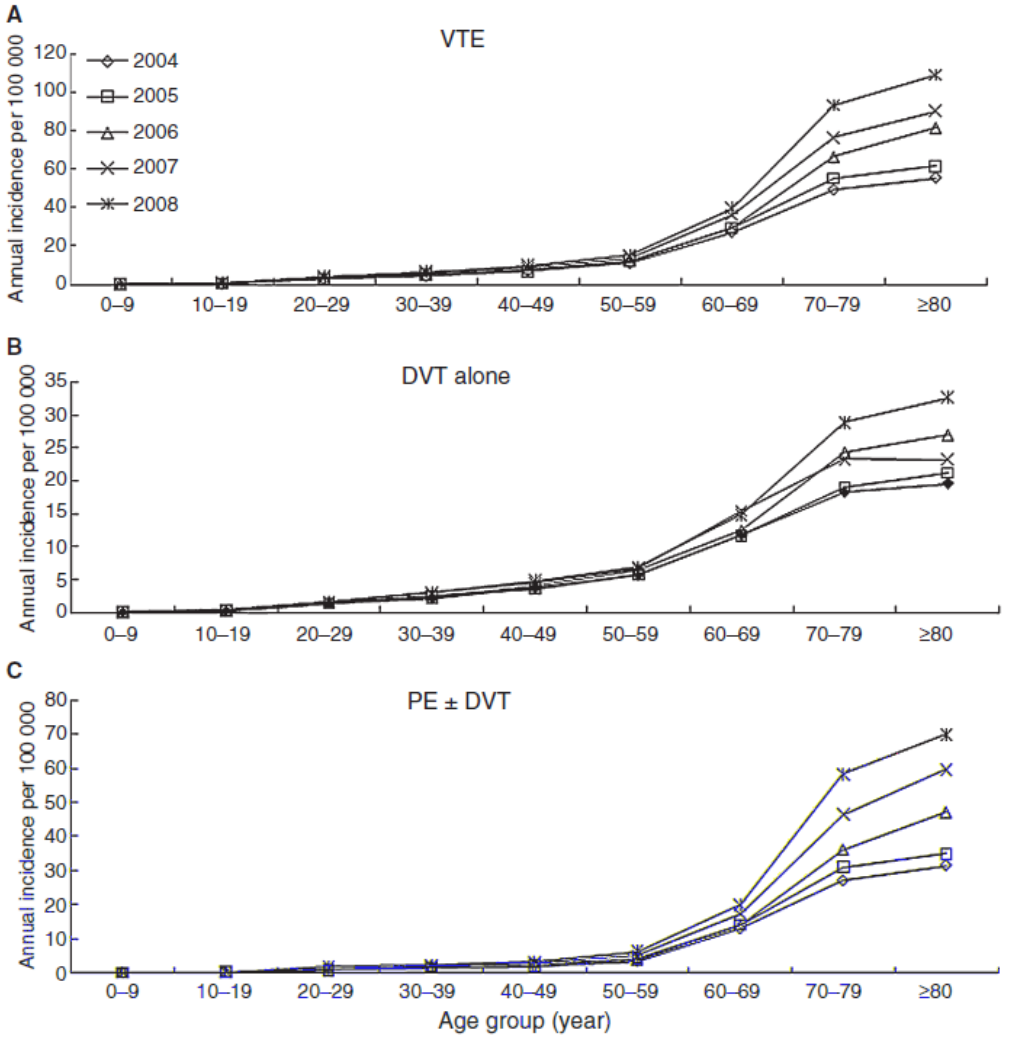
[illegible]	30–39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	40–49	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	50–59	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	60–69	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	70–79	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	80–	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Subtotal	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

100 000 population, directly age-adjusted to the 2006 population. †All rates are per 100 000 population, directly age and sex [illegible] 006 population. VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism. ‡All rates are per [illegible] adjusted to the 20

Jang et al, J thrombo & haemostasis, 2010;9:85

Annual incidence among different age group



Jang et al, J thrombo & haemostasis, 2010;9:85

Epidemiology

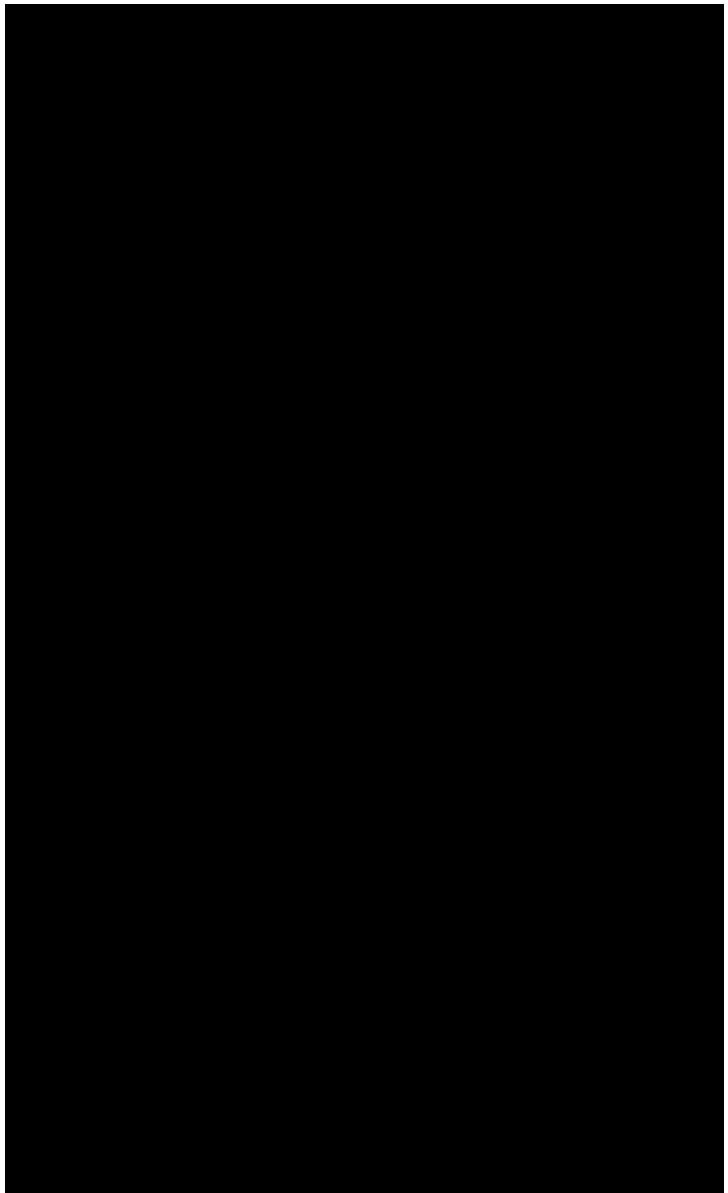
- Risk of DVT among hospitalized pts not receiving thromboprophylaxis
  - As high as 80% in those with major trauma, spinal cord injury and in critical care pts
- Risk of acute mortality: 7-11% /c PE

Table II. Prevalence of deep vein thrombosis in hospitalized patients not receiving thromboprophylaxis[20]

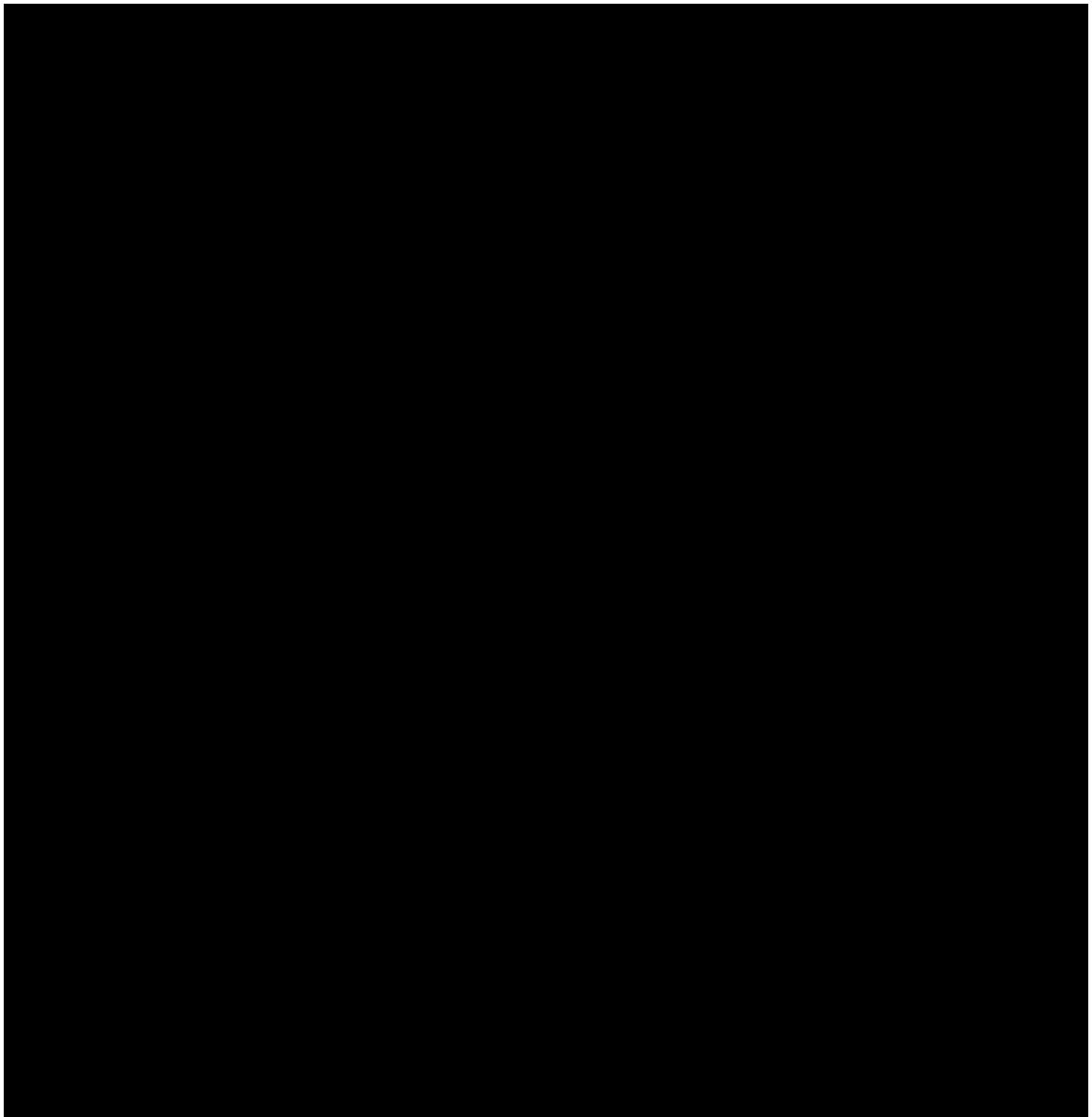
Patient group	DVT prevalence (%)
Medical patients	10–20
General surgery	15–40
Major gynaecological surgery	15–40
Major urological surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip fracture surgery, hip or knee arthroplasty	40–60
Major trauma	40–80
Spinal cord injury	60–80
Critical care patients	10–80

DVT = deep vein thrombosis.

Origin of thrombus and its propagation



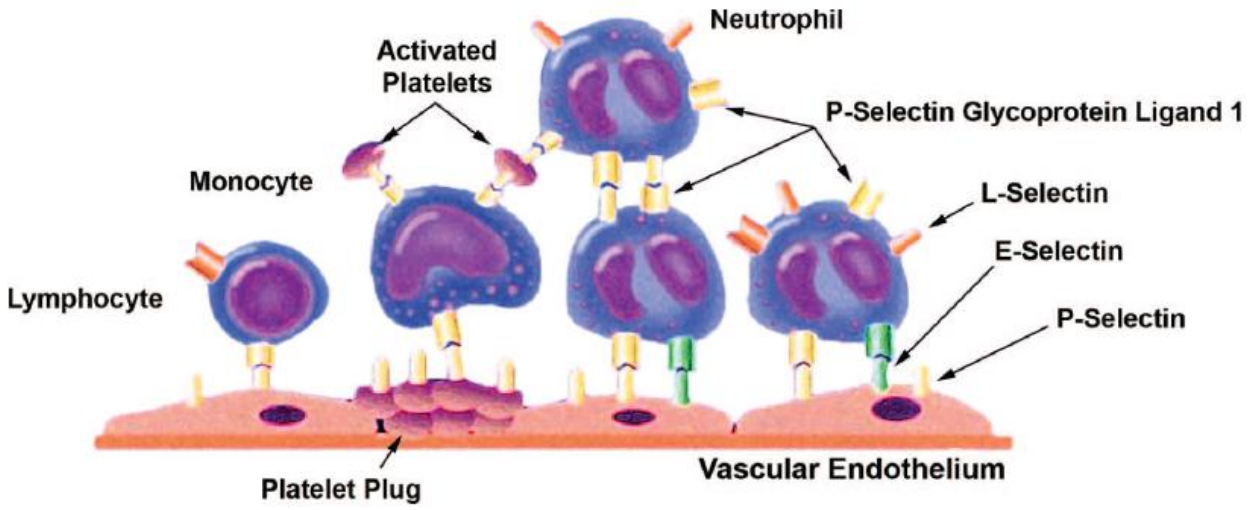
Natural Hx of venous thrombosis



Etiology of DVT

1865년 “

- Stasis
- Hypercoagulable state
- Vessel injury



Risk factors for VTE

- Acute provoking factors
  - Hospitalization
  - Surgery
  - Trauma or fracture of lower limbs or pelvis
  - Immobilization
  - Long-haul travel
  - Recently commenced estrogen therapy (eg, within previous 2 weeks)
  - Intravascular device (eg, venous catheter)

- Chronic predisposing factors
  - Inherited
    - Natural anticoagulant deficiency
    - Factor V Leiden
    - Prothrombin G20210A mutation
  - Inherited or acquired
    - High plasma homocysteine
    - High plasma coagulation factor VIII, IX, XI

- Acquired
  - Age
  - Obesity
  - Cancer (chemotherapy)
  - Leg paralysis
  - Estrogen therapy
  - Pregnancy or puerperium
  - Major medical illness
  - Previous VTE

Risk factors

- Among surgical pts, risk of DVT is highest for
  - Hip and knee surgery
  - Major abdominal surgery

Distal (calf v) DVT

- Most DVT starts in calf
- In 50% of pts, resolve spont within 72hrs
- In 1/6 of pts, extend to involve prox v
- Isolated calf DVT, asymptomatic
- Prox extension of calf v thrombus: <u>symptomatic > asymptomatic</u>

- <u>Harbingers for increased risk of PE</u>
  - Sx (+) (pain, swelling, tenderness, redness)
  - Prox progression

Prox (popliteal, thigh) DVT

- Sx of DVT do not develop until involvement of prox leg v
- ½ of pts /c Sx prox DVT: clinically silent PE at time of Dx
- 10% of pts: Sx PE
-
- /c adequate Tx
  - Regression of thrombus occur during first week
  - Recanalization and resolution of thrombus occur in ½ pts (within first 3mo)
  - Resolution of thrombus is less likely in pts /c extensive initial thrombosis or cancer

Post-thrombotic syndrome (1)

- 50% following resolution of DVT
- Clinical Sx
  - Constant or intermittent pain, swelling, heaviness, tingling and cramps in affected leg
- Severe Sx
  - Subcut atrophy
  - Skin ulceration

Post-thrombotic syndrome (2)

- Results from
  - Damage to v valve, by thrombus itself or by thrombus related inflammation
  - Partial obstruction of v by residual thrombus

- Results in valvular reflux, impaired v return →
  - v HT
  - Decreased perfusion of calf m
  - Increased tissue permeability

Clinical Dx

- AAFP/ACP guideline

Clinical features	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 > 3days or major surgery with 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 edema confined to the symptomatic leg	**1**
Collateral superficial veins (non-varicose)	**1**
Alternative diagnosis as likely or greater than that of DVT	**-2**

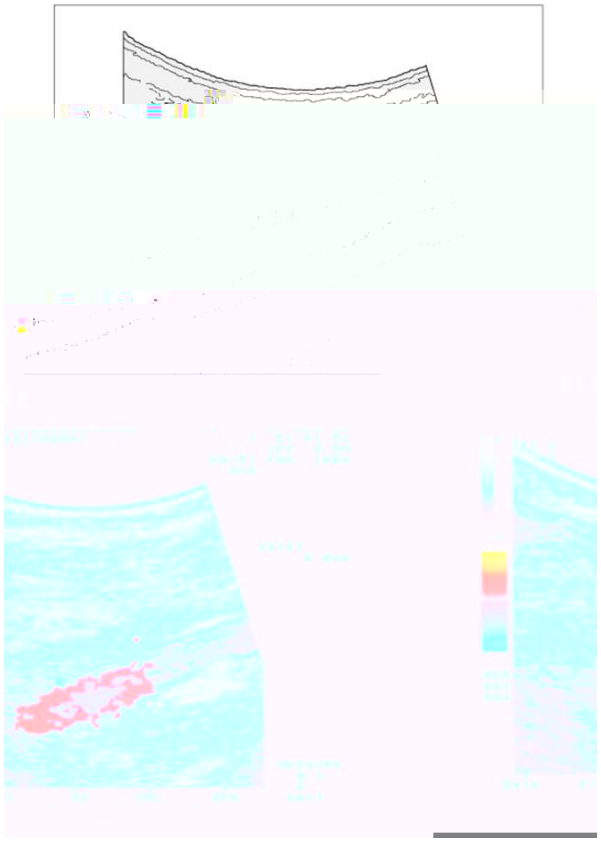
*Pretest probability is calculated as the sum of the scores: high ≤ 0.

Ho et al, MJA 2005;182:476

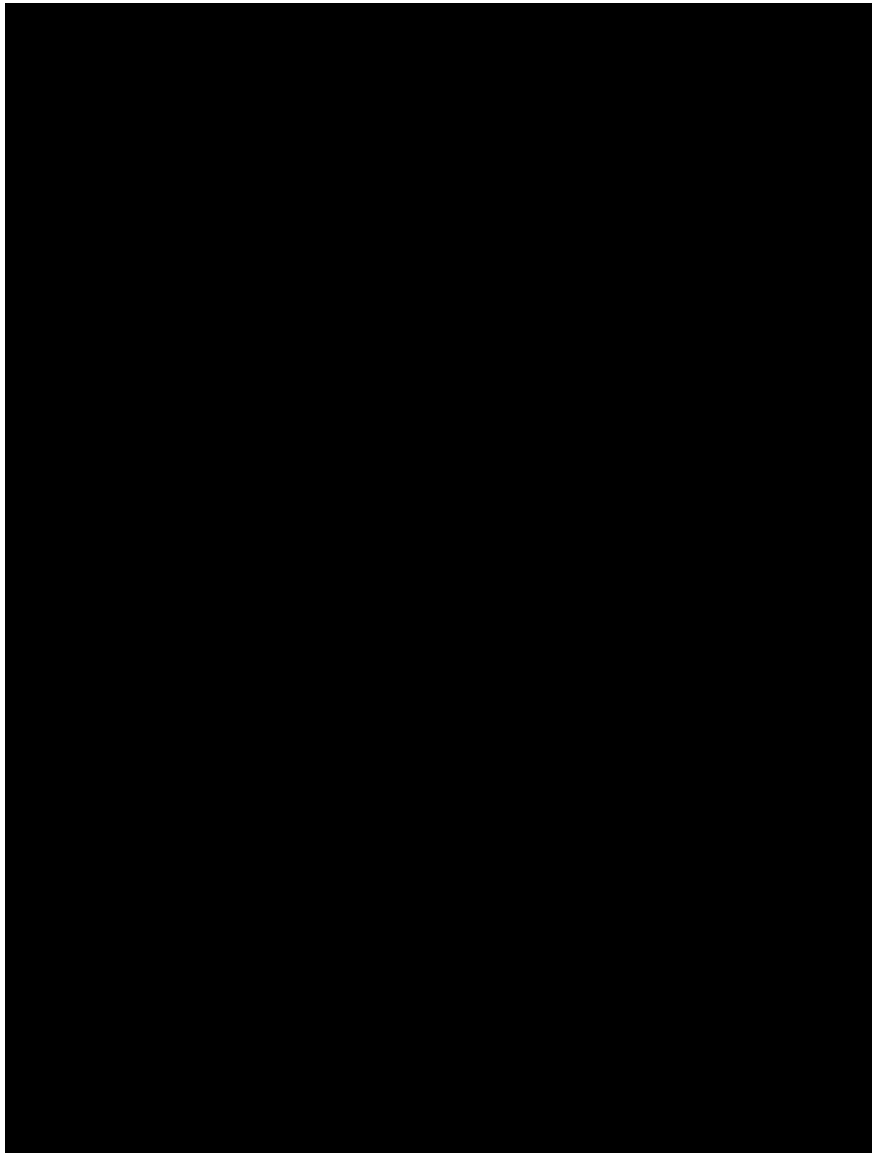
U/S

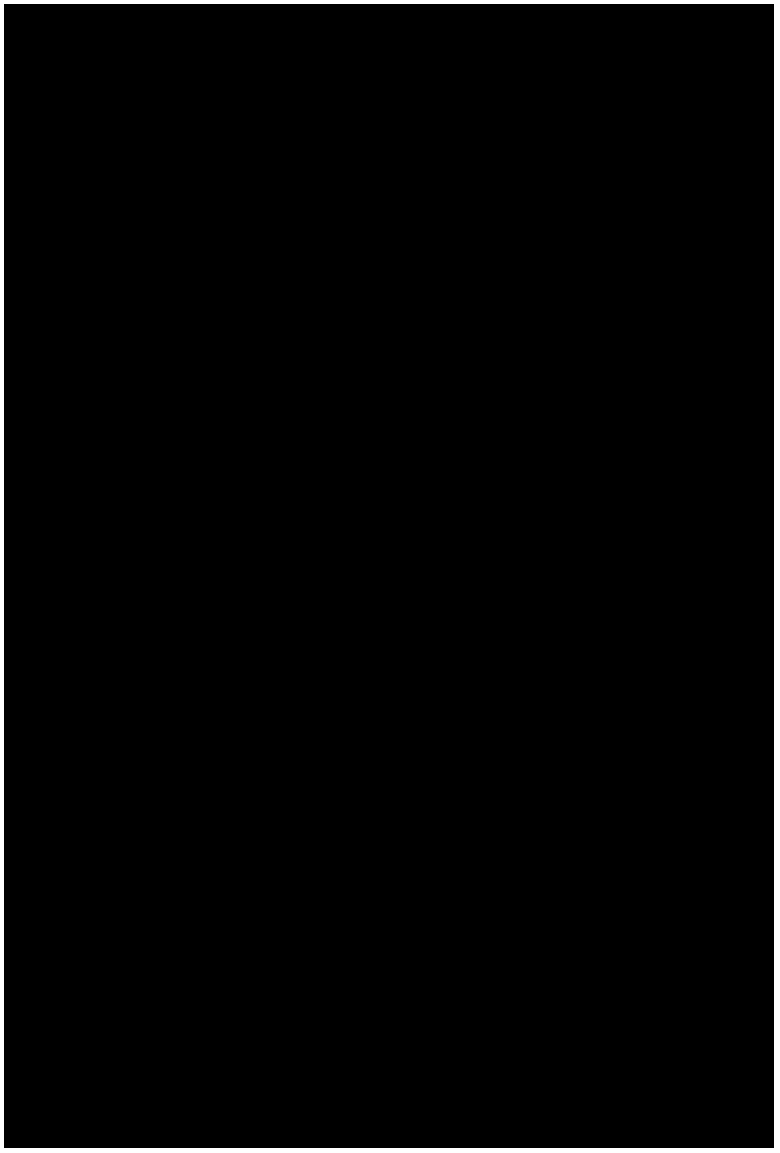
- Most frequently used imaging method for diagnosing DVT
- Features of DVT on U/S
  - Lack of compressibility of vessel lumen
  - Distended vessel
  - Lack of flow in vessel

Doppler U/S

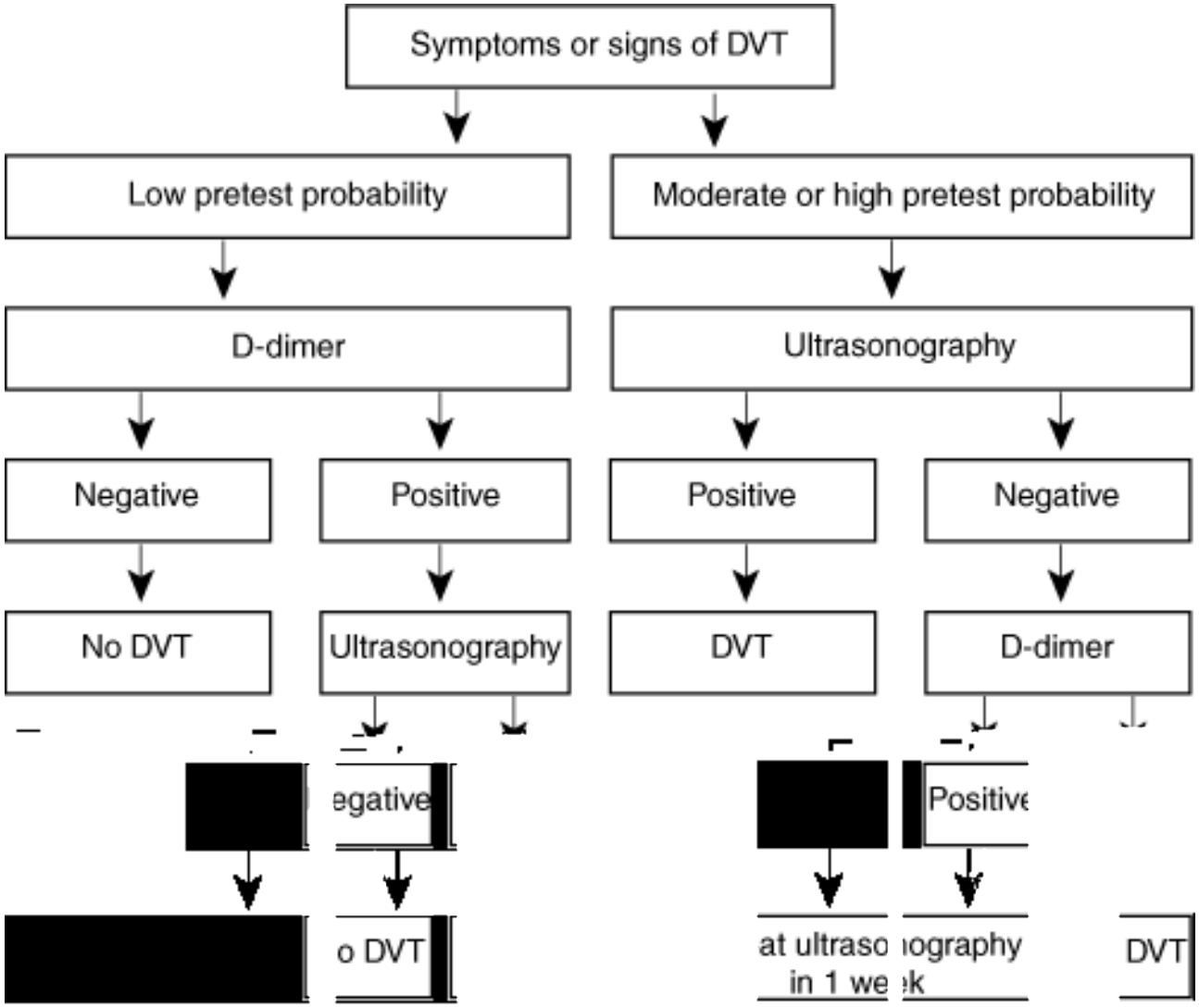


Venography





Clinical approach to Dx of DVT



Hirsh J et al, Blood 2002

Tx

- Aim of Tx
  - Relieve Sx
  - Reduce risk of PE
  - Prevent post-thrombotic synd
  - Prevent recurrence

Initial anticoagulation

- ACP/AAFP guideline
  - Initial DVT Tx → LMWH > UFH

5 Contraindications for anticoagulation and risk factors for anticoagulation-associated haemorrhage[22]

Absolute contraindications

Active bleeding

Relative contraindications

Recent bleeding

Gastrointestinal bleeding within 2 weeks (eg, bleeding peptic ulcer)

Intracranial bleeding within 3 months

Recent major trauma

Bleeding diathesis

Coagulation defect

Severe thrombocytopenia ($< 50 \times 10^9$/L); inherited or acquired platelet function defect

Uncontrolled hypertension

Endocarditis

Risk factors for anticoagulation-associated haemorrhage

Increasing age

Alcoholism

Cognitive impairment

Chronic corticosteroid use

Liver disease

Peptic ulcer disease

Polymorphisms for the gene encoding the hepatic microsomal enzyme CYP2CP and mutations of Ala-10 in the factor IX propeptide

6 Initial anticoagulation for treatment of deep vein thrombosis

Anticoagulant and dose	Monitoring*	Target
Unfractioned heparin		
Loading dose 80 IU/kg; Infusion 18 IU/kg per hour.†	Measure APTT 6 hours after the bolus dose and adjust infusion accordingly.	APTT corresponding to anti-Xa 0.3–0.7 U/mL (E2).
Low-molecular-weight heparin‡		
Dalteparin 100 IU/kg twice daily or 200 IU/kg once daily. Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily.	Renal failure; obesity (eg, > 130 kg); pregnancy (E4).	Anti-Xa 0.6–1.0 U/mL for twice daily dosing or 1.0–2.0 anti-Xa U/mL for once daily dosing (E4).

APTT = activated partial thromboplastin time. * Platelet counts should be measured twice weekly in all patients to monitor for the development of heparin-induced thrombocytopenia. † Based on the nomogram by Raschke et al. Patients requiring more than 40 000 IU/day of unfractionated heparin to achieve a therapeutic APTT are considered heparin-resistant, and dose should be adjusted according to results of the plasma anti-Xa activity. ‡ Dalteparin and enoxaparin are the only low-molecular-weight heparin preparations currently available in Australia.

Advantages of LMWH over UFH

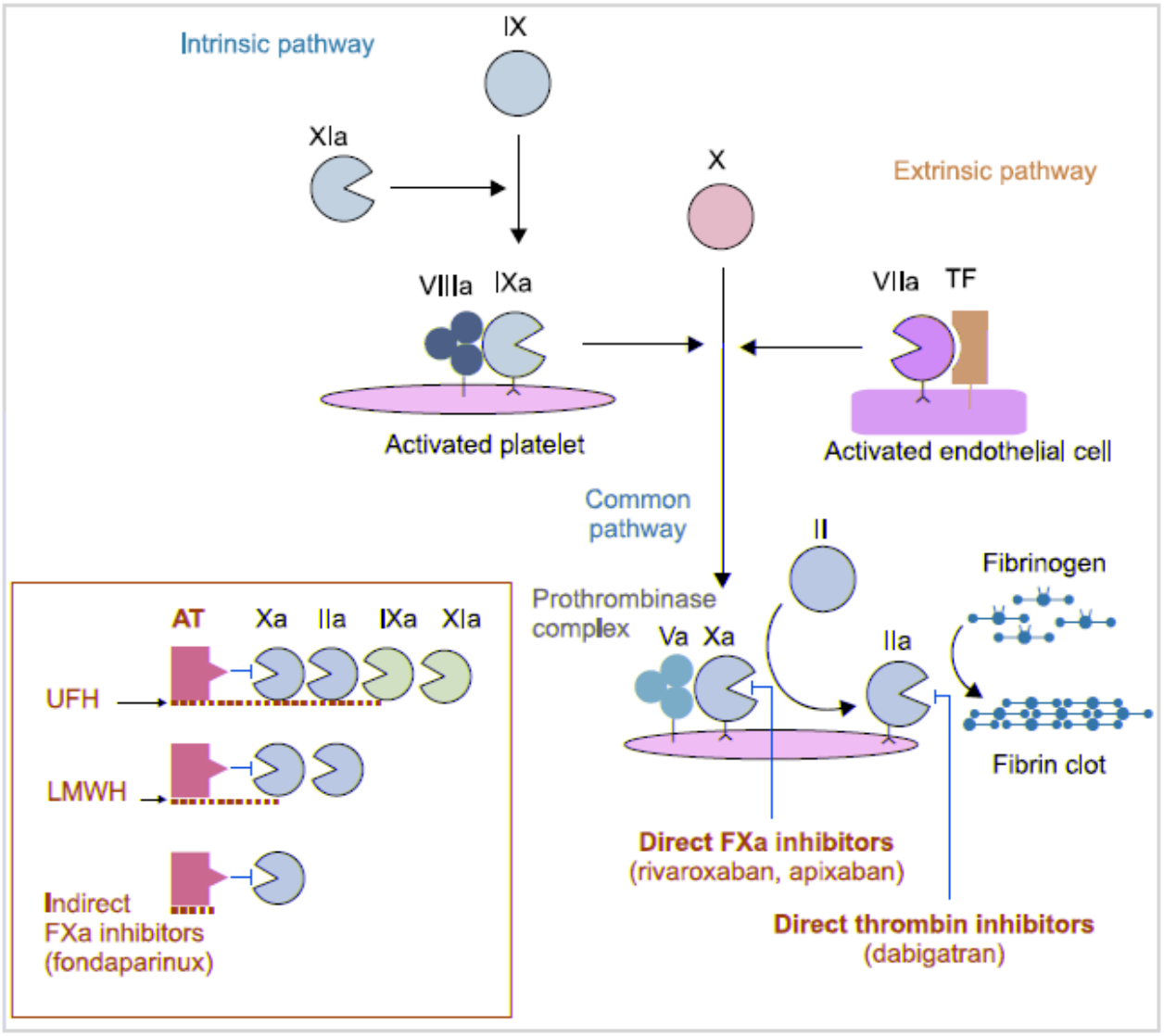
BIOLOGIC	CLINICAL
Lower avidity to bind nonspecifically to plasma proteins and cells	Once-daily sc injection
Dose-independent renal clearance	Weight-adjusted dosing with no laboratory monitoring
Lower incidence of heparin-dependent Ab	Rarely associated with heparin-induced thrombocytopenia
Reduced activation of osteoclasts	Low risk of osteoporosis with long-term use

UFH > LMWH

- High risk of bleeding
- Undergoing invasive procedure
- Renal failure

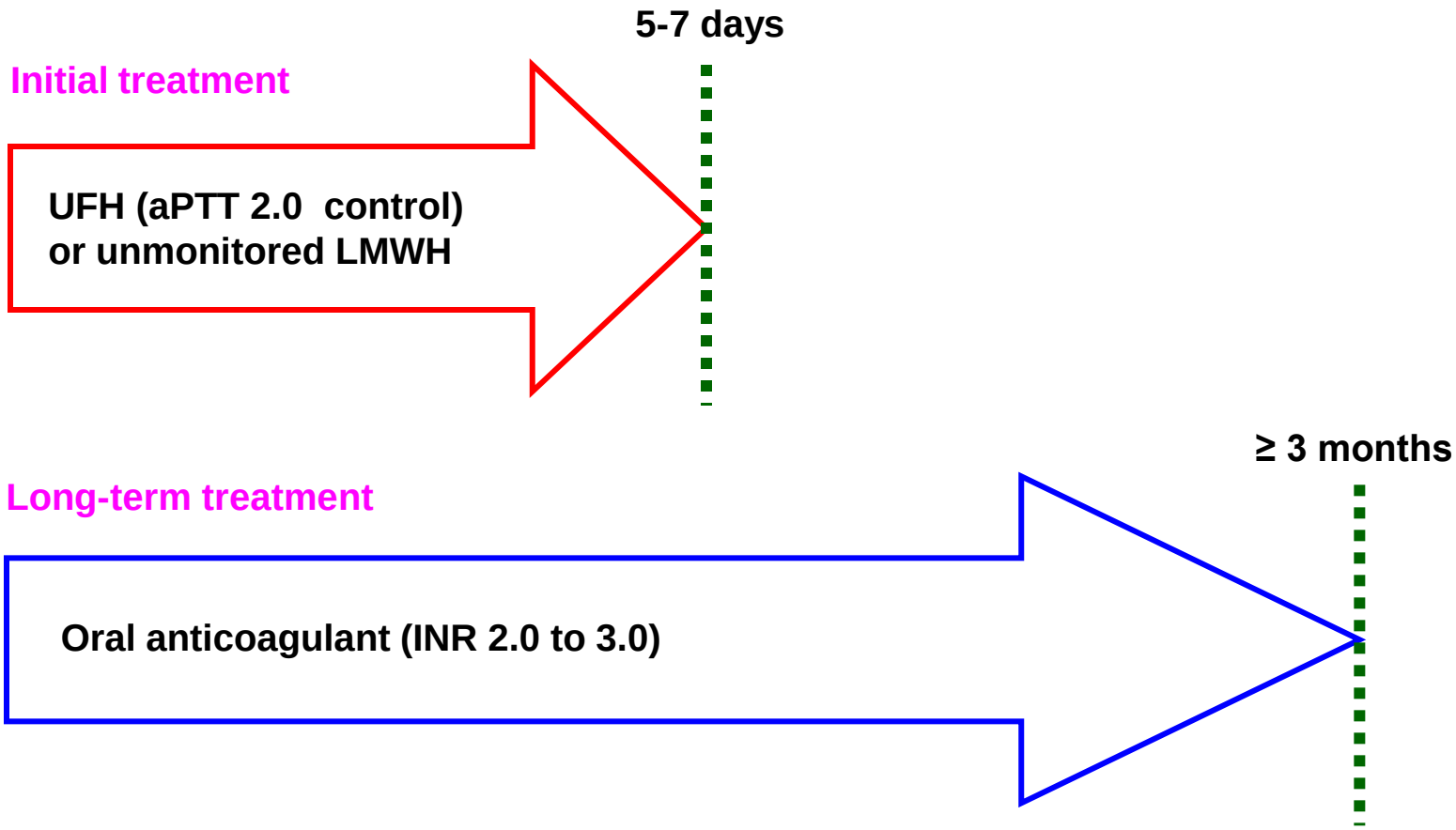
- Because of
  - Shorter half-life
  - Reversibility with protamine sulfate
  - Extra-renal metabolism

Antithrombotic agents in coagulation pathways



Ageno et al, KJH 2010;45:8

Tx of VTE

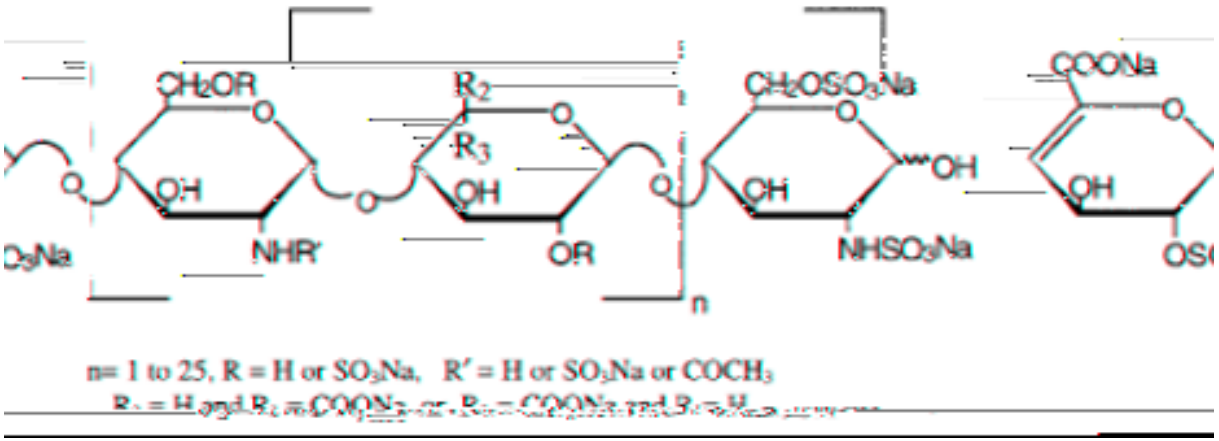


Factor II level/activity are most resistant to warfarin therapy
→ Favtor II activity must be reduced for anticoagulated with warfarin
Rapid reduction in protein C functional activity

Cancer pts

- To prevent recurrent VTE
  - Long-term LMWH > warfarin

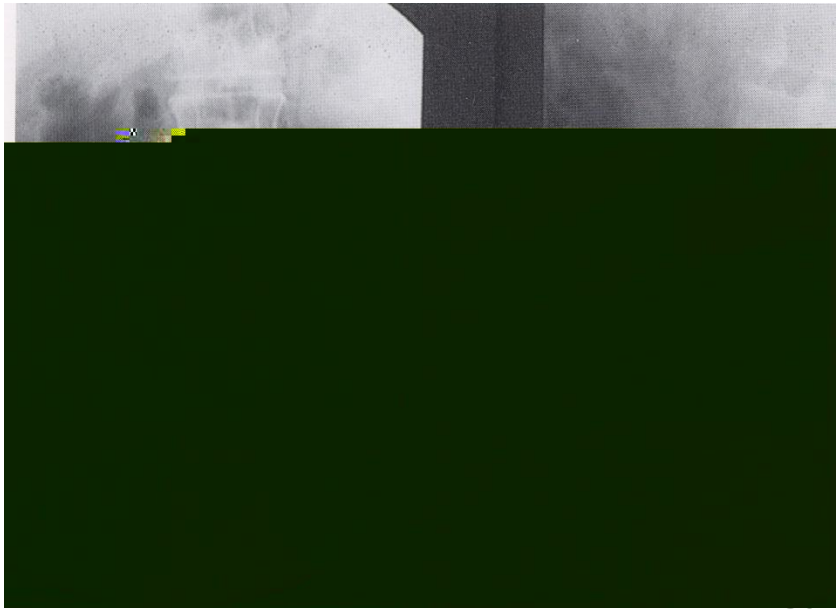
Innohep® (tinzaparin sodium)



- LMWH
- Inhibitor of factor Xa and IIa (thrombin)

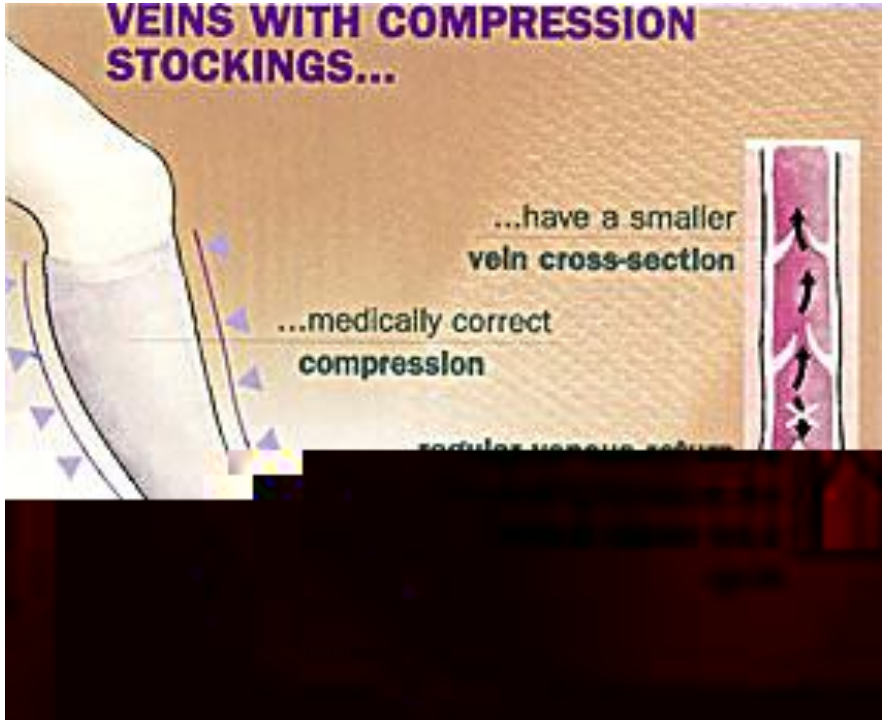
Indwelling filter in IVC

- Ix: prevent PE
  - Pts with DVT who are ineligible for anticoagulant therapy
  - Experience PE despite adequate anticoagulation



Graduated compression stocking

- Reduce risk of post-thrombotic synd



Prevention of VTE

- VTE risk-stratification and recommended prophylactic methods for each risk group

Risk	Patients or Surgery	Thromboprophylaxis
Low	Minor surgery in mobile patients, Medical patients who are fully mobile	Not necessary and Early ambulation
Moderate	General open gynecological surgery, General open urologic surgery,	GCS, IPC, LMWH, LDUH or Fondaparinux
High	THR, TKR, HFS, Major trauma, Spinal cord injury, Major surgery in patients with previous VTE or thrombophilia	LMWH, Warfarin or Fondaparinux; IPC*

Recommended for patients with a risk of bleeding; consider switching to anticoagulants when the bleeding risk abates.

VTE, venous thromboembolism; GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; THR, total hip replacement; TKR, total knee replacement; HFS, hip fracture surgery.

PE

Incidence

- 0.5-1/1000 person each year

Highly suspect of PE

- New dyspnea
- Tachycardia
- Resp distress
- Unexplained hypotension
- Atrial flutter or fibrillation
- Persisting atelectasis
- Reduced SaO2 on pulse oxymetry, reduced O2 tension on ABGA in absence of pul infiltrate or pneumothorax on chest radiography

Estimating pretest probability of PE

Feature	Score
Clinical Sg and Sx of DVT (minimum of leg swelling and pain /c palpation of deep v.	3
Alternative Dx less likely than PE	3
Heart rate above 100 beats/min	1.5
Immobilisation or surgery in previous 4 weeks	1.5
Previous DVT or PE	1.5
hemoptysis	1
Cancer	1

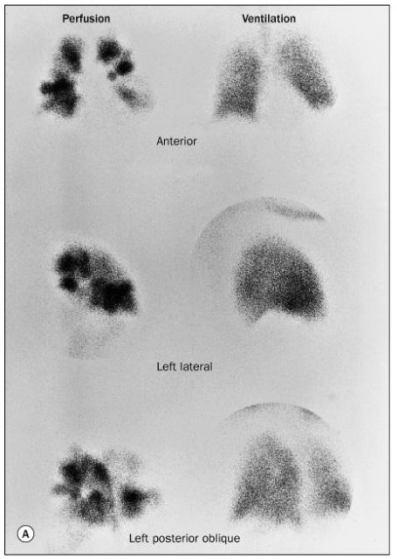
Low pretest probability if score is <2; moderate if 2-6 points; high if >6.

Geneva score

Geneva score (high risk: ≥9; moderate risk: 5–8; low risk: ≤4)	
Clinical variable	Score
Age (years)	
60–79	1
≥80	2
Previous PE or DVT	2
Recent surgery	3
Pulse rate >100 beats/min	1
$PaCO_2$ (kPa)	
<4.8	2
4.8–5.19	1
PaO_2 (kPa)	
<6.5	4
6.5–7.99	3
8–9.49	2
9.5–10.99	1
[illegible]	Chest X-ray
1	Platelike atelectasis
1	Elevation of hemidiaphragm

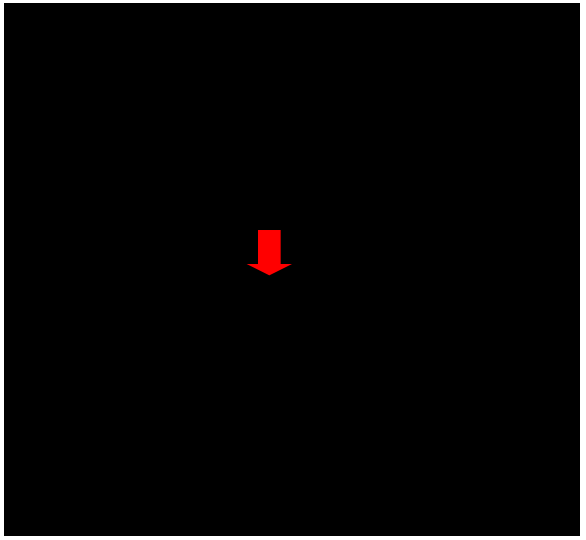
Dx of PE

- Ventilation-perfusion scan
  - High probability scan + clinically mod to highly suggestive of emboli



Hallett et al: Comprehensive Vascular and Endovascular Surgery © 2004 Elsevier Ltd.

  - Low or intermediate probability + clinical suspicion remain high

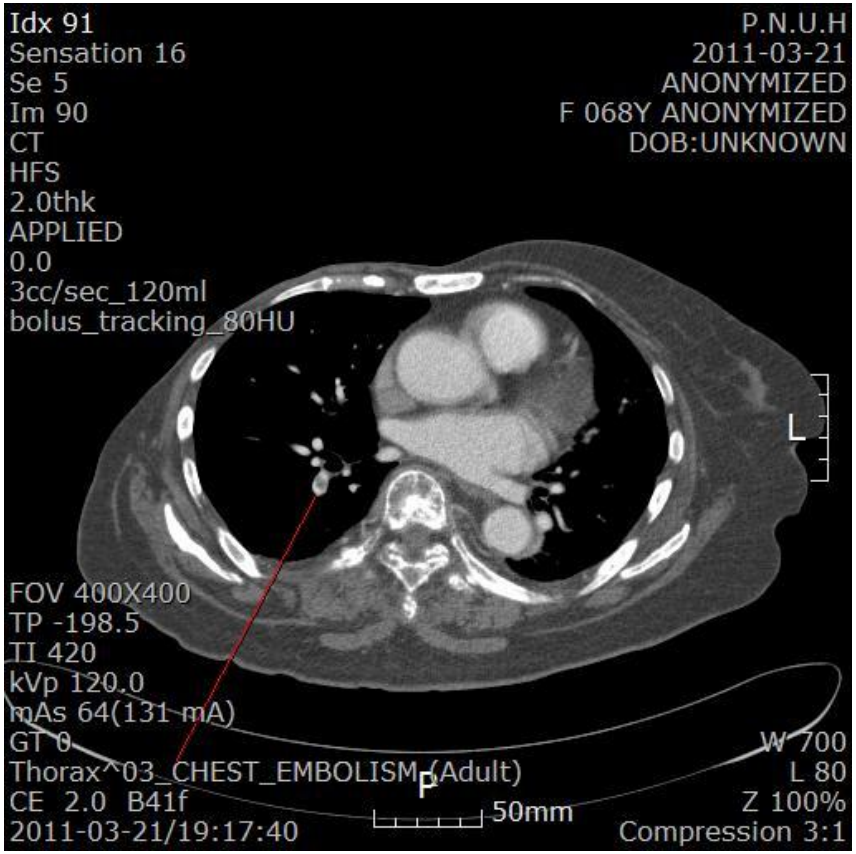


Dx of PE

- high-resolution CT angiography

- Positive test for evidence of DVT (at presumed site of clot leading to PE)

Case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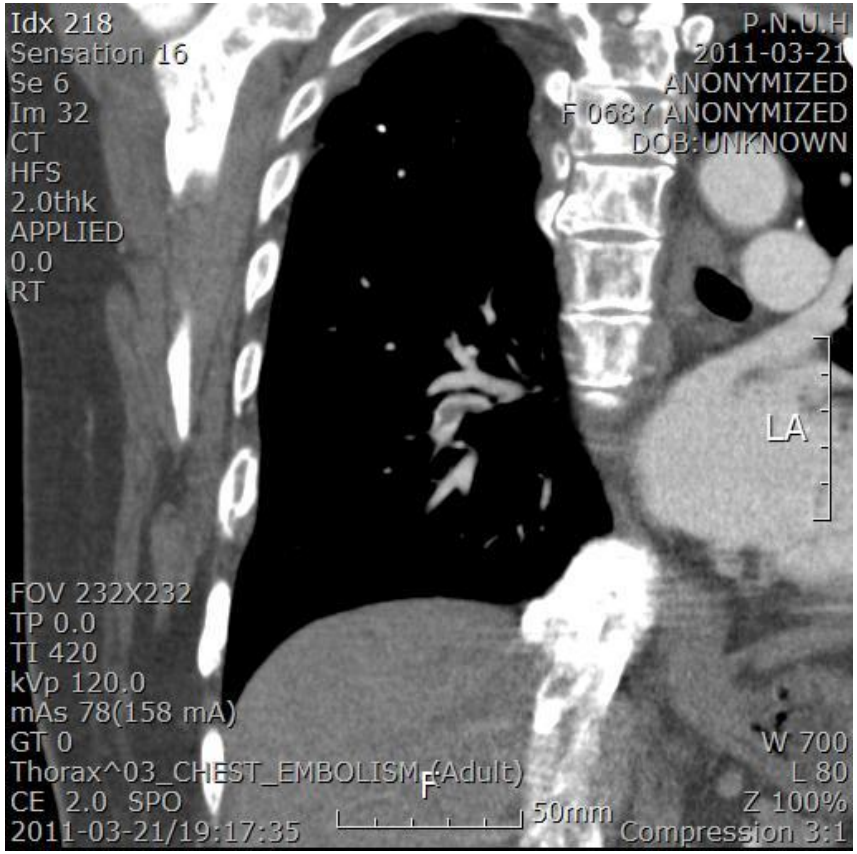
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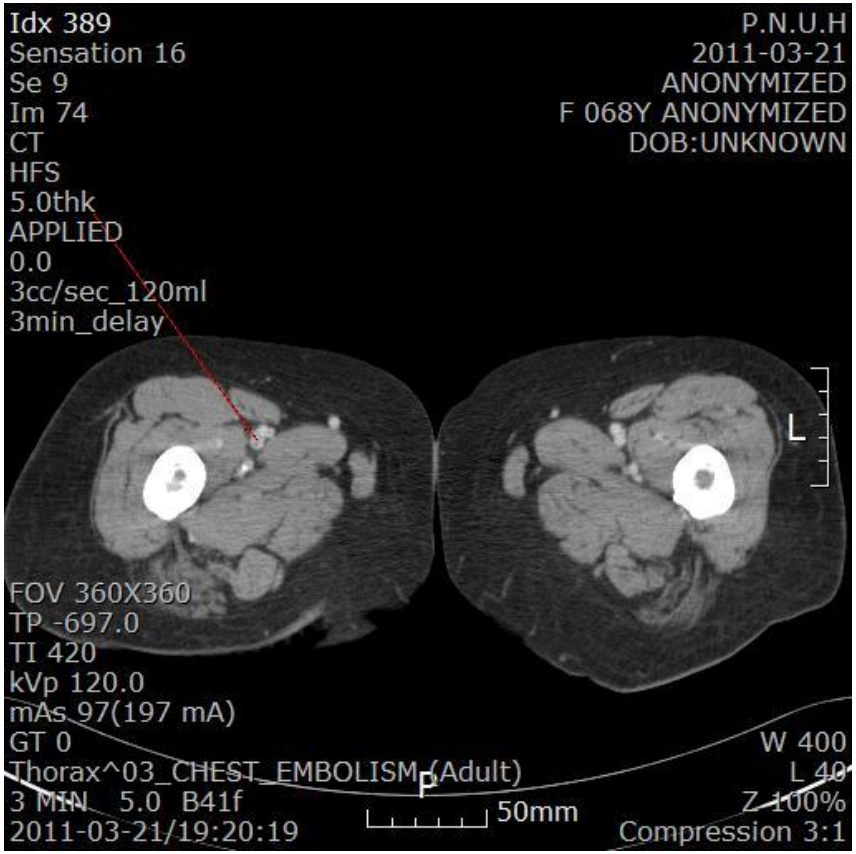
Compression 3:1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L
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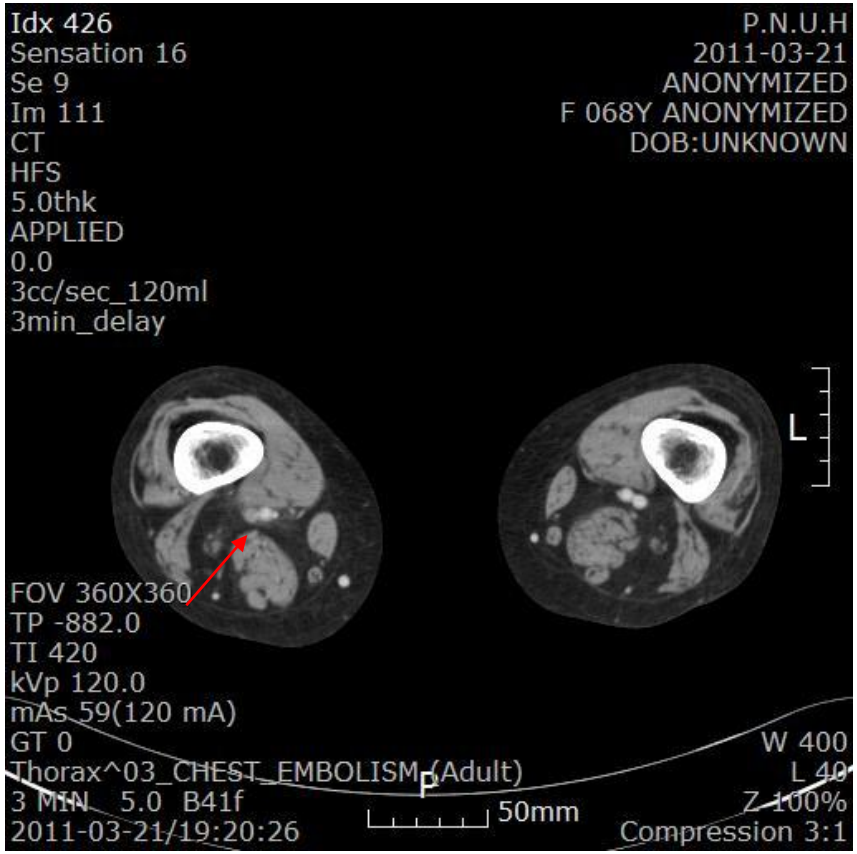
kVp 120.0
mAs 97(197 mA)
GT 0
Thorax^03_CHEST_EMBOLISM (Adult)
3 MIN 5.0 B41f
2011-03-21/19:20:19
P
50mm
W 400
L 40
Z 100%
Compression 3:1


Idx 426
Sensation 16
Se 9
Im 111
CT
HFS
5.0thk
APPLIED
0.0
3cc/sec_120ml
3min_delay
P.N.U.H
2011-03-21
ANONYMIZED
F 068Y ANONYMIZED
DOB:UNKNOWN
L
FOV 360X360
TP -882.0
TI 420
kVp 120.0
mAs 59(120 mA)
GT 0
Thorax^03_CHEST_EMBOLISM (Adult)
3 MIN 5.0 B41f
2011-03-21/19:20:26
P
50mm
W 400
L 40
Z 100%
Compression 3:1

Px

- 10% of symptomatic PE die within 1hr of onset of Sx
- Mortality rate: 10% at 2 weeks, 25% at 1yr

Tx

- ACP/AAFP guideline
  - Initial PE Tx → LMWH or UFH
  - Initial DVT + PE Tx → LMWH, UFH or fondaparinux

European society of cardiology guideline

- High-risk PE
  : UFH
- High-risk PE + cardiogenic shock +/- persistent HoT
  : Thrombolytic therapy
- Non-high-risk PE
  : LMWH or fondaparinux

➢ Continue for at least 5 days → switch to VKA

Embolectomy

- Ix of percut transcatheter or surgical embolectomy
  - Hemodynamically unstable or shocked
  - Have CIx or do not respond to thrombolysis

Thanks for your attention