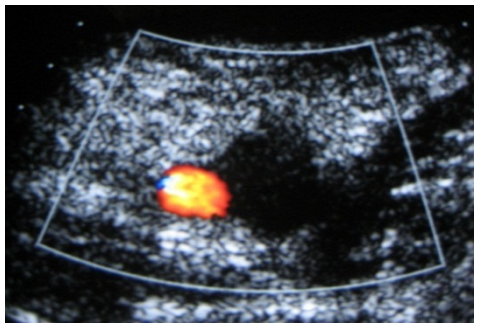
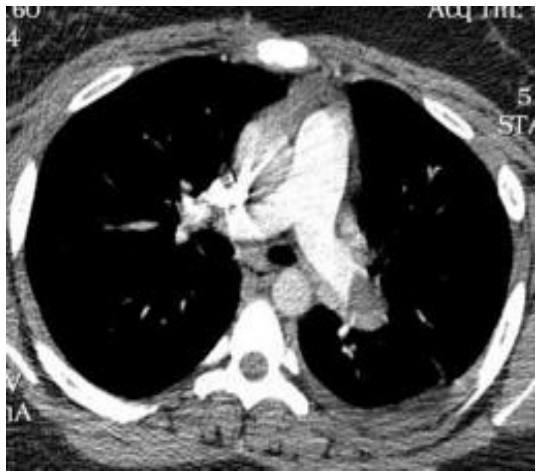
Case 7:

49 yr old lady complains of painful swelling and hotness of her L leg following coming back from visiting her relatives in USA. She had repeated attacks of cough with hemoptysis and shortness of breath. P/E

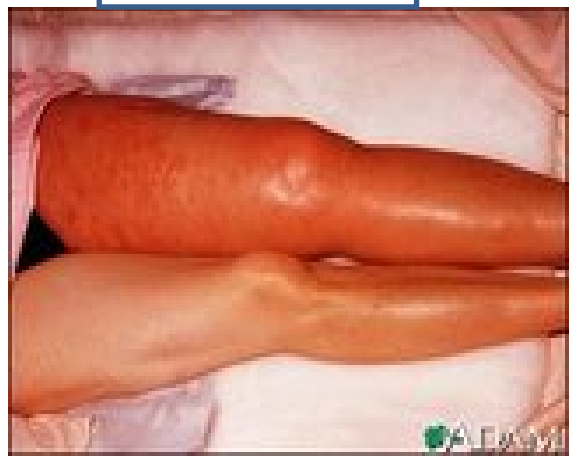
Duplex Us: DVT common femoral vein with

PE

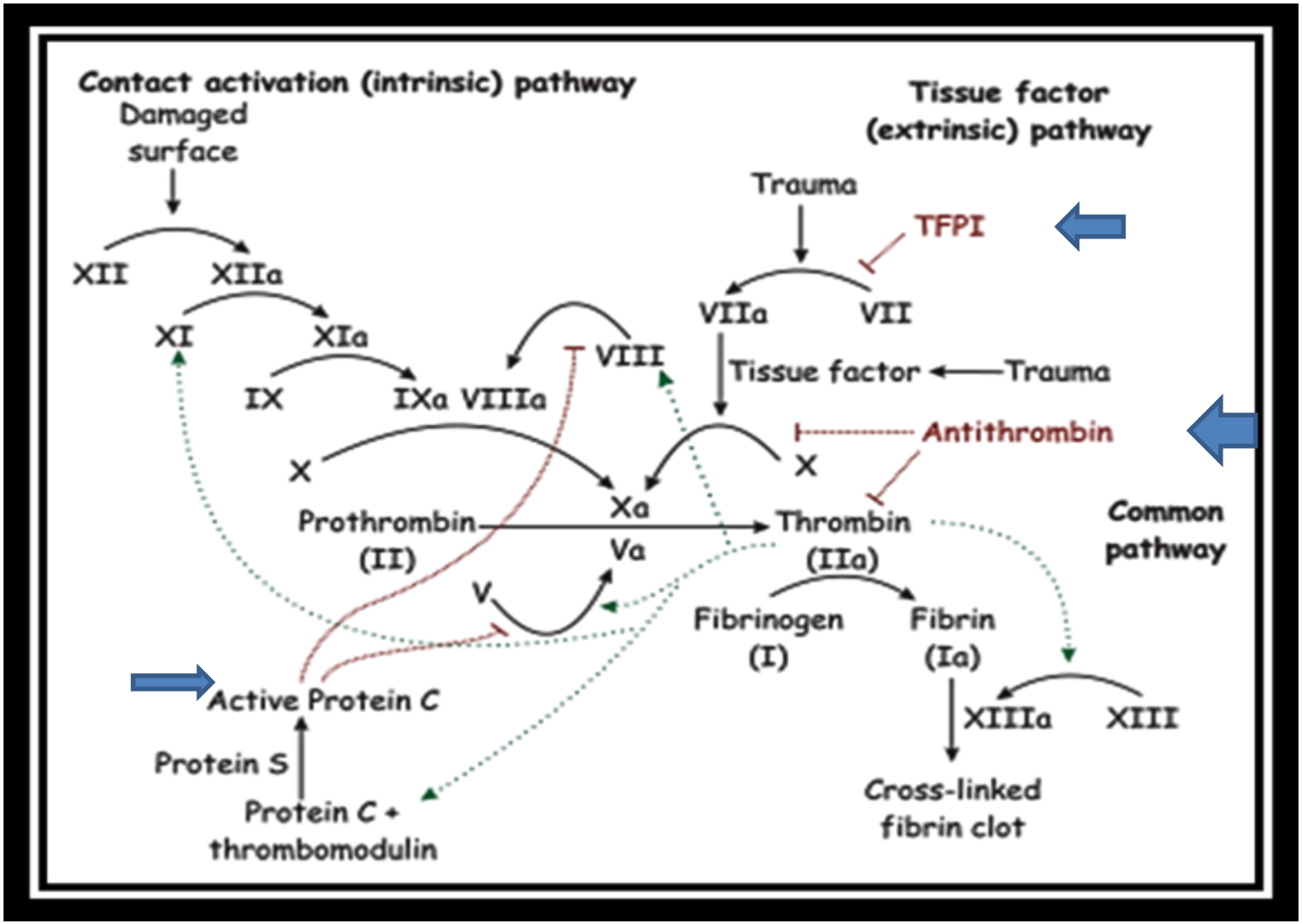




DVT



Case 10 investigation & Diagnosis



Importance of VTE (DVT/PE)

A- PREVENTABLE

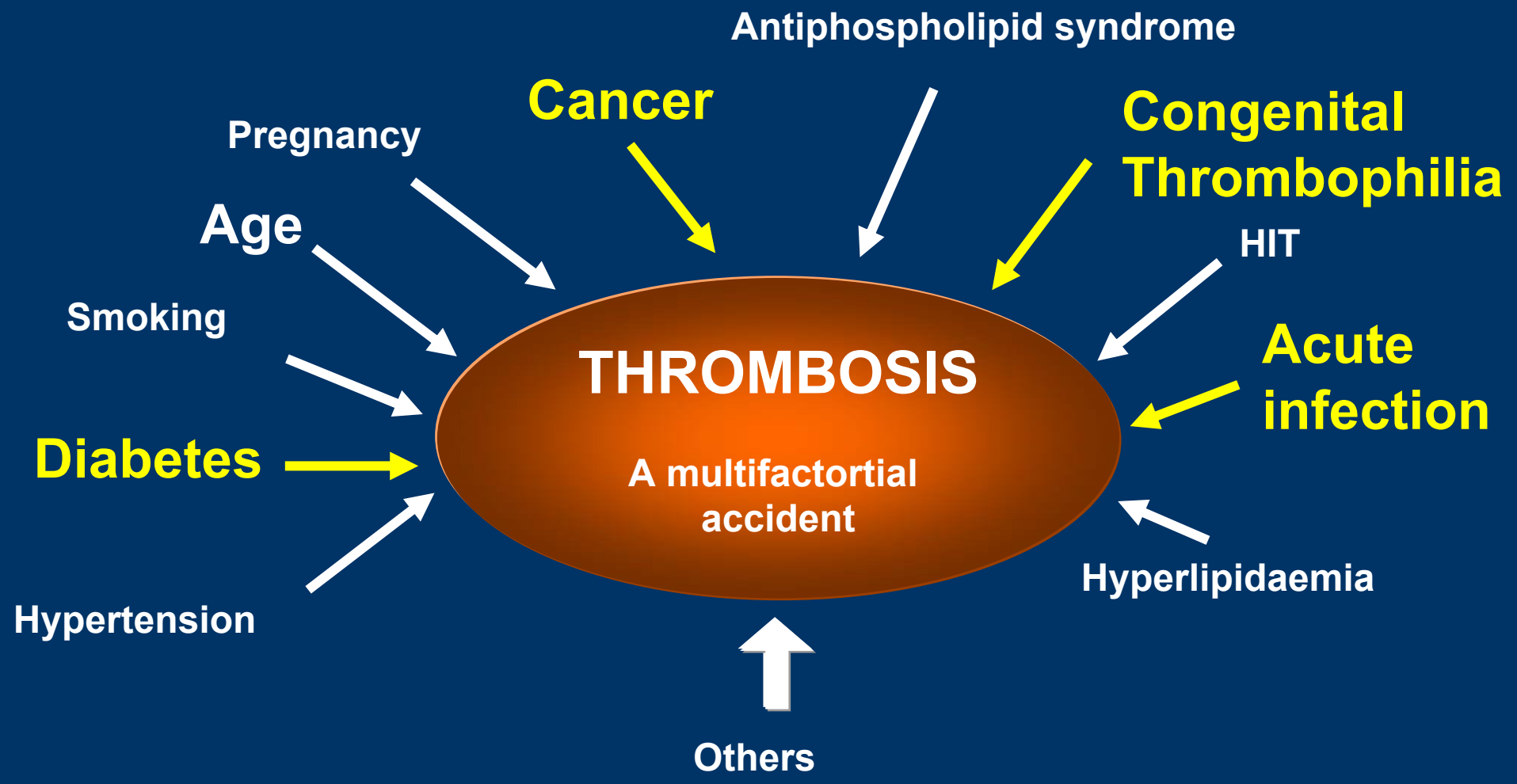
B- LIFE THREATENING

C- LONG TERM COMPLICATIONS

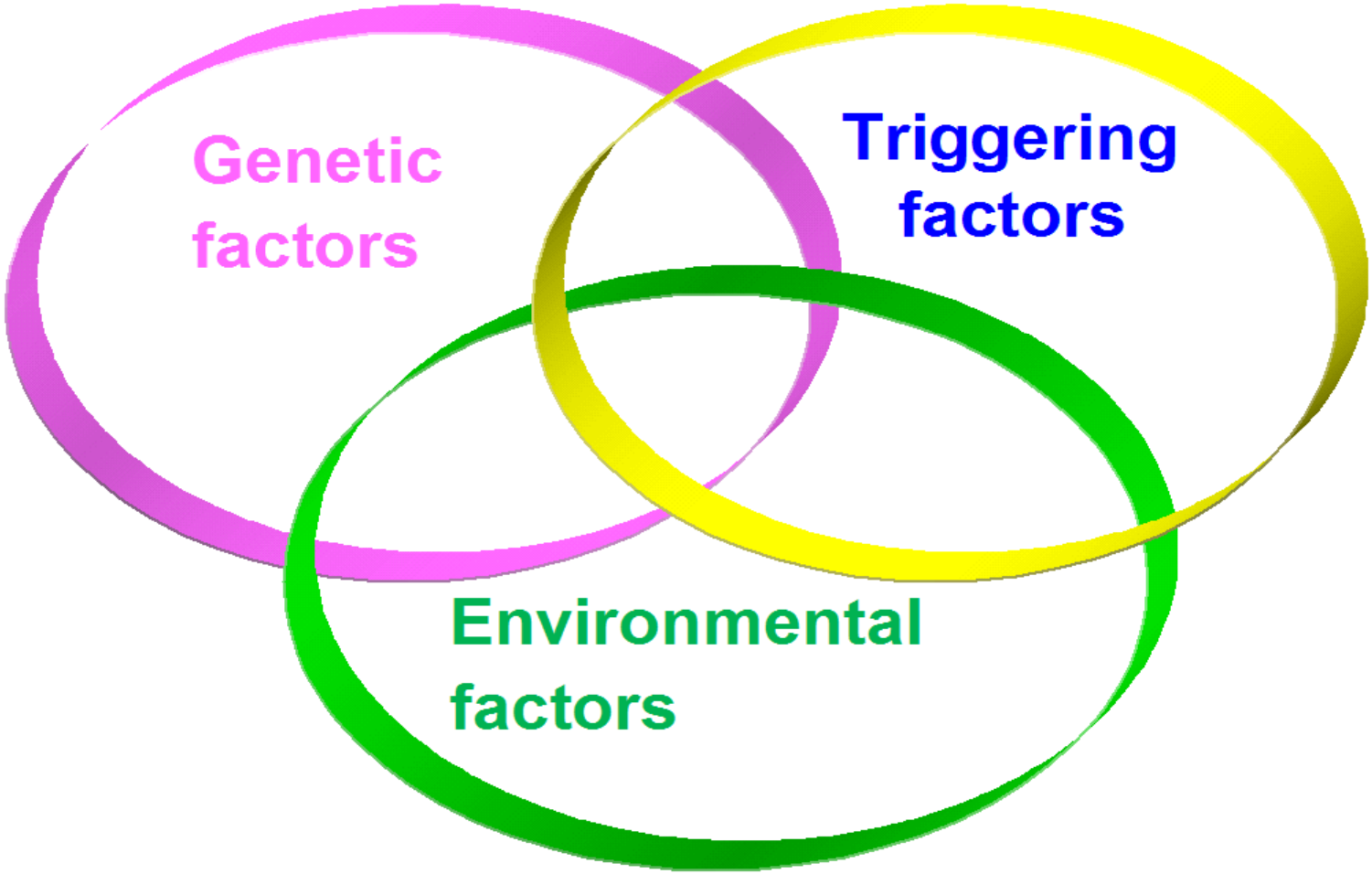
D- COMMON

E- COSTLY

VTE is a multifactorial and often silent disease



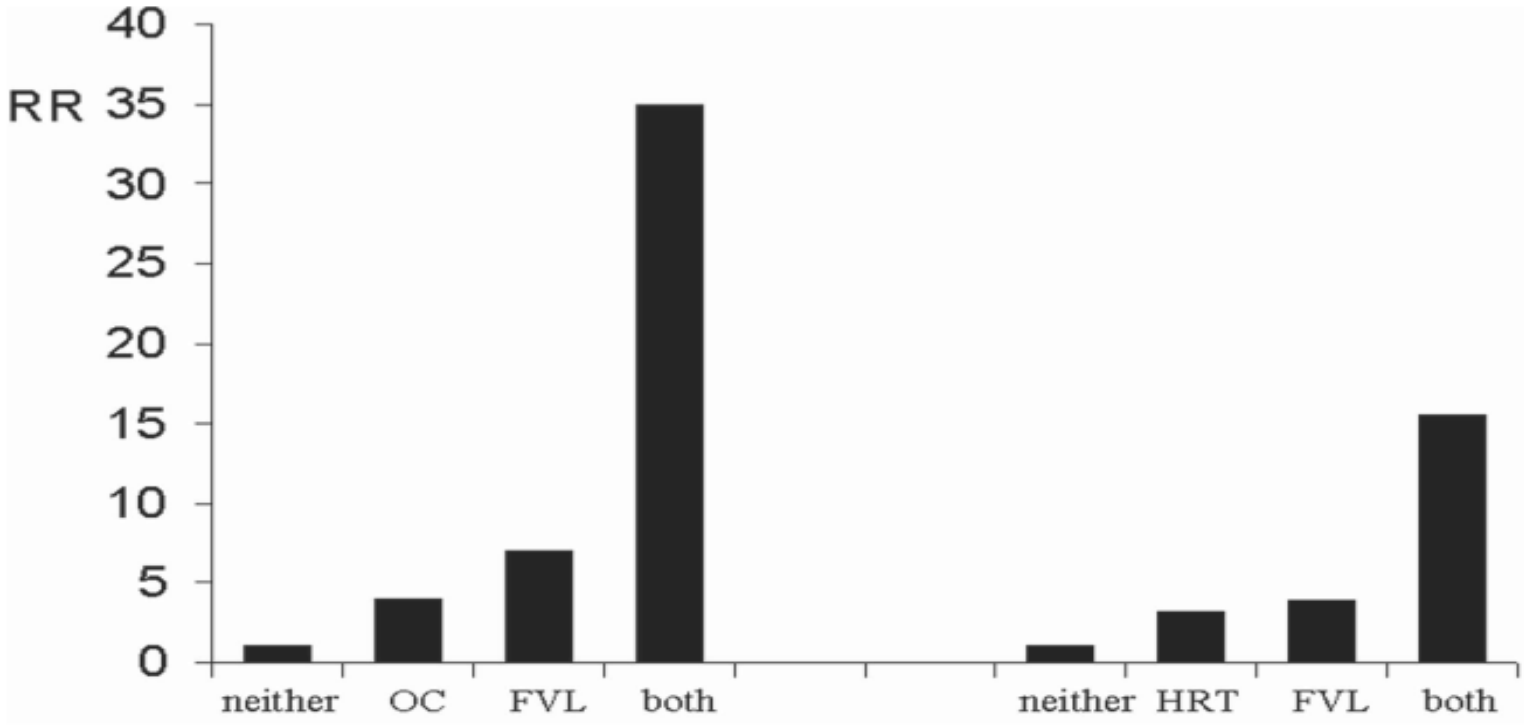
Venous thrombo-embolism is a multifactorial disease



Important Genetic Factors

1- Protein C defeiciency
2- Protein S deficiency
3- ATIII deficiency
4- Factor V Leiden mutation
5- Prothrombin (factor II) mutation

Combined risk factors (inherited + acquired) are key to high risk for VTE



Absolute risk 1 per 16,000/yr healthy premenopausal women

Figure 1. Interaction of factor V Leiden and oral contraceptive use (left panel),[89] and factor V Leiden and hormonal replacement therapy (right panel).[90]

Risk Factors for VTE

Stasis

- Age > 40
- Immobility
- CHF
- Stroke
- Paralysis
- Spinal Cord injury
- Hyperviscosity
- Polycythemia
- Severe COPD
- Anesthesia
- Obesity
- Varicose Veins

Hypercoagulability

- Cancer
- High estrogen states
- Inflammatory Bowel
- Nephrotic Syndrome
- Sepsis
- Smoking
- Pregnancy
- Thrombophilia

Endothelial Damage

- Surgery
- Prior VTE
- Central lines
- Trauma

Anderson FA Jr. & Wheeler HB. *Clin Chest Med* 1995;16:235.

Risk Factors for VTE

Stasis

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- Paralysis
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Hypercoagu

- Cancer
- High
- I
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- egnancy
- Thrombophilia

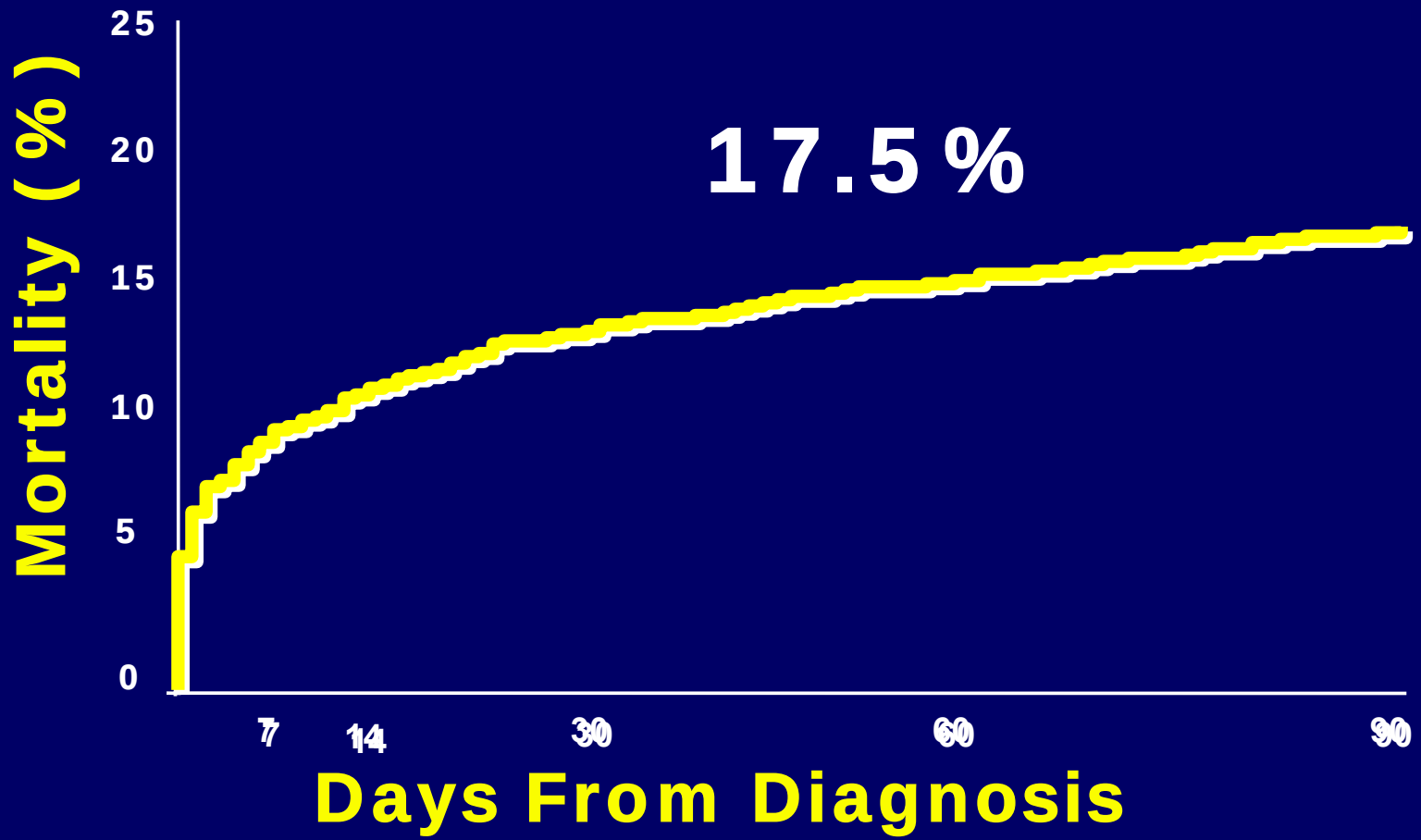
othelial Damage

- Surgery
- Prior VTE
- Central lines
- Trauma

Most hospitalized patients have at least one risk factor for VTE

Anderson FA Jr. & Wheeler HB. *Clin Chest Med* 1995;16:235.
Bick RL & Kaplan H. *Med Clin North Am* 1998;82:409.

ICOPER: Cumulative Mortality after Diagnosis



Lancet. 1999;353:1386-1389.

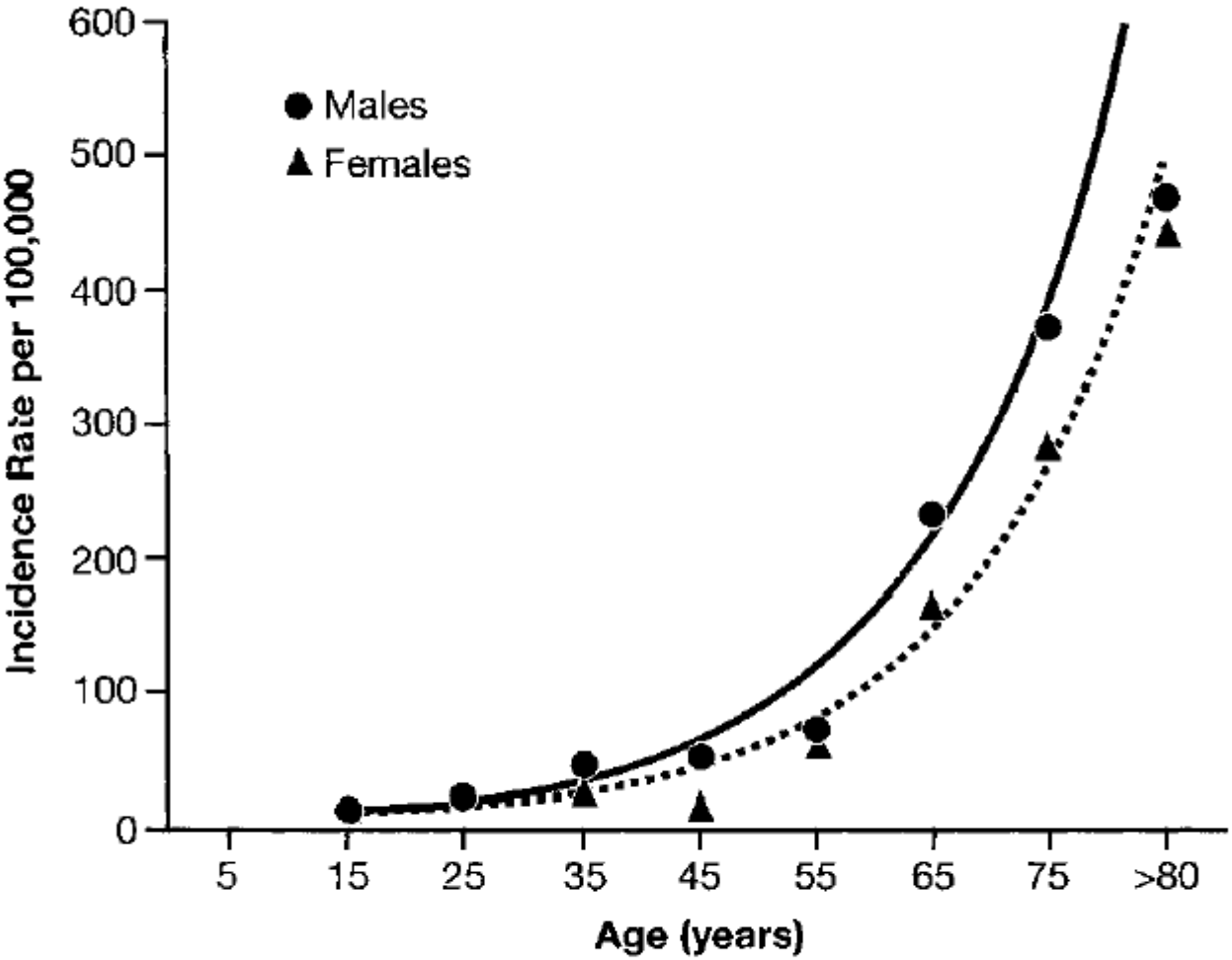
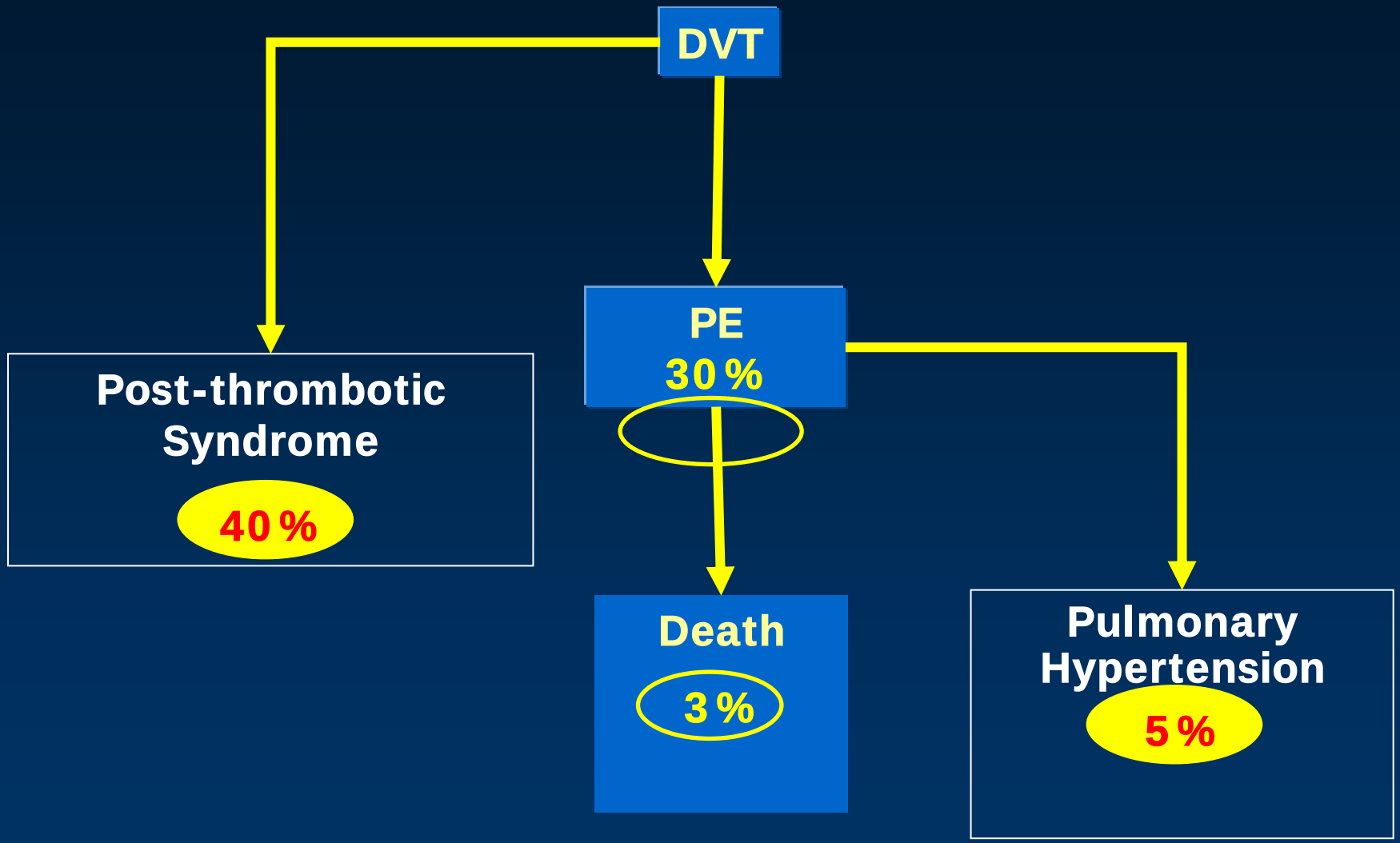


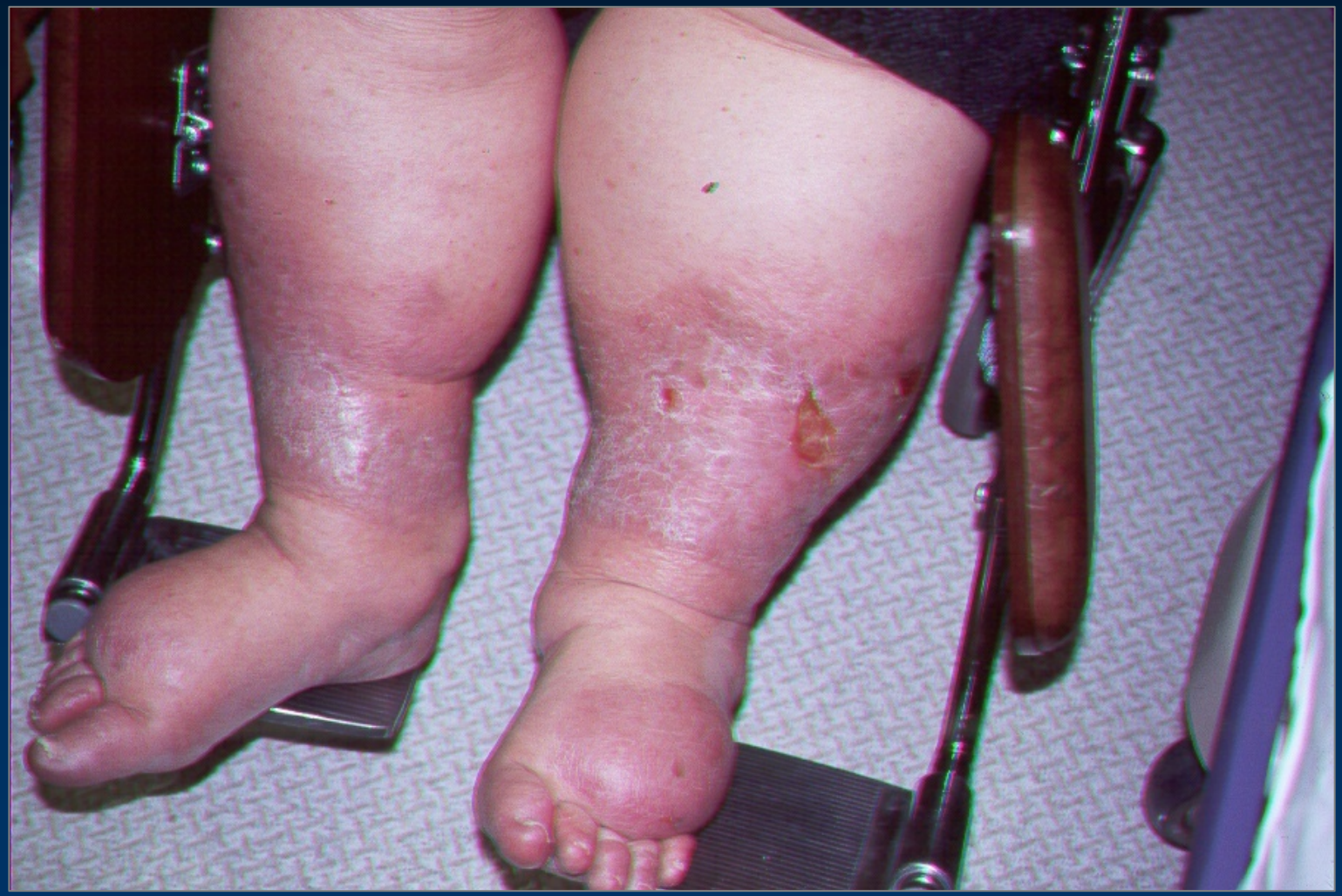
Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. *Arch Intern Med*. 1991;151:933–938.)

The Burden of Venous Thrombo Embolism

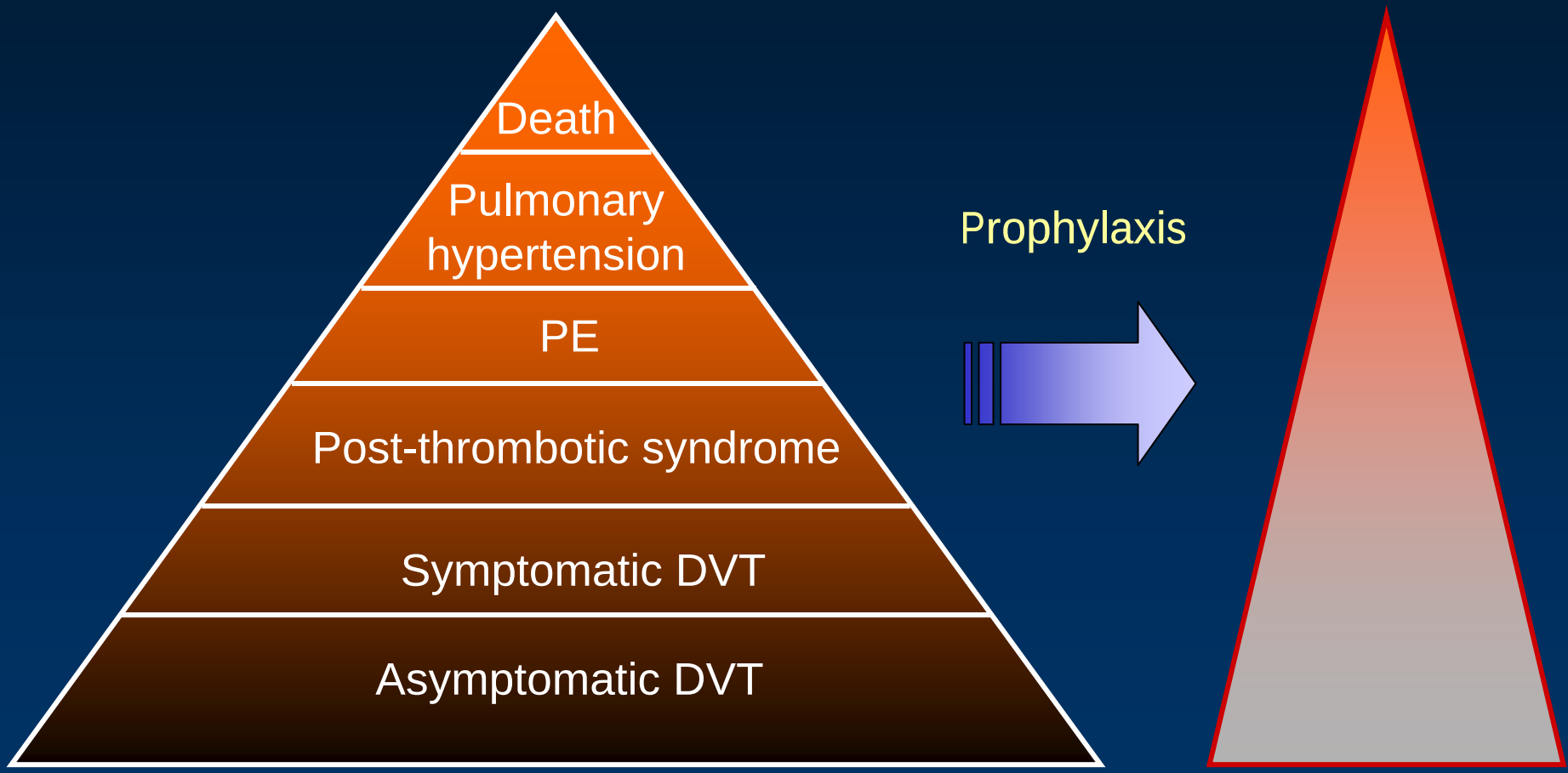


[1]Brandjes DP et al. Lancet 1997;349:759-62
[2]Kahn SR et al. Arch Intern Med. 2004 Jan 12;164(1):17-26.
[3]Hirsh J & Hoak J. Circulation 1996;93:2212-45
[4]Peng et al. NEJM 2004;350:2257-64

Post DVT Syndrome/ V.Stasis



Thromboprophylaxis reduces the burden of VTE



Hirsh J, Hoak J. Circulation. 1996;93:2212-45.

Risk Assessment for VTE

Identifying at-risk patient

Counselling at-risk patient

Prescribing thromboprophylaxis

Jordan University Hospital

Venous Thromboembolism Risk Factor Assessment

Patient's Name:_____ Age: ____ Sex: ____ Wgt:____Kg.

Choose All That Apply

Hospital No. _____

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI >30)
- ❑ Acute myocardial infarction (< I month)
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Leg plaster cast or brace
- ❑ Other risk factors_____

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ Major surgery lasting 2-3 hours
- ❑ BMI > 50 (venous stasis syndrome)
- ❑ History of SVT, DVT/PE
- ❑ **Family history of DVT/PE**
- ❑ Present cancer or chemotherapy
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive Lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other thrombophilia Type_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Major surgery (> 60 minutes)
- ❑ Arthroscopic surgery (> 60 minutes)
- ❑ Laparoscopic surgery (> 60 minutes)
- ❑ Previous malignancy
- ❑ Central venous access
- ❑ Morbid obesity (BMI >40)

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)
- ❑ Major surgery lasting over 3 hours

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion ($\geq$ 3), premature birth with toxemia or growth - restricted infant

Total Risk Factor Score ☐

VTE Risk and Suggested Prophylaxis

Total Risk Factor Score	Incidence of DVT	Risk Level	Prophylaxis Regimen**
0-1	<10%	Low Risk	No specific measures; early ambulation.
2	10-20%	Moderate Risk	LWMH, UFH (5000U BID), ES, or IPC.
3-4	20-40%	High Risk	LMWH, UFH (5000U TID), or IPC.
5 or more	40-80% - 1-5% mortality	Highest Risk	Pharmacological: LMWH*, UFH, Warfarin*, or in combination with ES or IPC.

Legend

ES- Elastic Stockings
IPC- Intermittent Pneumatic Compression
UFH- Unfractionated Heparin
LMWH- Low Molecular Weight Heparin

* Use for major orthopedic surgery
** For the appropriate prophylaxis is in a particular patient, check with your consultant concerning best method and dose.

Choice of VTE prophylaxis: _____ Duration: _____ Days: _____

Signature_____Date_____

Based on: Geerts WH et al: Prevention of Venous Thromboembolism. Chest 2004;126(suppl 3):338S-400S; Nicolaides AN et al: 2001 International Consensus Statement: Prevention of Venous Thromboembolism, Guidelines According to Scientific Evidence.; Arcelus JI, Caprini JA, Traverso CI. International perspective on venous thromboembolism prophylaxis in surgery. Semin Thromb Hemost 1991; 17(4):322-5.; Borow M, Goldson HJ. Postoperative venous thrombosis. Evaluation of five methods of treatment. Am J Surg 1981;141(2):245-51.; Caprini JA, Arcelus I, Traverso CI, et al . Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991;17(suppl 3):304-12.; Caprini JA, Arcelus JI et al: State-of-the-Art Venous Thromboembolism Prophylaxis. Scope 2001; 8: 228-240.; Caprini JA, Arcelus JI, Reyna JJ. Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease.*Seminars in Hematology*, April 2001;38(2)Suppl 5:12-19.; Caprini, JA. Thrombosis risk assessment as a guide to quality patient care, Dis Mon 2005;51:70-78.; Oger E: Incidence of Venous Thromboembol ism: A Community-based Study in Western France. Thromb Haemost 2000; 657-660.; Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs. Enoxaparin for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery: A Meta-analysis of 4 Randomized Double-Blind Studies. Arch Intern Med 2002; 162(16):1833--40.; Ringley et al: Evalution of intermittent pneumatic compression boots in congestive heart failure. American Surgeon 2002; 68(3): 286-9.; Morris et al. Effects of supine intermittent compression on arterial inflow to the lower limb. Archives of Surgery 2002. 137(11):1269-73.; Sugarman HJ et al, Ann Surg: 234 (1) 41-46, 2001

Venous thromboembolism

MAIN OBJECTIVES OF TREATMENT

- Reduction of fatality
- Prevention of recurrence
- Prevention of late sequelae

PULMONARY EMBOLISM and DVT TREATMENT

INITIAL

Thrombolytic treatment

Heparin (UFH or LMWH)

Oral anticoagulant therapy (OAT) and new antithrombotics

LONG -TERM

OAT and new antithrombotics
LMWH

HOME

OAT and new antithrombotics

LMWH

TREATMENT OF VTE

***HEPARIN(UFH)??:80u/kg loading>18u/kg/hr**
PTT 1.5-2.5

OR

***HEPARIN(LMW):**

1mg/kgx2 enoxaparin

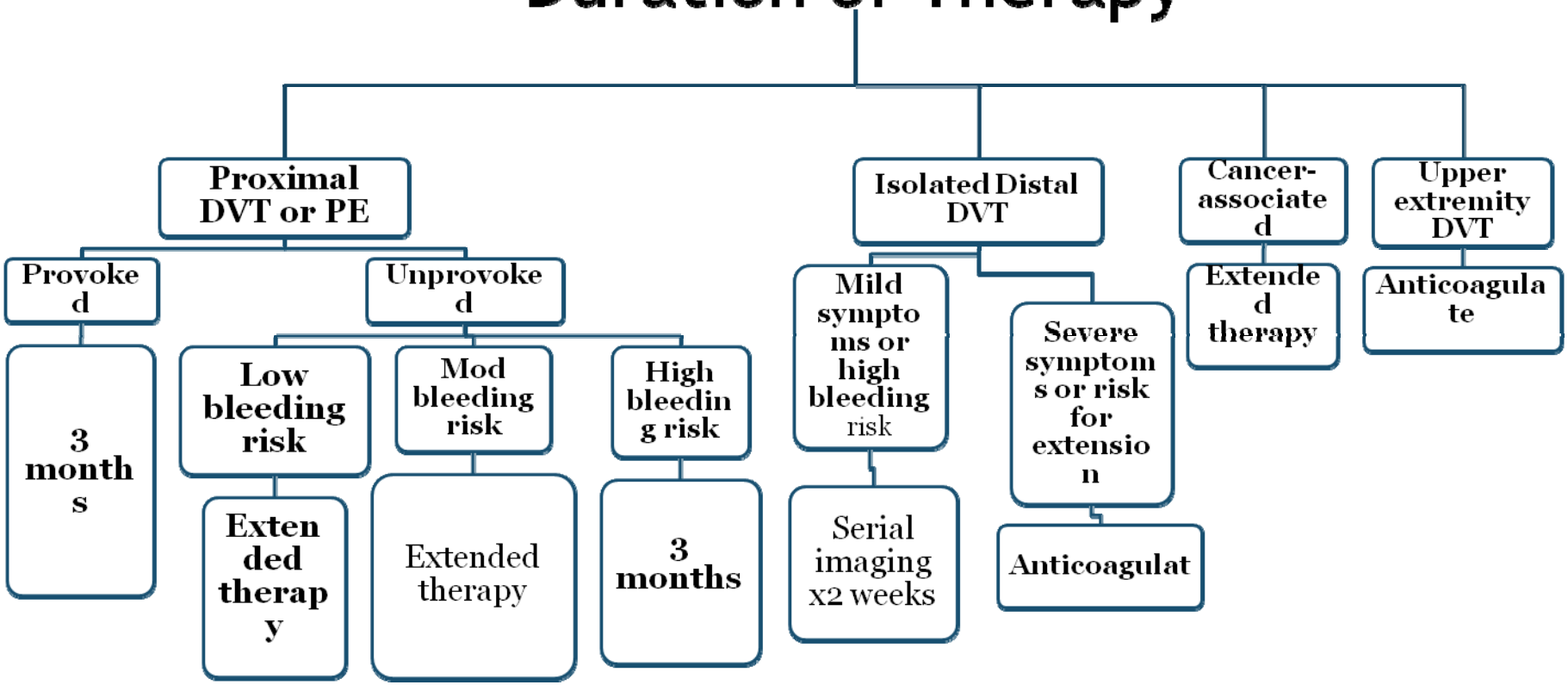
175u/kgx1 tinzaparin

***WARFARIN: start with 5mgx1 keep INR 2-3**

OVERLAP HEPARIN+WARFARIN

*** OR NEW ORAL ANTICOAGULANTS**

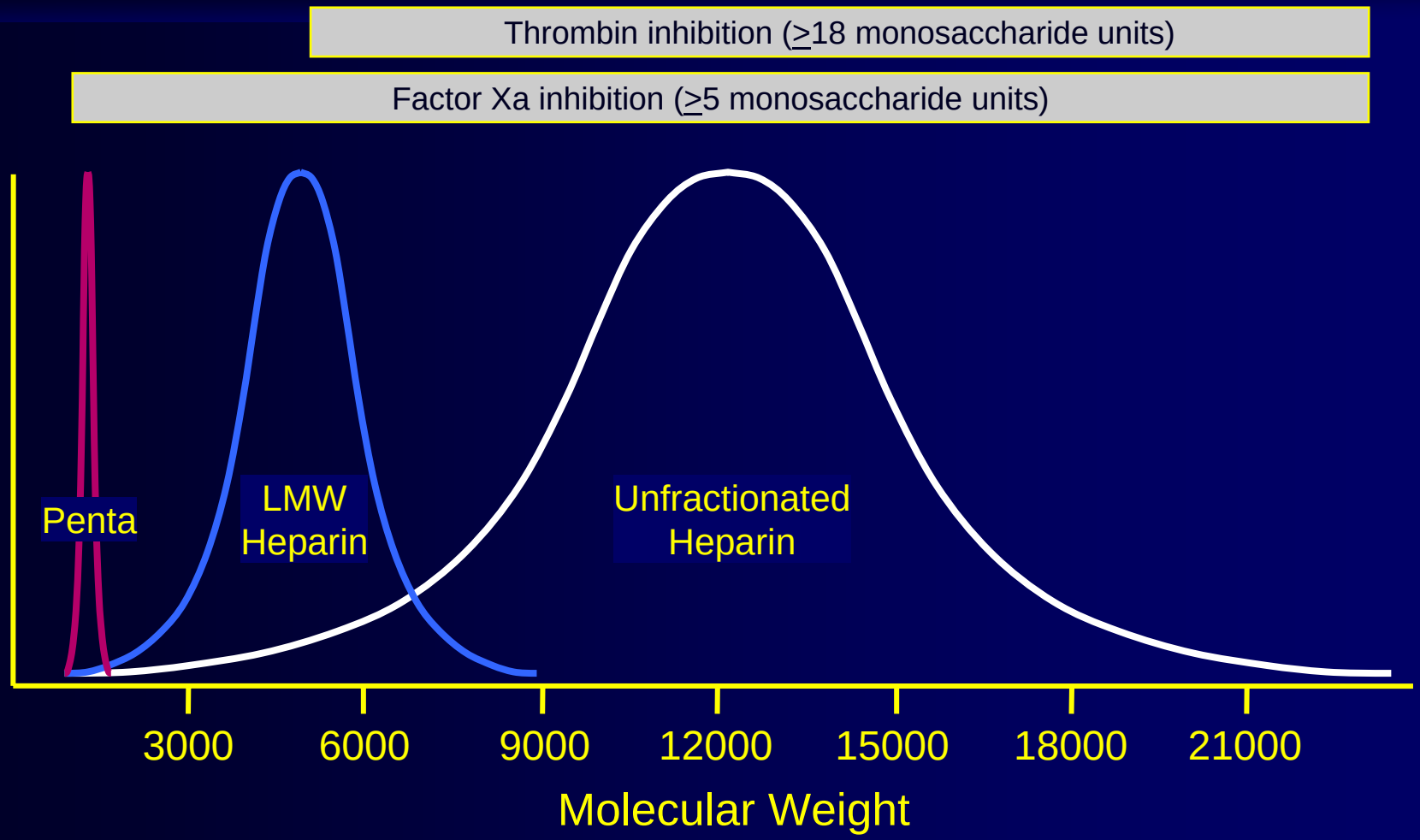
Duration of Therapy



VTE:OTHER TREATMENT MODALITIES

* THROMBOLYTIC THERAPY
* V.Thrombectomy
* IVC Filters
* Pulmonary embolectomy
* Post DVT syndrome

Heparin Preparations Used Clinically



Warfarin

Pharmacokinetics

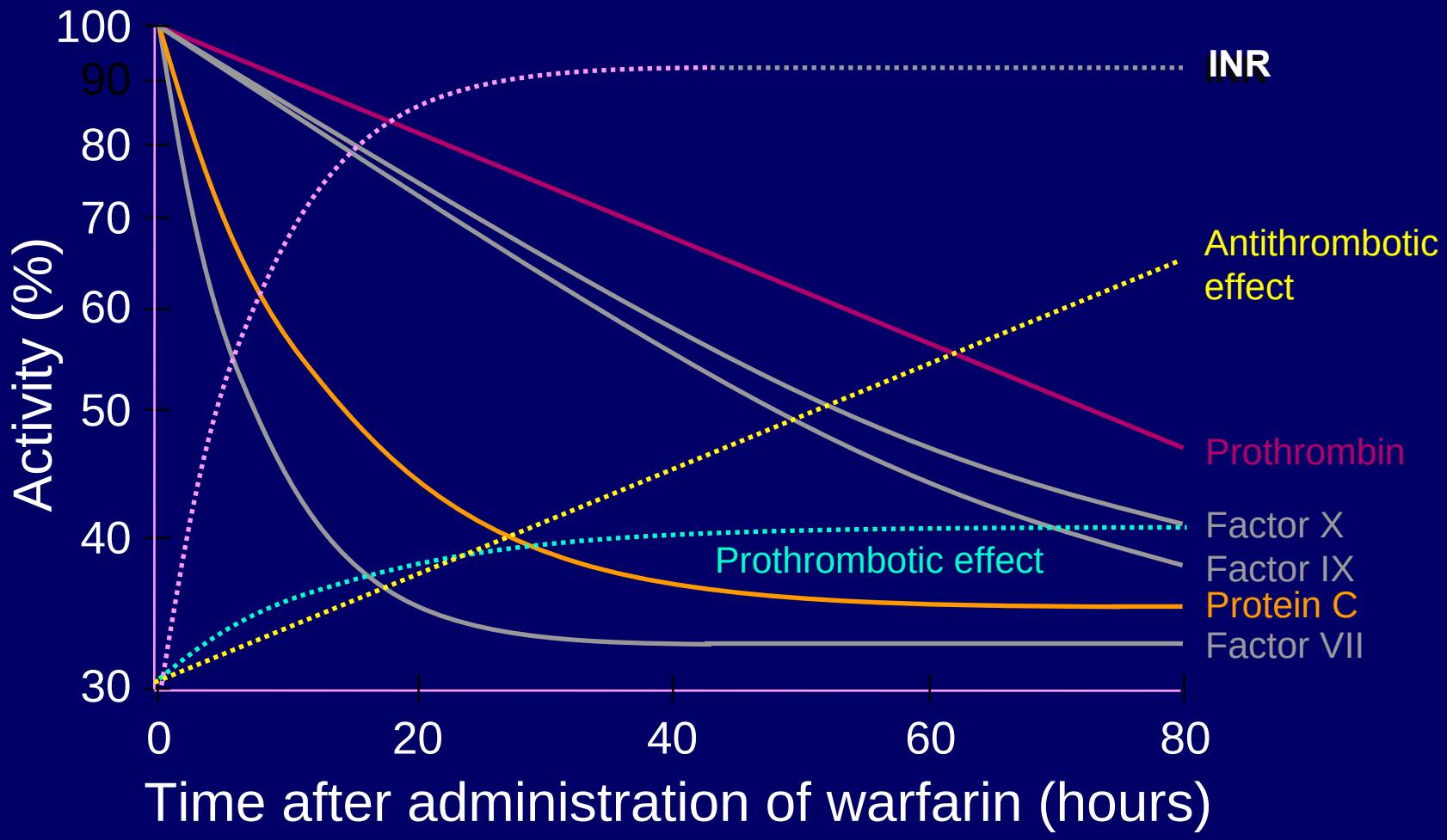
Plasma concentration peaks 2-8 h after an oral dose
99% bound to plasma proteins (albumin)
Half-life in plasma ~25-60 h

Inhibits biosynthesis of vitamin K-dependent zymogens (delayed onset of action)

Prothrombin(II)
Factor VII
Factor IX
Factor X
} procoagulant

Protein C
Protein S
} anticoagulant

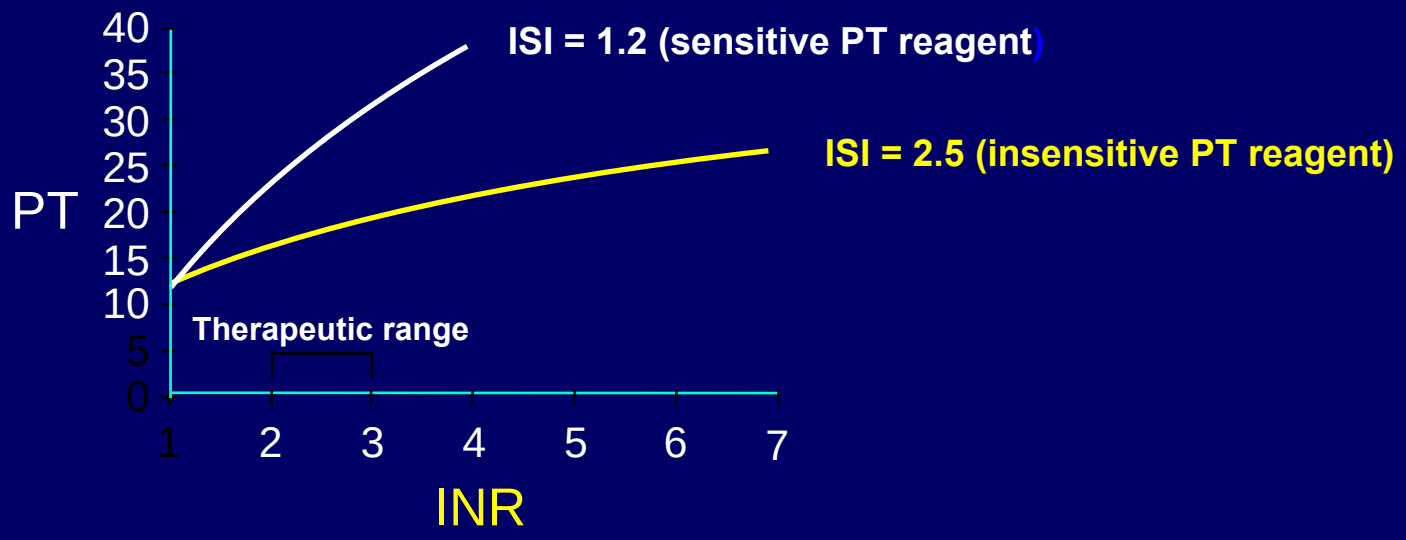
Clearance of Vitamin K-dependent Proteins



International Normalized Ratio (INR)

$$INR = \left(\frac{\text{Patient PT}}{\text{Control PT}} \right)^{C}$$

C = International Sensitivity Index



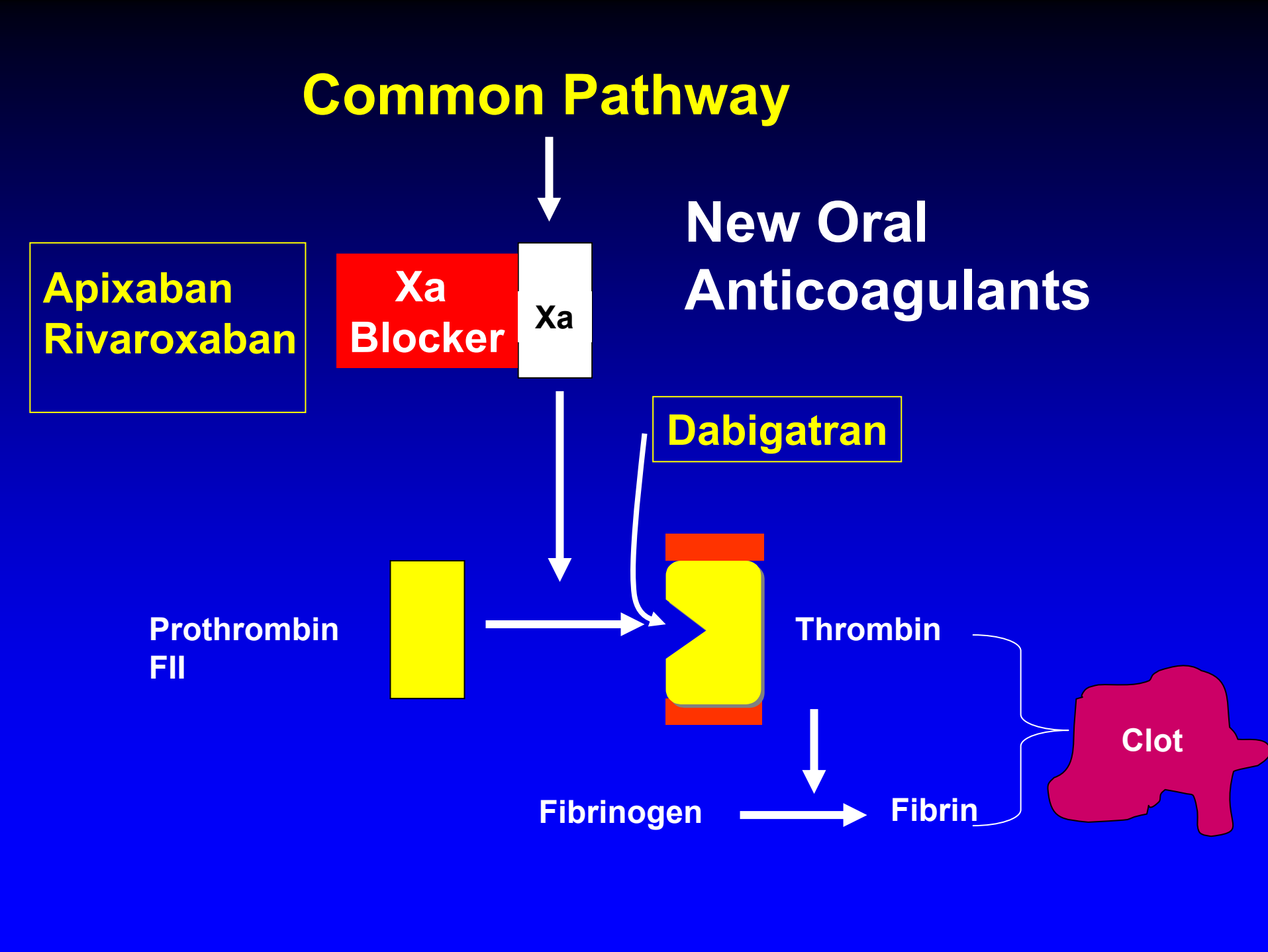
Complications of Warfarin Therapy

Bleeding

Birth defects and abortion

Contraindicated during pregnancy

Skin necrosis
Microvascular thrombosis
In patients with heterozygous protein C or S deficiency if a high initial dose is used or heparin overlap is inadequate


Common Pathway
New Oral Anticoagulants
Apixaban
Rivaroxaban
Xa Blocker
Xa
Dabigatran
Prothrombin
FII
Thrombin
Fibrinogen
Fibrin
Clot

NOAC indications include:

- Reduces risk of stroke in non-valvular atrial fibrillation
- Prevention of VTE following hip or knee replacement
- Treatment and ongoing prevention of VTE

Contraindications to NOAC therapy include:

- Renal impairment
  - a reduced dose may be used in moderate renal impairment, depending on renal function, NOAC and indication
- Disorders of haemostasis
- Clinically significant active bleeding
- Prosthetic heart valve
- Liver disease
- Pregnant and breastfeeding women
- Children under 18 years

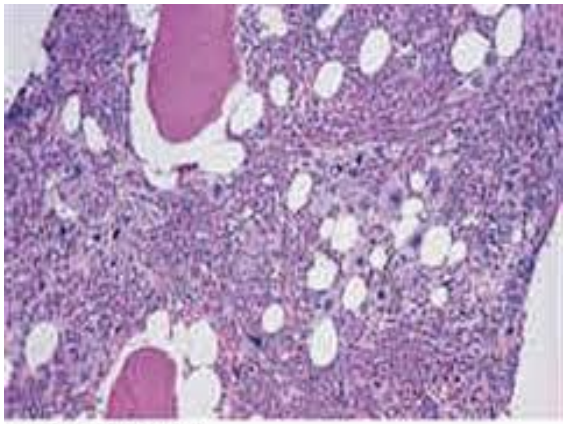
NOAC adverse effects

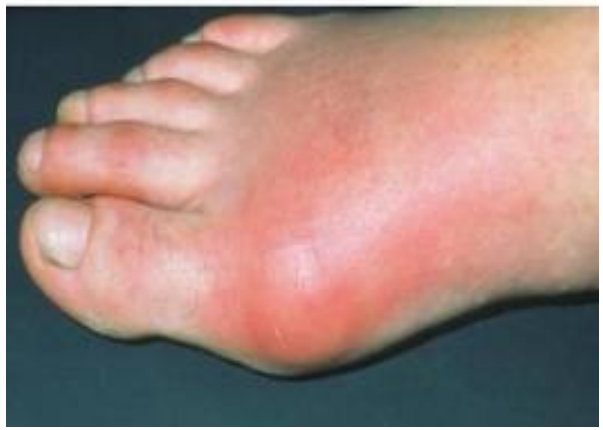
	Dabigatran	Apixaban	Rivaroxaban
Common	bleeding anaemia nausea dyspepsia gastritis abdominal pain	bleeding anaemia dyspepsia GI bleeding	bleeding anaemia peripheral oedema itch, skin blisters muscle spasm
Infrequent	increased liver enzymes	thrombocytopenia increased liver enzymes	increased liver enzymes
Rare	allergic reactions	allergic reactions	allergic reactions

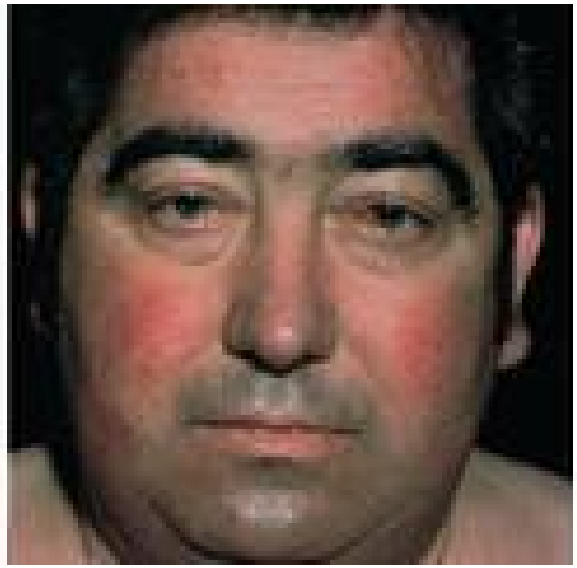
Case 8

50 yr old man complains for several weeks of hotness in his face, itching and severe acute pain in his big toe.Hb 19, WBC 17k, Platelets 500K, Serum Uric acid 12mg/dl, Po2 Saturation 95%, serum erythropoeitin 10 mU/ml. JakII Mutation +.

Diagnosis: polycythemia rubra vera with acute gouty arthritis.







Myeloid Malignancies

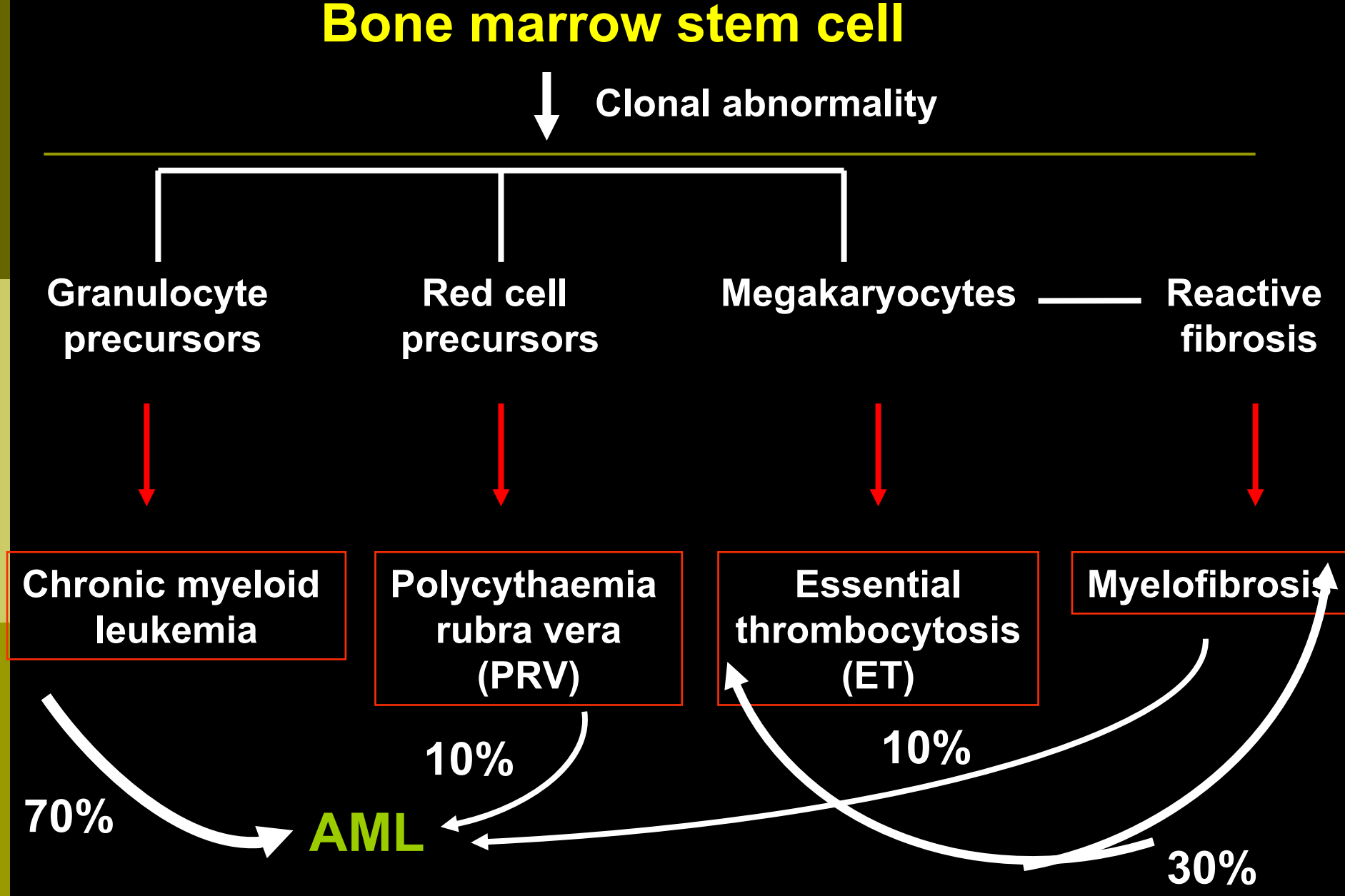
1- CML
2- AML
3- CMPN or disorders:
PRV
ET
MF

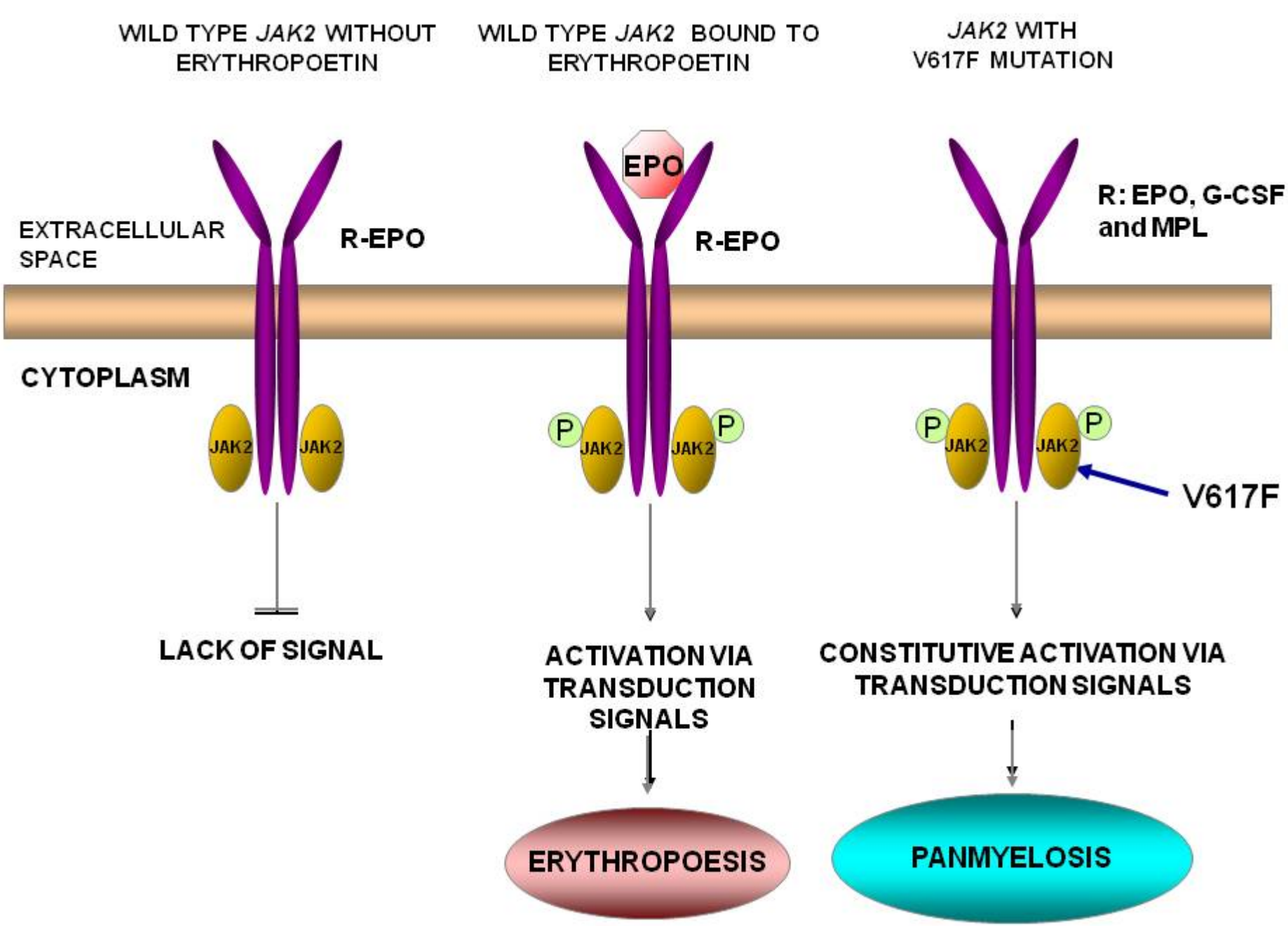
Myeloproliferative Neoplasms

Common features

- Specific clincopathologic criteria for diagnosis and distinct diseases, have common features
- Increased number of one or more myeloid cells
- splenomegaly
- Hypercatabolism: wt loss, gout
- Clonal marrow hyperplasia without dysplasia
- Predisposition to evolve

- Generalized pruritus (after bathing)
- Unusual thrombosis (e.g., Budd-Chiari syndrome)


Bone marrow stem cell
Clonal abnormality
Granulocyte precursors
Red cell precursors
Megakaryocytes
Reactive fibrosis
Chronic myeloid leukemia
Polycythaemia rubra vera (PRV)
Essential thrombocytosis (ET)
Myelofibrosis
70%
10%
10%
30%
AML



Adapted from Saharinen *et al.*, Mol Cell Biol. 2000; 20:3387-95
& Campbell and Green, N Engl J Med. 2006; 355:2452-66

Janus Kinase 2 (JAK2-V617F)

- Gain-of-function mutation is present in
  - ~95% of cases of PV
  - 23-57% of cases of ET
  - 43-57% of cases of MF

Risk classification of PV and ET

High risk*

- Age > 60 years
- Previous thrombosis

Low risk

- Age ≤ 60 years
- No previous thrombosis

* For practical purposes, platelets > 1,500 x 10^9/L also considered high risk

Barbui *et al.*, JCO 2011 (E-pub ahead of print)

Polycythemia Vera Diagnostic Criteria

Table 4. WHO diagnostic criteria for P-vera

Major Criteria
1. Elevated RBC mass > 25% above mean normal predicted value or hemoglobin > 18.5 gm/dL (male) or 16.5 gm/dL (female)
2. Presence of JAK2 V617F
Minor Criteria
1. BM trilineage myeloproliferation
2. Low serum erythropoietin levels
3. Endogenous erythroid colony formation

Diagnosis requires both major criteria or one major and two minor criteria

First-line therapy of PV

When:

- High-risk (age >60 years, thrombosis)
- Poor tolerance to or high need of phlebotomy
- Symptomatic or progressive splenomegaly
- Platelet >1.500 x 10^9/L
- Progressive leukocytosis
- Disease-related symptoms

How:

- Phlebotomy (Hct < 45%)
- Low-dose aspirin
- Hydroxyurea or IFN-α
  - Caveat on HU for young < 40 years
- Busulphan in elderly
- Manage generic cardiovascular risk factor

ELN recommendations: Barbui T. et al., J Clin Oncol. 2011 Jan 4. [Epub ahead of print]

Essential Thrombocythemia: Diagnostic Criteria

- **Platelet count ≥ 450,000**
- **JAK2 V617F^{+} OR no evidence of reactive thrombocytosis**
- **Not meeting WHO criteria for other MPNs (e.g PV, CML)**
- **Megakaryocyte proliferation with large and mature morphology; no or little granulocyte or erythroid proliferation**

- ALL FOUR CRITERIA ARE "REQUIRED"

First-line therapy of ET

When:

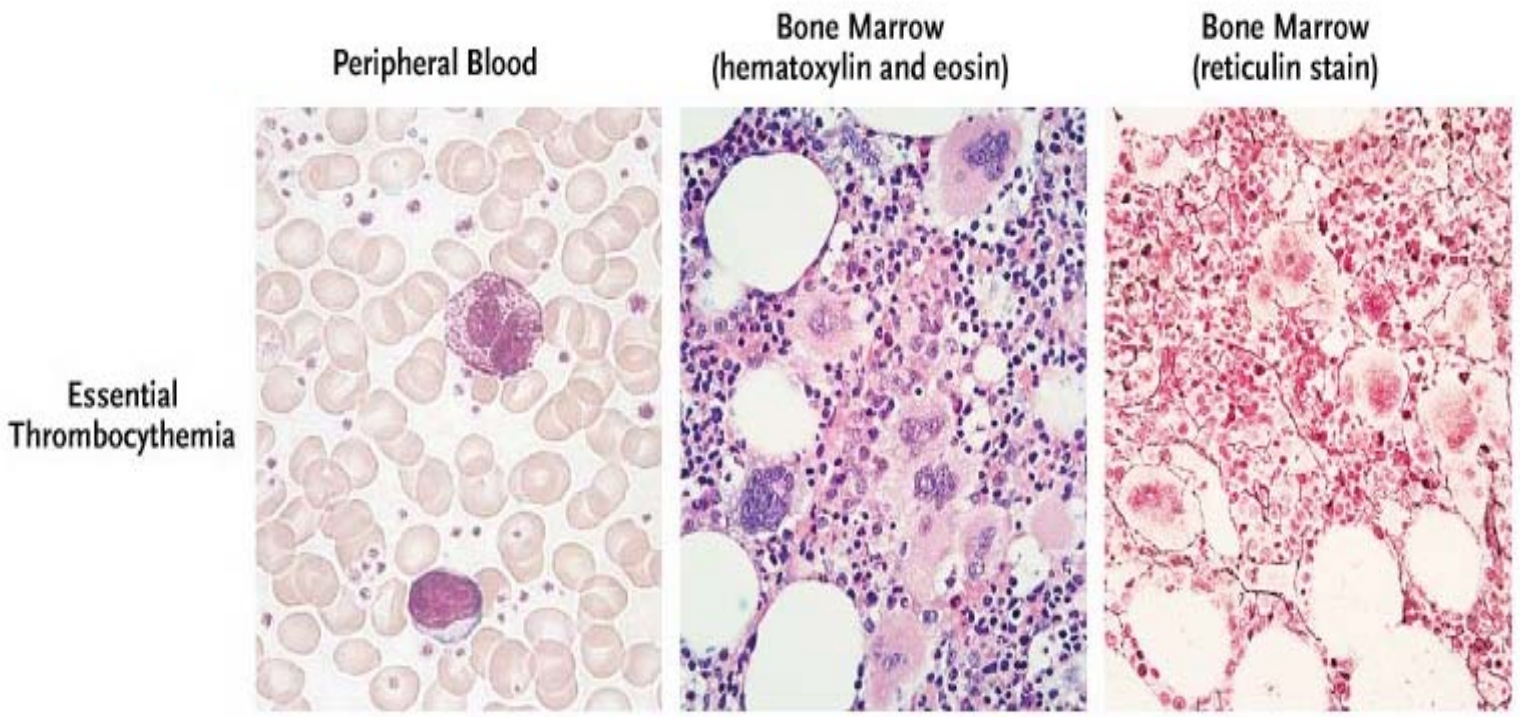
- High-risk patients (age > 60 years, prior thrombosis)

How:

- Hydroxyurea at any age
- Manage generic cardiovascular risk factors
- Aspirin if microvascular disturbances

ELN recommendations: Barbui T. et al., J Clin Oncol. 2011 Jan 4. [Epub ahead of print]

Essential Thrombocythemia



- **Bone marrow: Hypercellularity with marked megakaryocytic hyperplasia**

Ruxolitinib in the treatment of MPN

Selective JAK I & II inhibitor

Second line after hydroxyurea

Offers improvement of systemic symptoms, trx requirements.

No survival benefit as yet