

Chronic Myeloproliferative Disorders (VTE)

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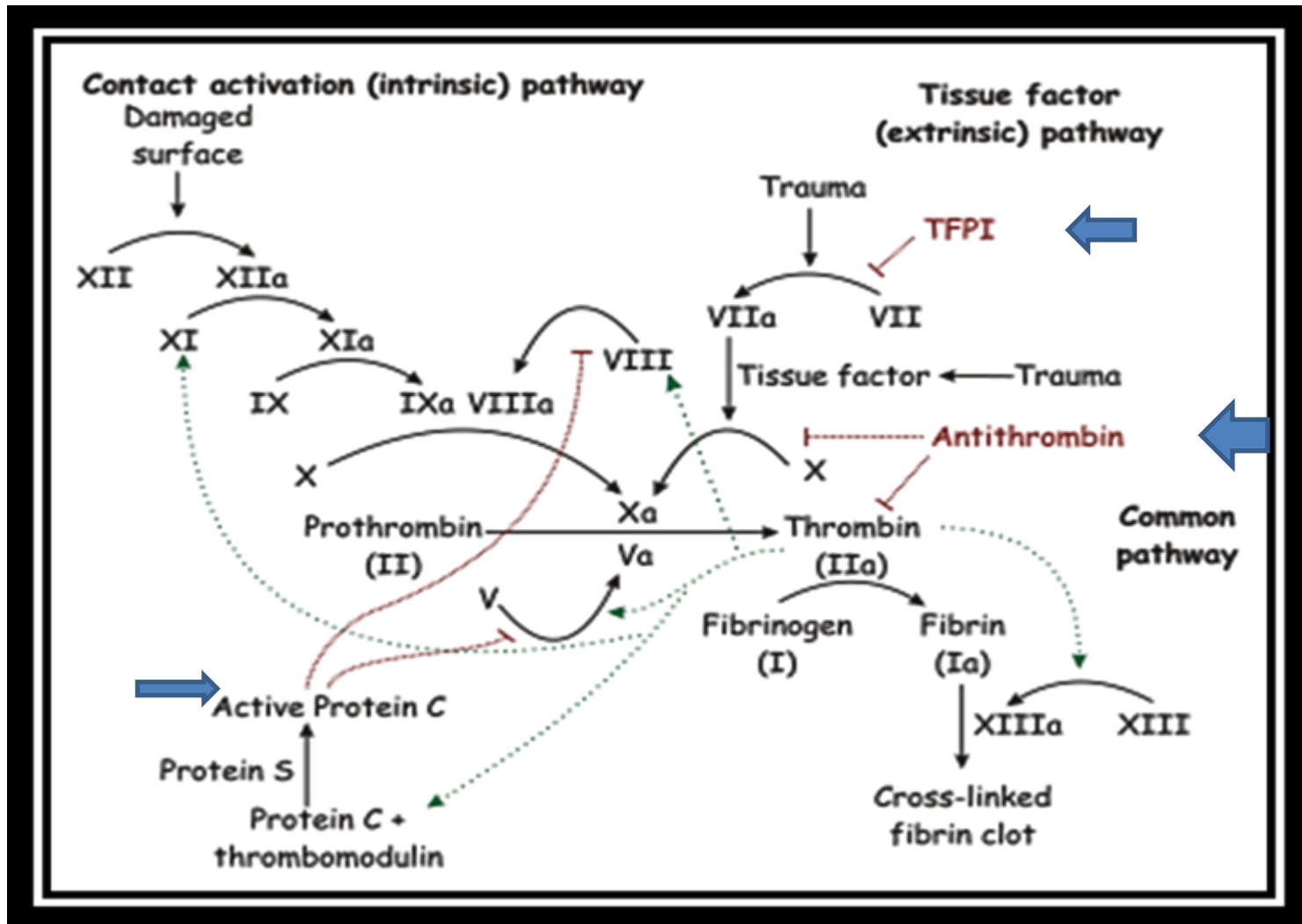
Case 7:

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



Case 10 investigation & Diagnosis



Importance of VTE (DVT/PE)

A- PREVENTABLE

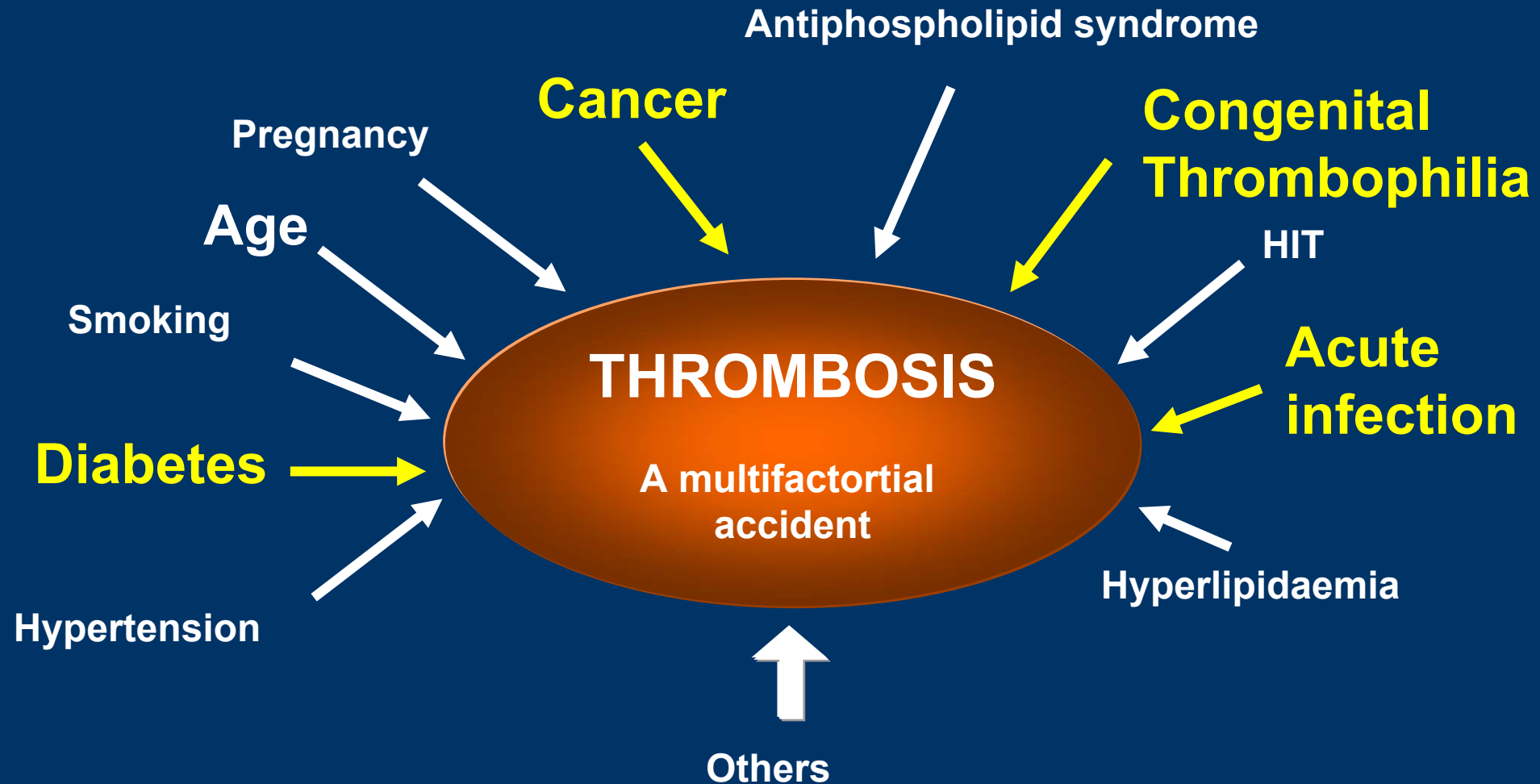
B- LIFE THREATENING

C- LONG TERM COMPLICATIONS

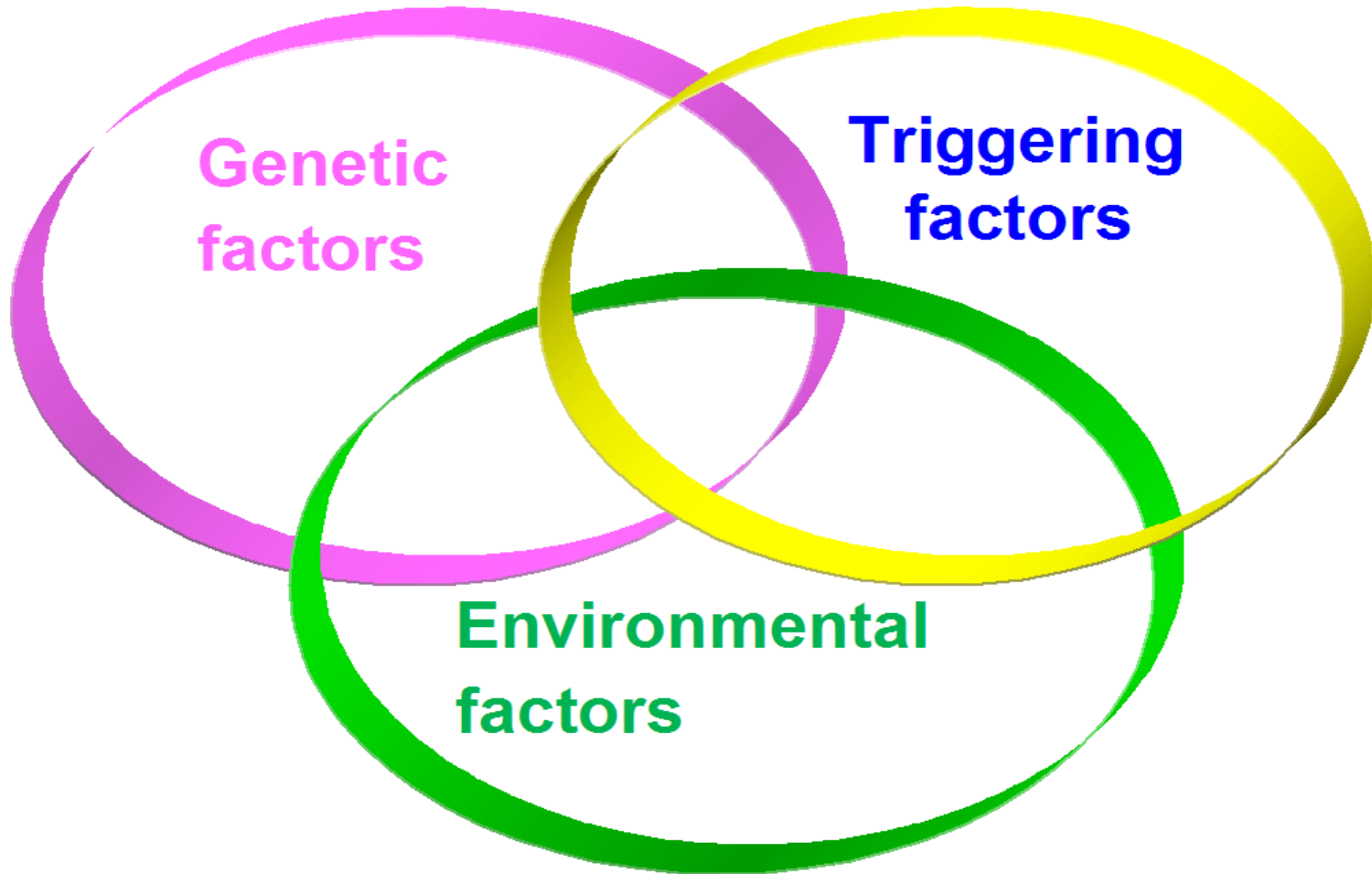
D- COMMON

E- COSTLY

VTE is a multifactorial and often silent disease



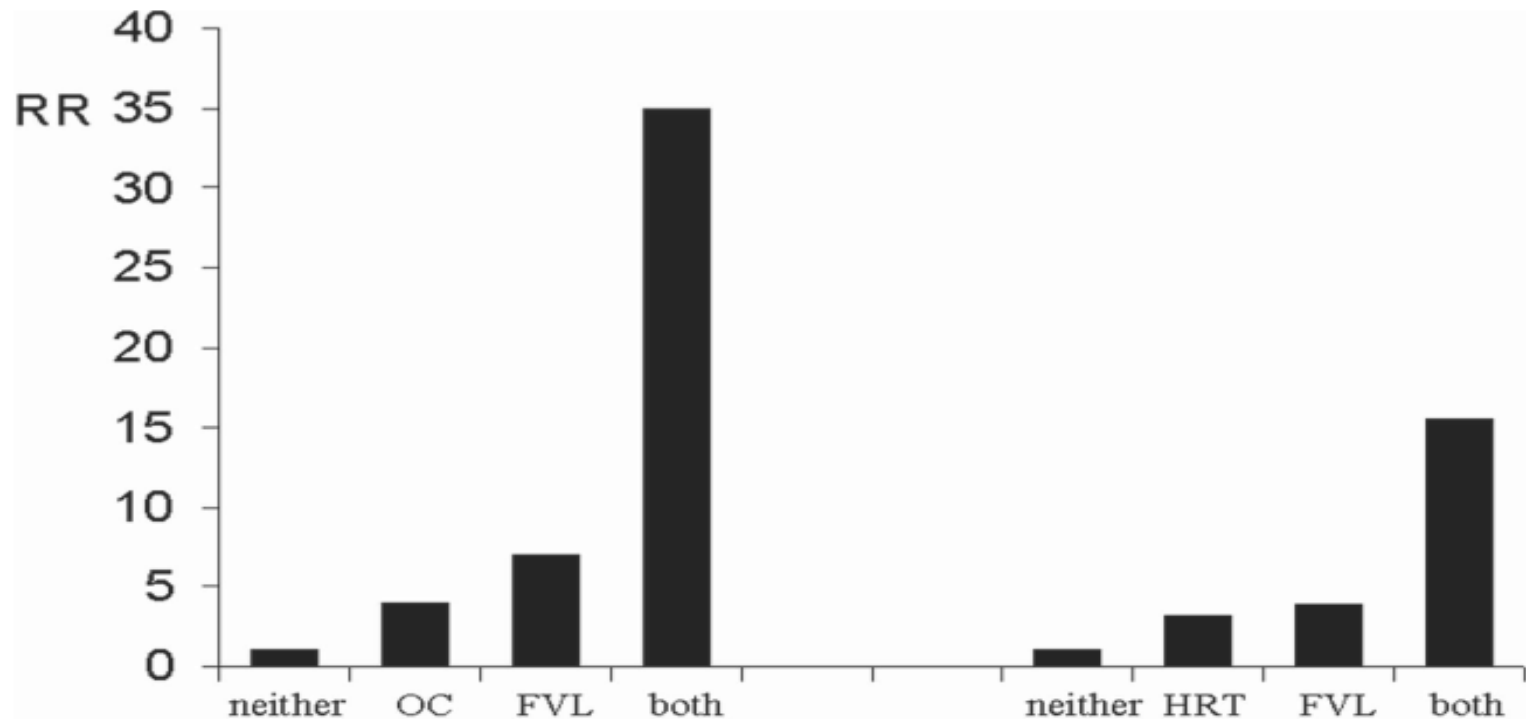
Venous thrombo-embolism is a multifactorial disease



Important Genetic Factors

- 1- Protein C deficiency**
- 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

Risk Factors for VTE

Stasis

Age > 40
Immobility
CHF
Stroke
Paralysis
Spinal Cord Injury
Hypertension
Polycythemia
Severe COPD
Anesthesia
Obesity
Varicose Veins

Hypercoagulability

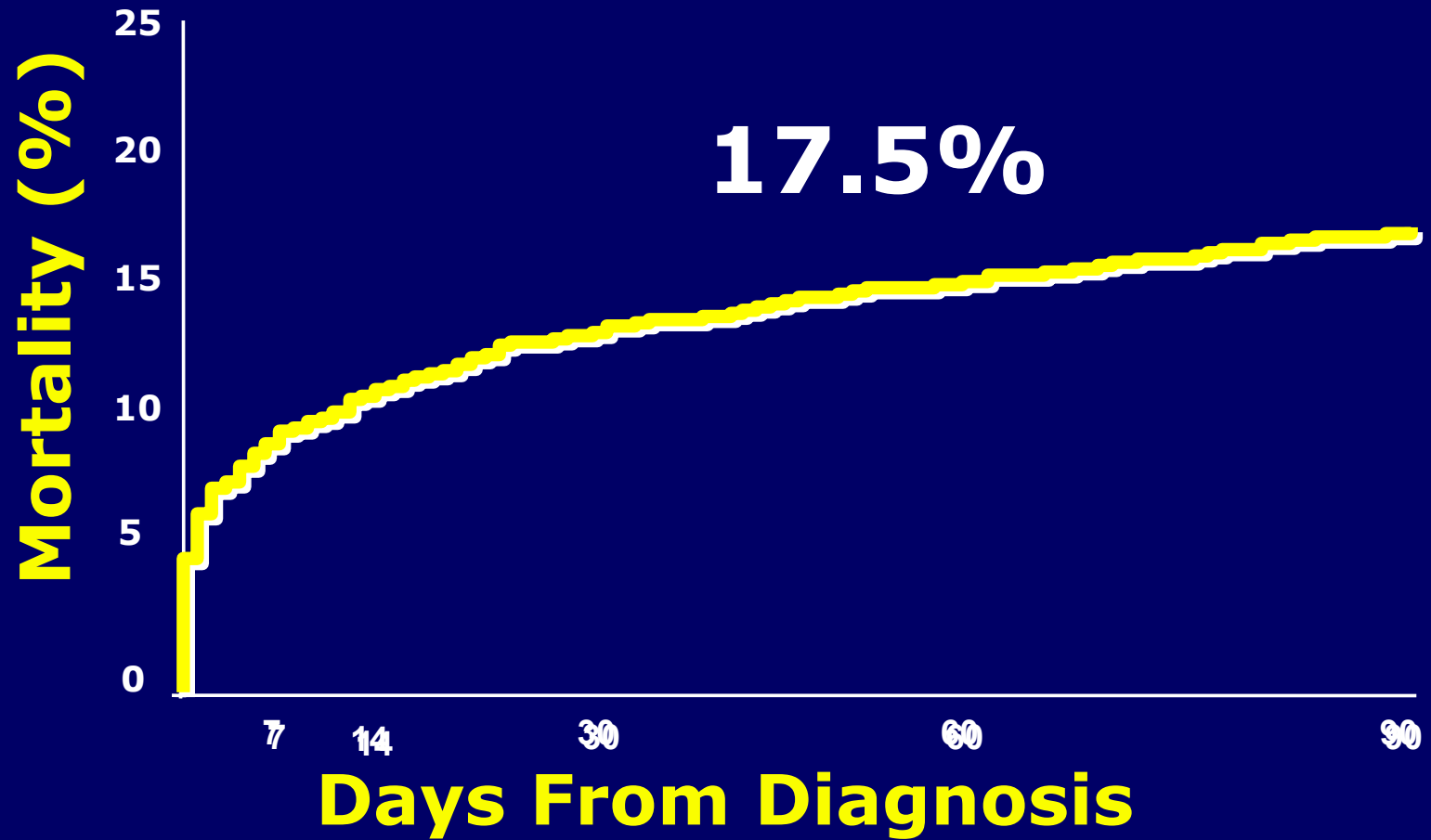
Cancer
High Homocysteinemia
Inherited Thrombophilia
Pregnancy
Thrombophilia

Endothelial Damage

Surgery
Prior VTE
Central lines
Trauma

Most hospitalized patients have at least one risk factor for VTE

ICOPER: CUMULATIVE MORTALITY AFTER DIAGNOSIS



Lancet. 1999;353:1386-1389.

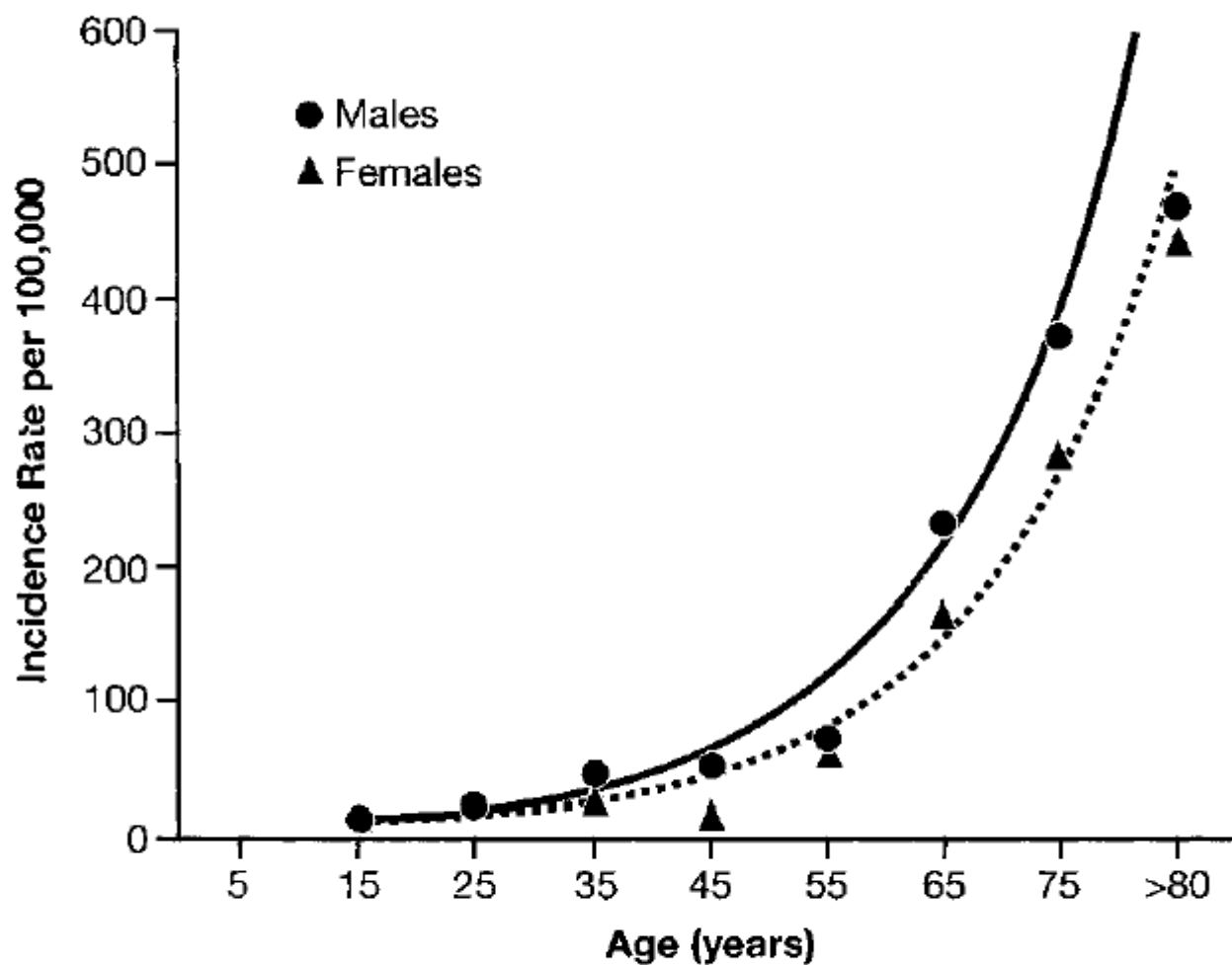
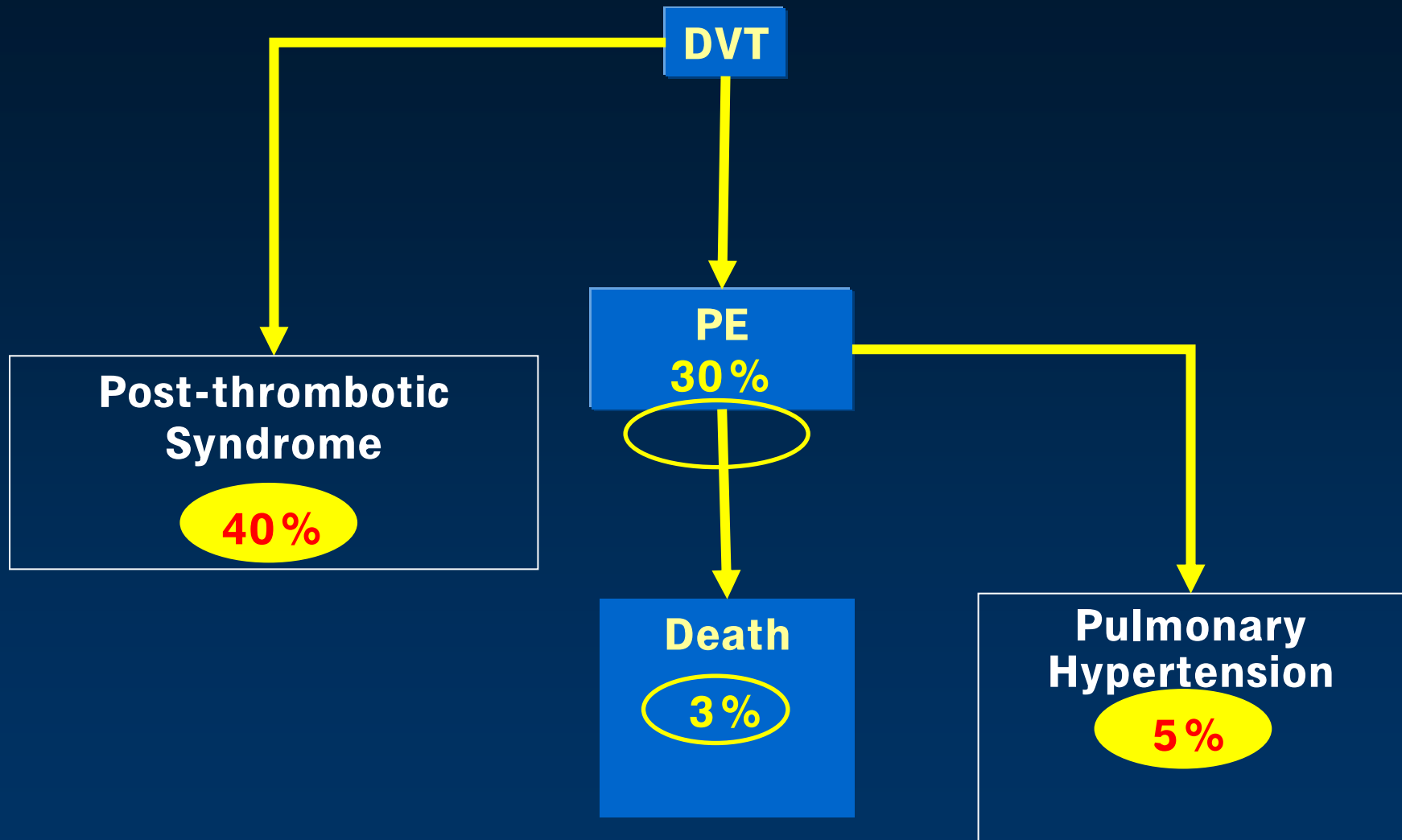


Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. *Arch Intern Med.* 1991;151:933–938.)

The Burden of Venous Thrombo Embolism



¹Brandjes DP et al. *Lancet* 1997;349:759-62

²Kahn SR et al. *Arch Intern Med.* 2004 Jan 12;164(1):17-26.

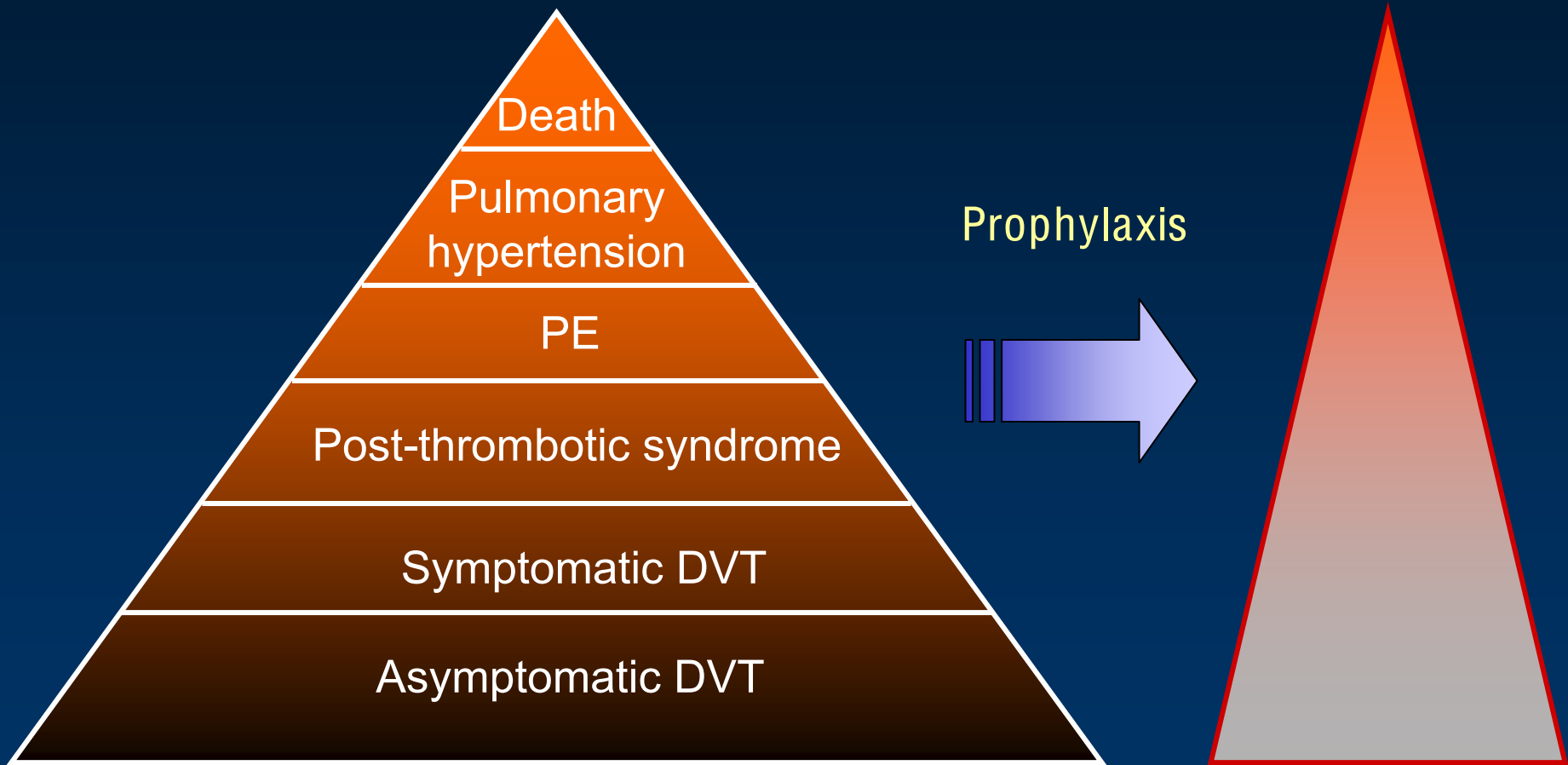
³Hirsh J & Hoak J. *Circulation* 1996;93:2212-45

⁴Peng et al. *NEJM* 2004;350:2257-64

Post DVT Syndrome/ V.Stasis



Thromboprophylaxis reduces the burden of VTE



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 (< 1 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 (≥ 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**	Legend
0-1	<10%	Low Risk	No specific measures; early ambulation.	ES- Elastic Stockings IPC- Intermittent Pneumatic Compression UFH- Unfractionated Heparin LMWH- Low Molecular Weight Heparin
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.	

* 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; Nicolaidis AN et al: 2001 International Consensus Statement: Prevention of Venous Thromboembolism, Guidelines According to Scientific Evidence. J 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 Thromboembolism: 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: Evaluation 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

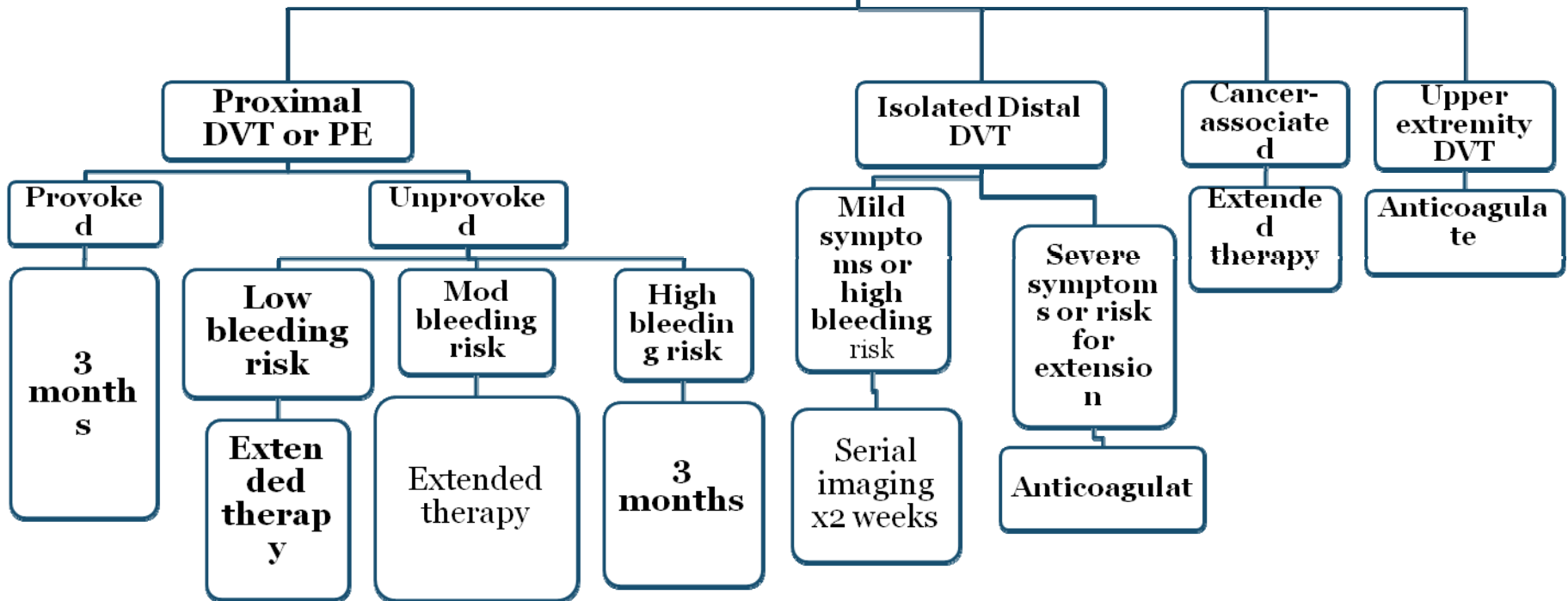
175u/kgx1 tinzaparin

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

OVERLAP HEPARIN+WARFARIN

*** OR NEW ORAL ANTICOAGULANTS**

Duration of Therapy



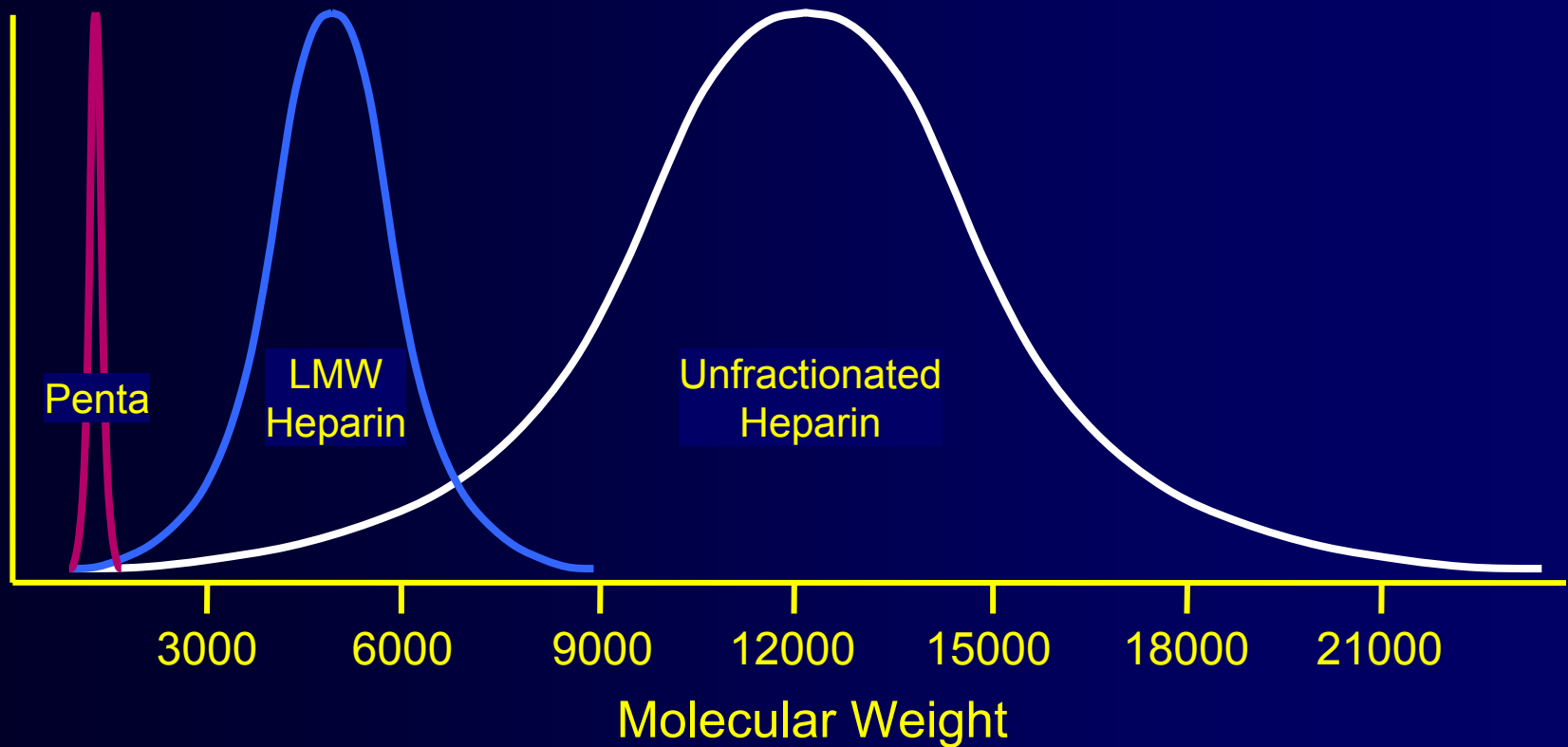
VTE:OTHER TREATMENT MODALITIES

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

Heparin Preparations Used Clinically

Thrombin inhibition (≥ 18 monosaccharide units)

Factor Xa inhibition (≥ 5 monosaccharide units)



Warfarin

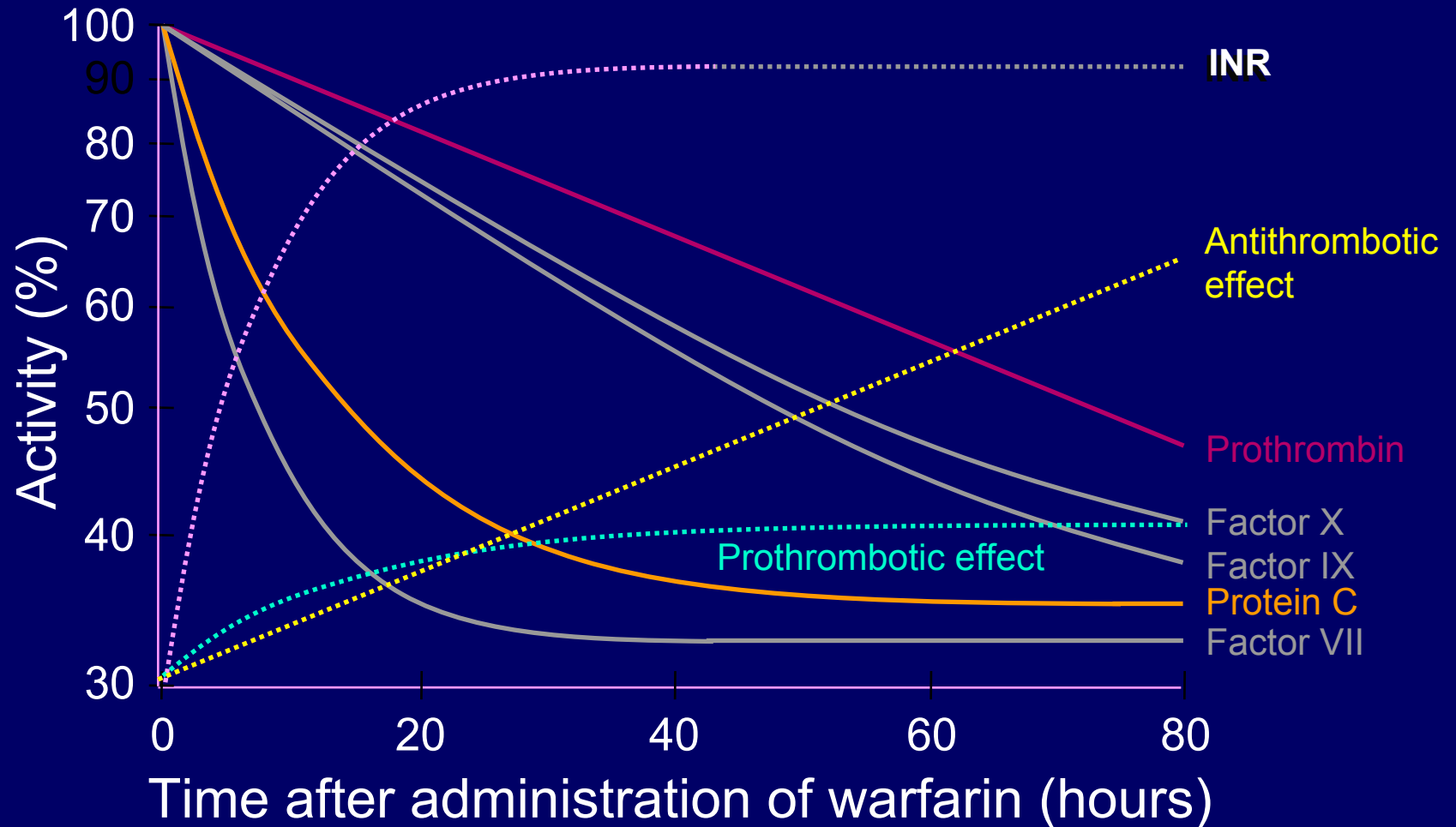
Pharmacokinetics

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)	}	procoagulant
Factor VII		
Factor IX		
Factor X		
Protein C	}	anticoagulant
Protein S		

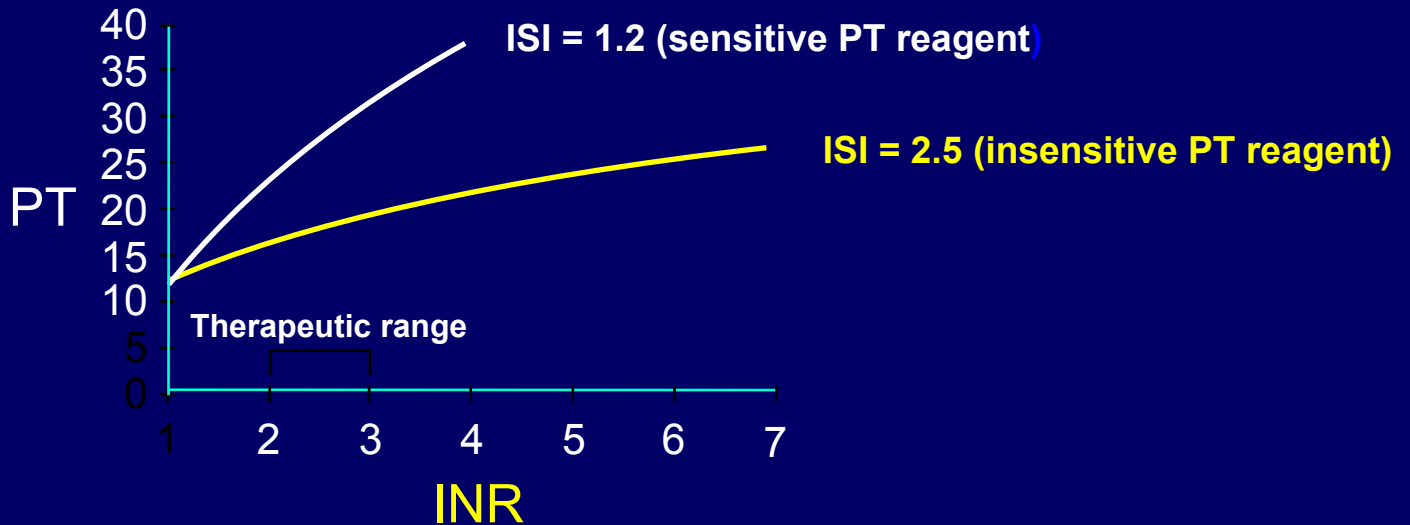
Clearance of Vitamin K-dependent Proteins



International Normalized Ratio (INR)

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

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

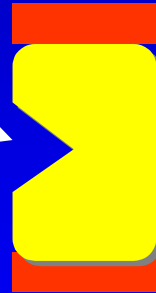
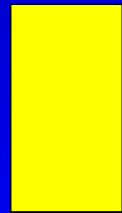
Apixaban
Rivaroxaban



New Oral
Anticoagulants

Dabigatran

Prothrombin
FII

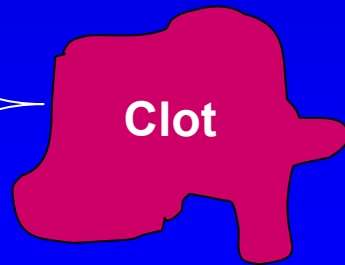


Thrombin

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**

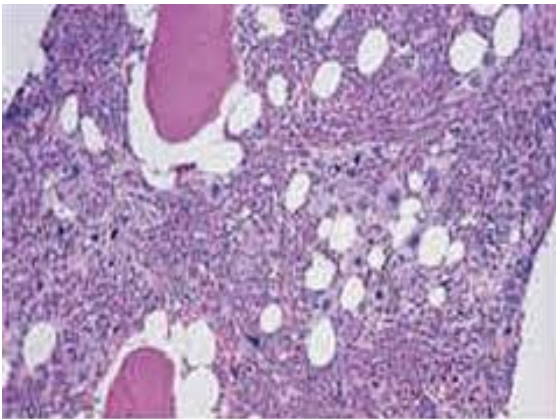
NOAC adverse effects

	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 erythropoietin 10 mU/ml. Jak2 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 clinopathologic 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



Chronic myeloid leukemia

Polycythaemia rubra vera (PRV)

Essential thrombocytosis (ET)

Myelofibrosis

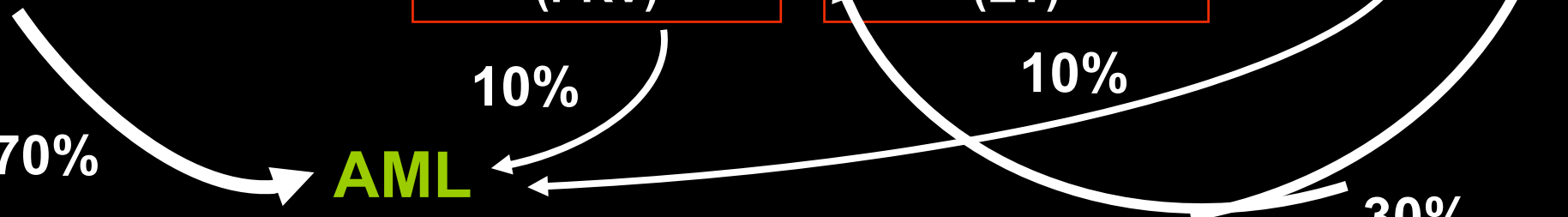
70%

AML

10%

10%

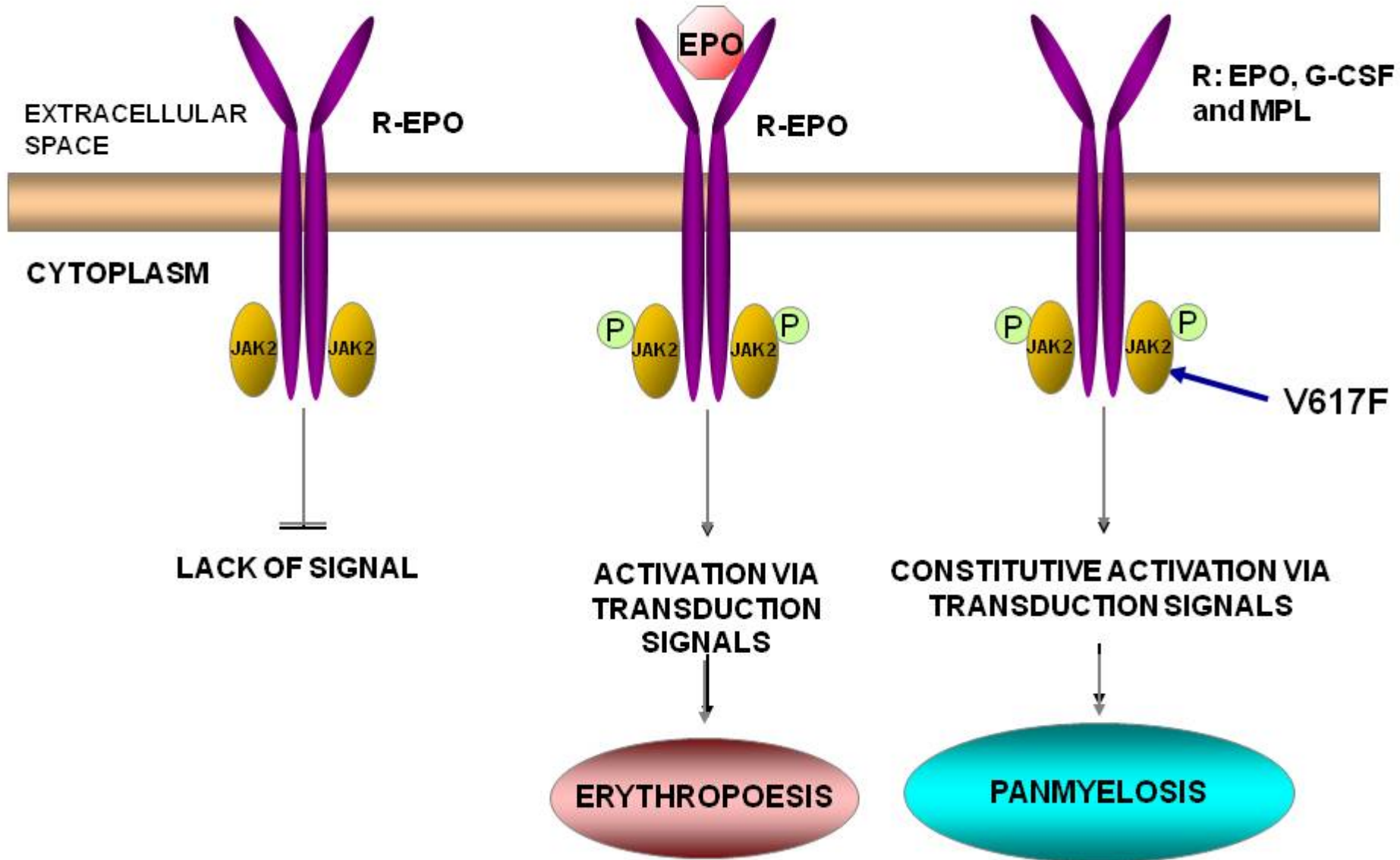
30%



WILD TYPE JAK2 WITHOUT
ERYTHROPOETIN

WILD TYPE JAK2 BOUND TO
ERYTHROPOETIN

JAK2 WITH
V617F MUTATION



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 \leq 60 years
 - No previous thrombosis
-

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

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 > $1.500 \times 10^9/L$
- 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

Essential Thrombocythemia: Diagnostic Criteria

- Platelet count $\geq 450,000$
- 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

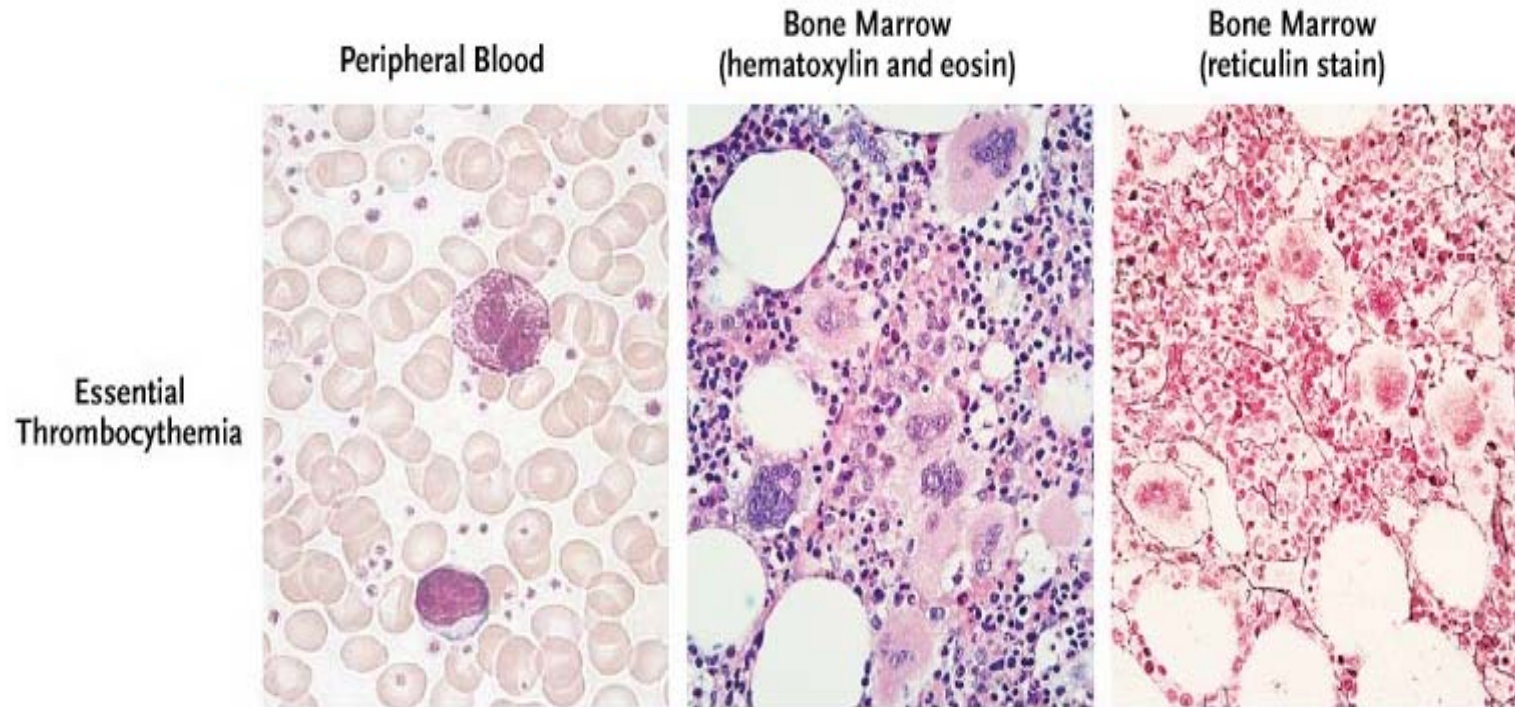
When:

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

How:

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

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