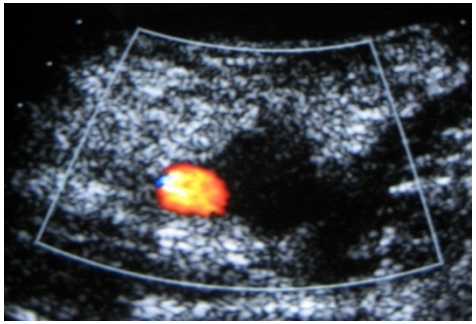
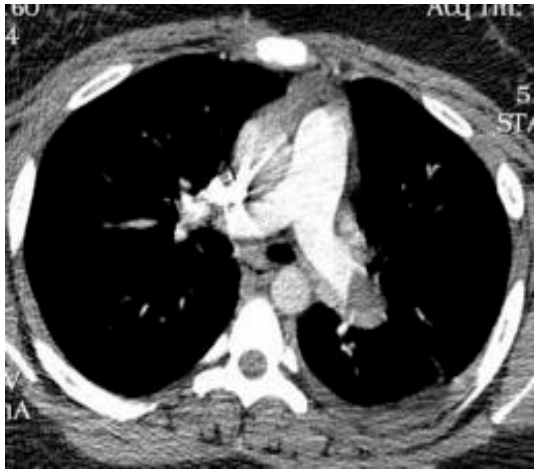
Case 7: VTE/ MS4
29/Oct/2015

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

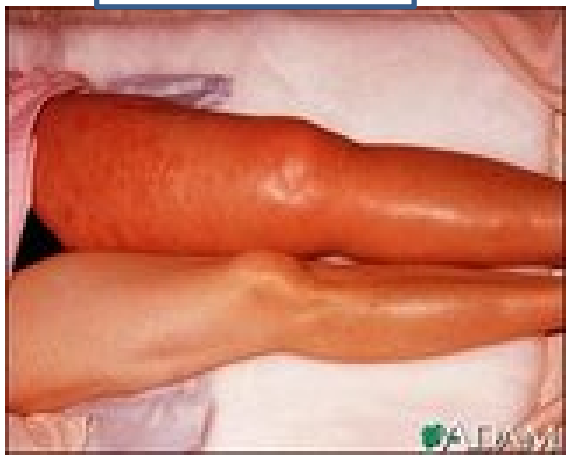
Duplex Us: DVT common femoral vein with

PE

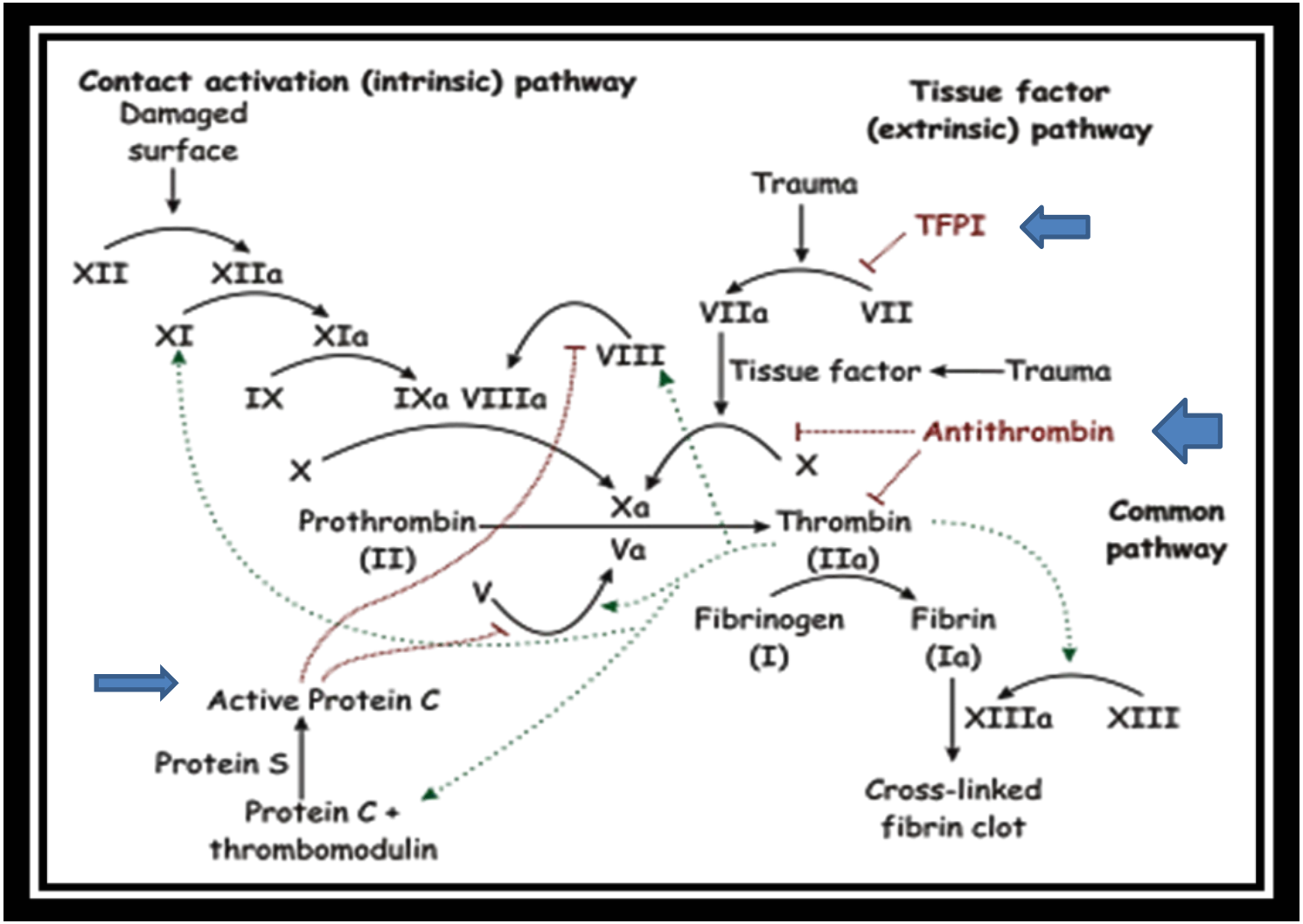




DVT



Case 10 investigation & Diagnosis



Importance of VTE (DVT/PE)

A- PREVENTABLE

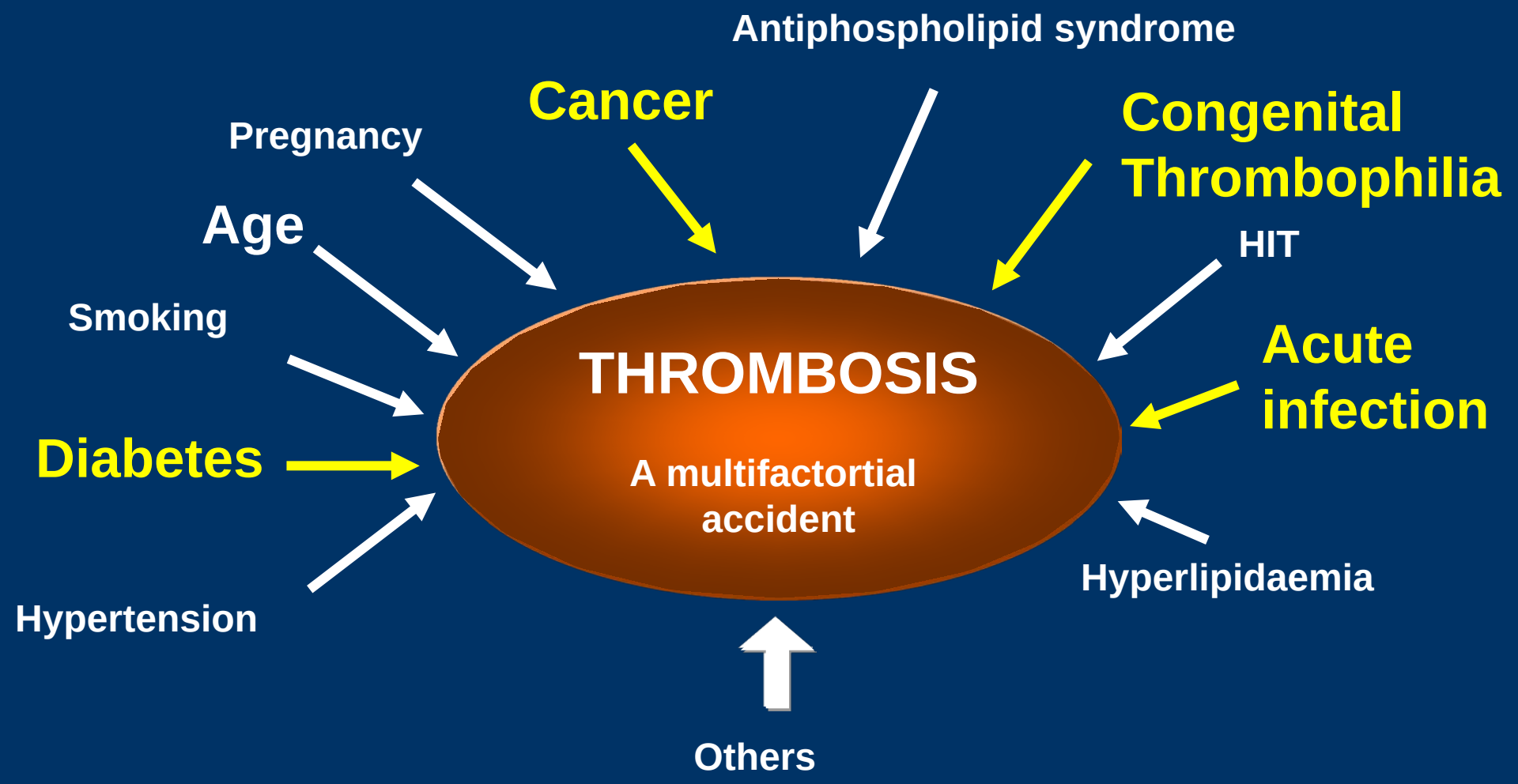
B- LIFE THREATENING

C- LONG TERM COMPLICATIONS

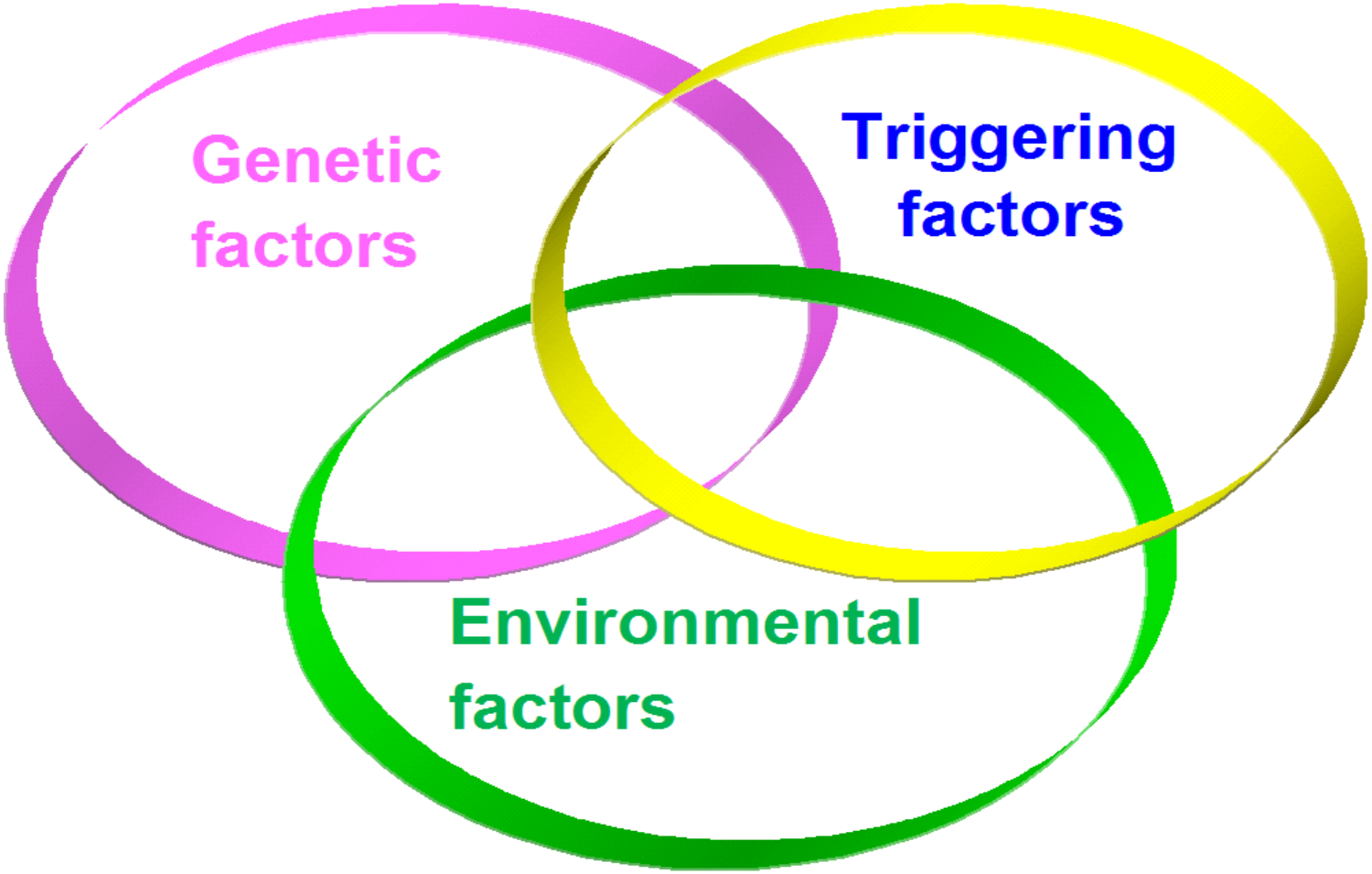
D- COMMON

E- COSTLY

VTE is a multifactorial and often silent disease



Venous thrombo-embolism is a multifactorial disease



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

- Age > 40
- Immobility
- CHF
- Stroke
- Paralysis
- Spinal C
- Hyper
- Polycyt
- Severe C
- Anesthesia
- Obesity
- Varicose Veins

Hypercoagu

- Cancer
- High
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- egnancy
- Thrombophilia

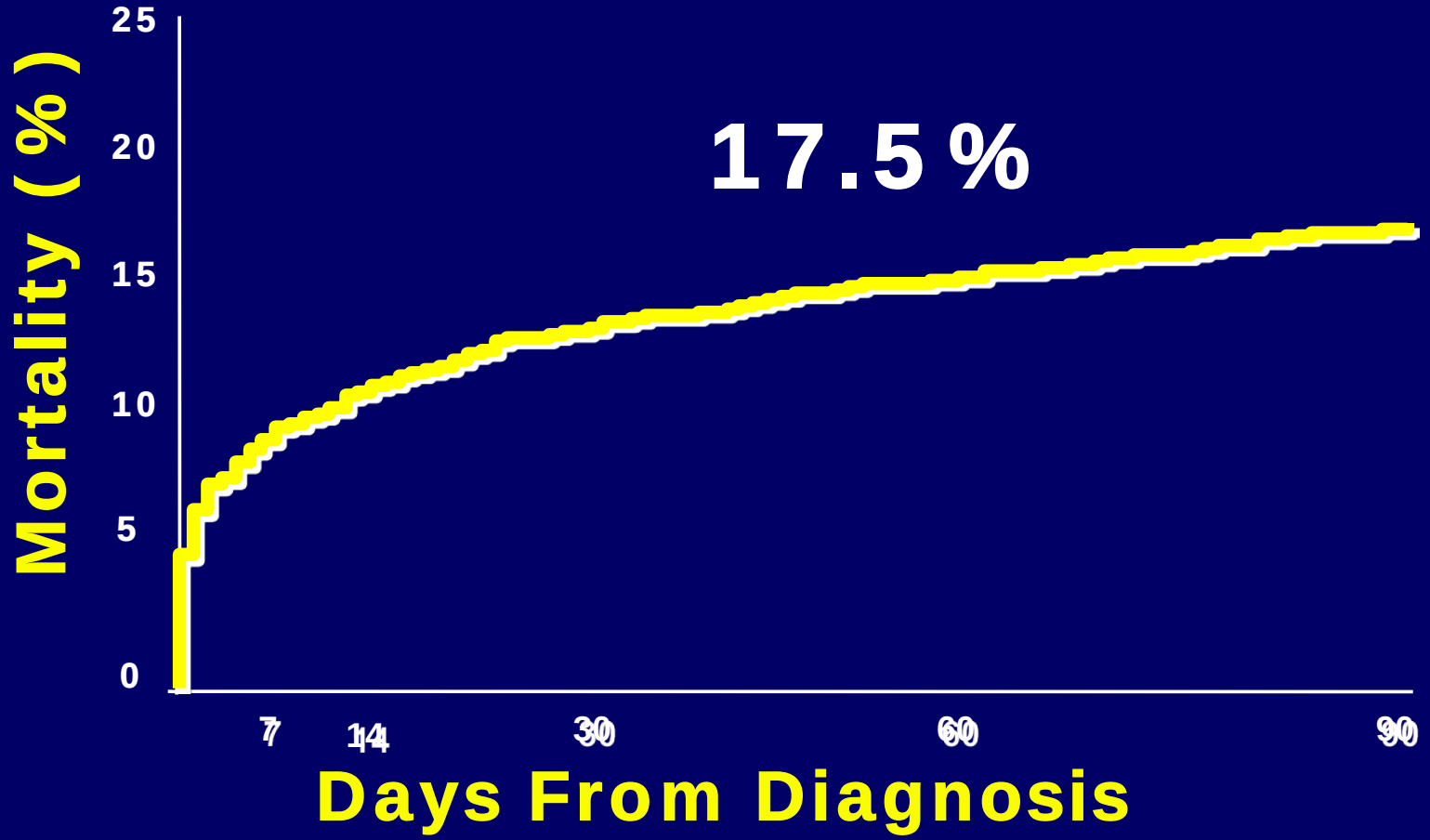
othelial Damage

- 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.

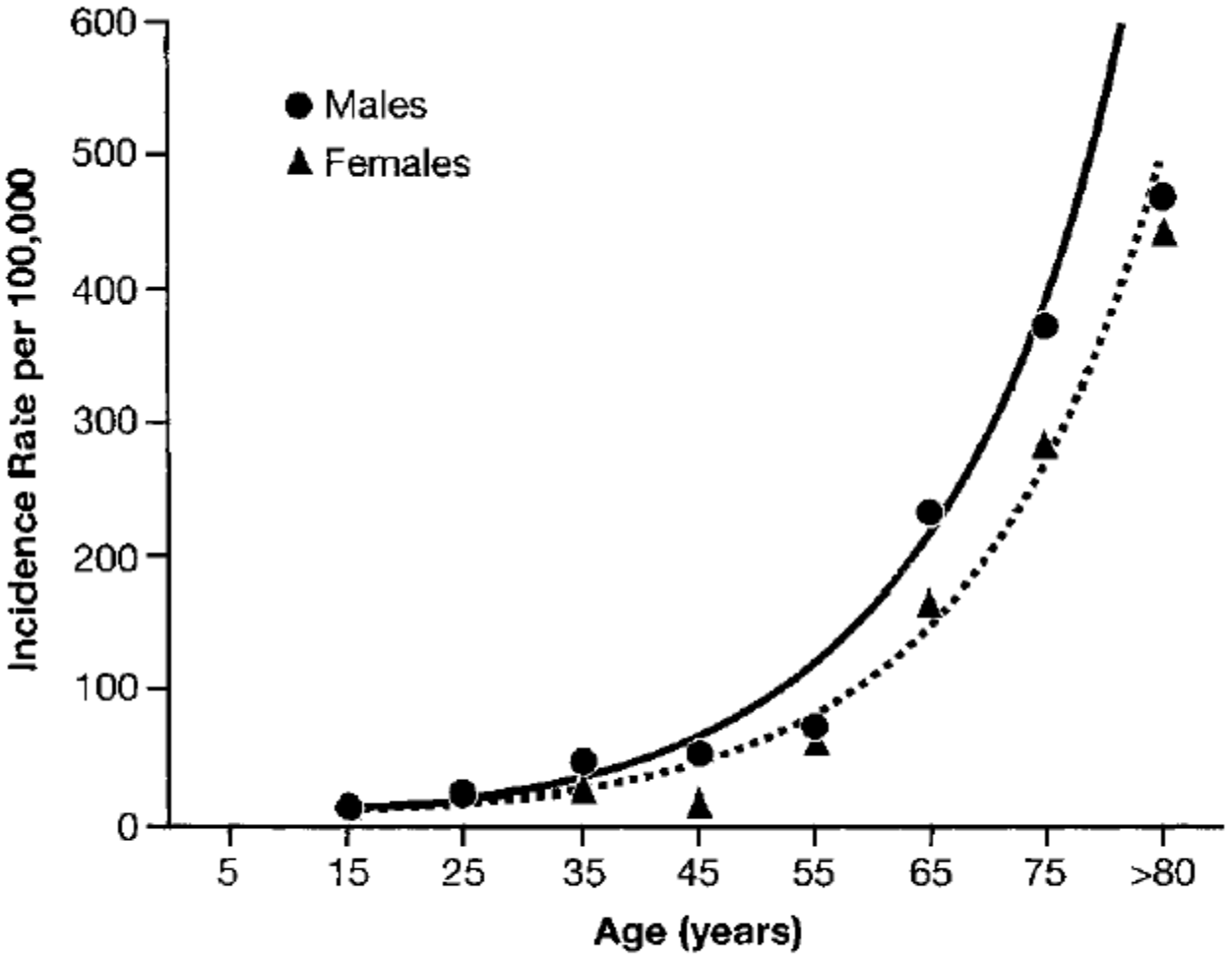
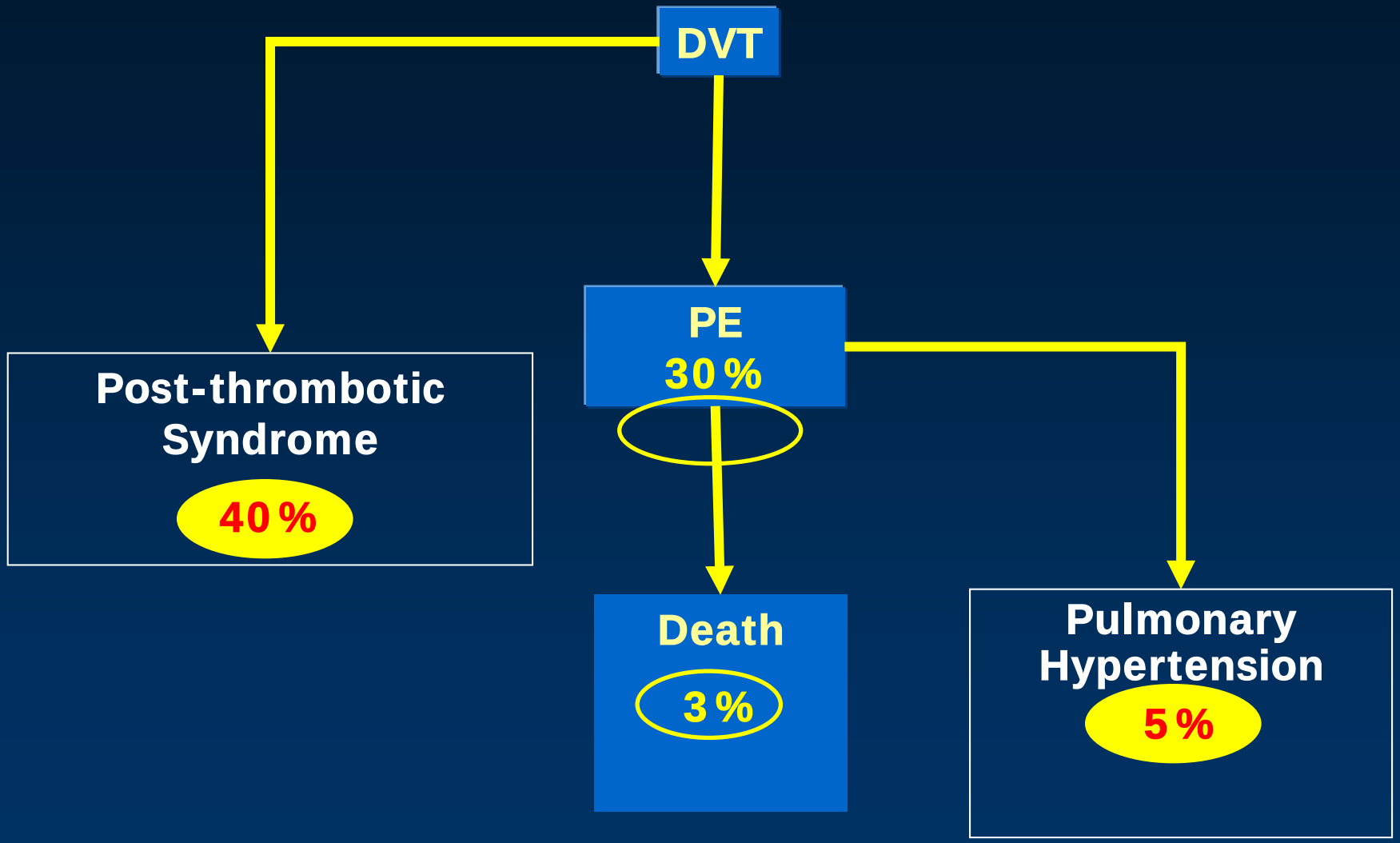


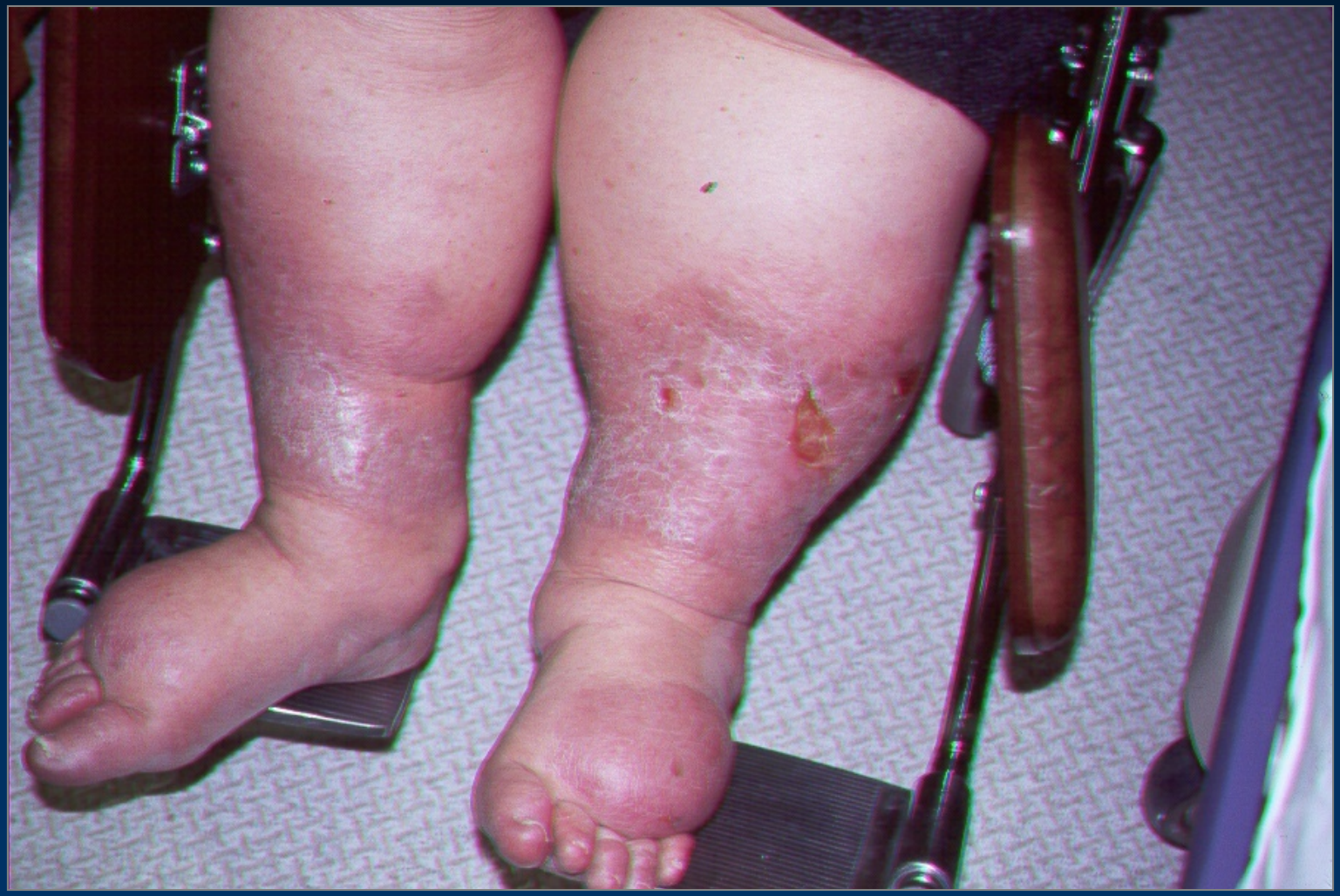
Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. *Arch Intern Med*. 1991;151:933–938.)

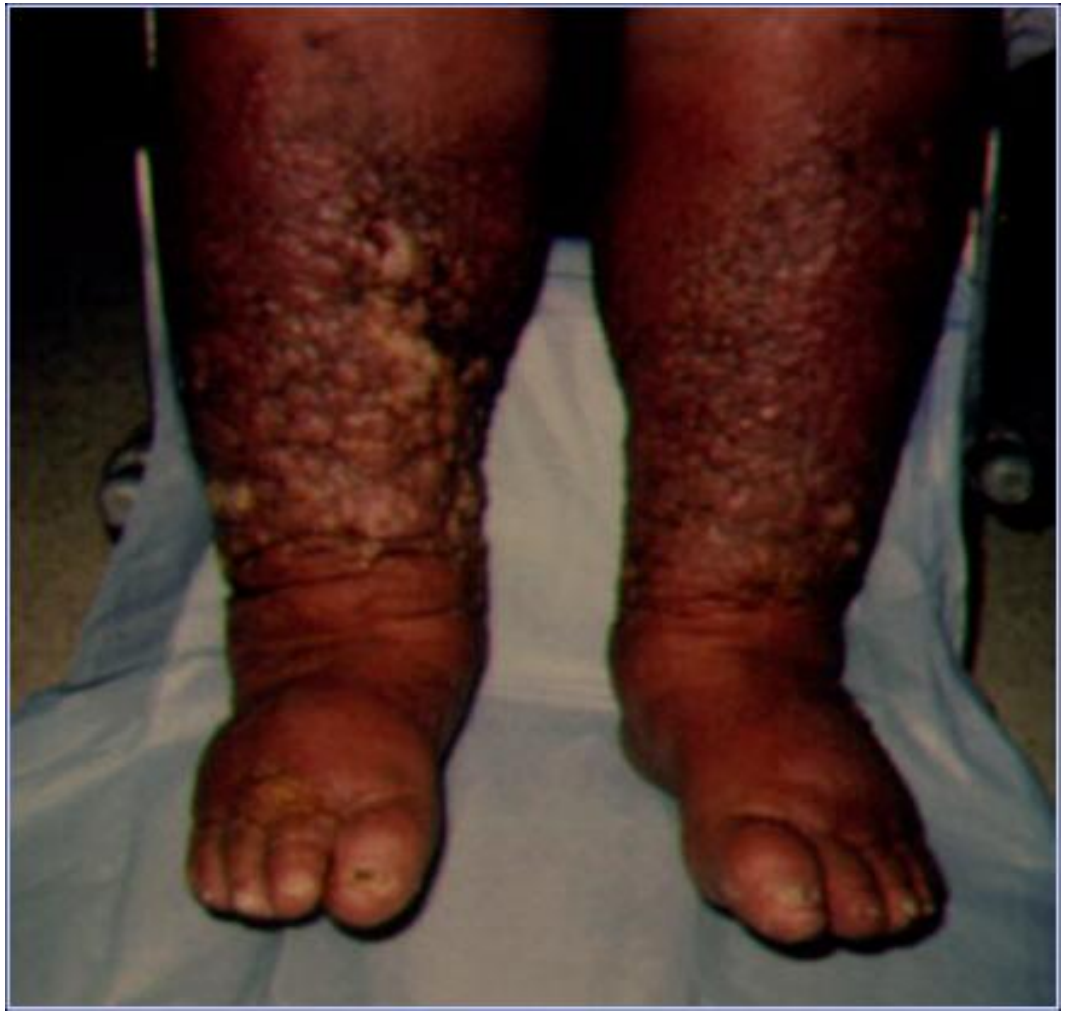
The Burden of Venous Thrombo Embolism

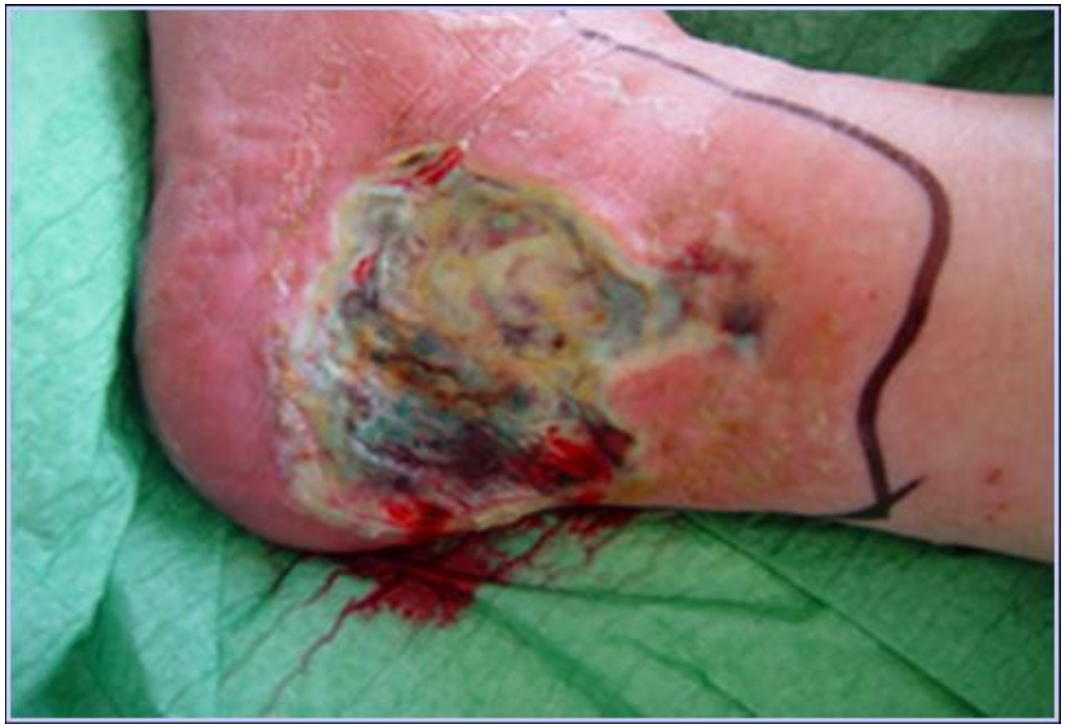


[1]Brandjes DP et al. Lancet 1997;349:759-62
[2]Kahn SR et al. Arch Intern Med. 2004 Jan 12;164(1):17-26.
[3]Hirsh J & Hoak J. Circulation 1996;93:2212-45
[4]Peng et al. NEJM 2004;350:2257-64

Post DVT Syndrome/ V.Stasis







VTE - A Public Health matter

- Annually, 1.5 million VTE events occur in the European Union and 900,000 in the United States[1,2].
- The subsequent yearly VTE-related complications account for more than 500,000 deaths in Europe and 300,000 fatalities in the United States[1,2].

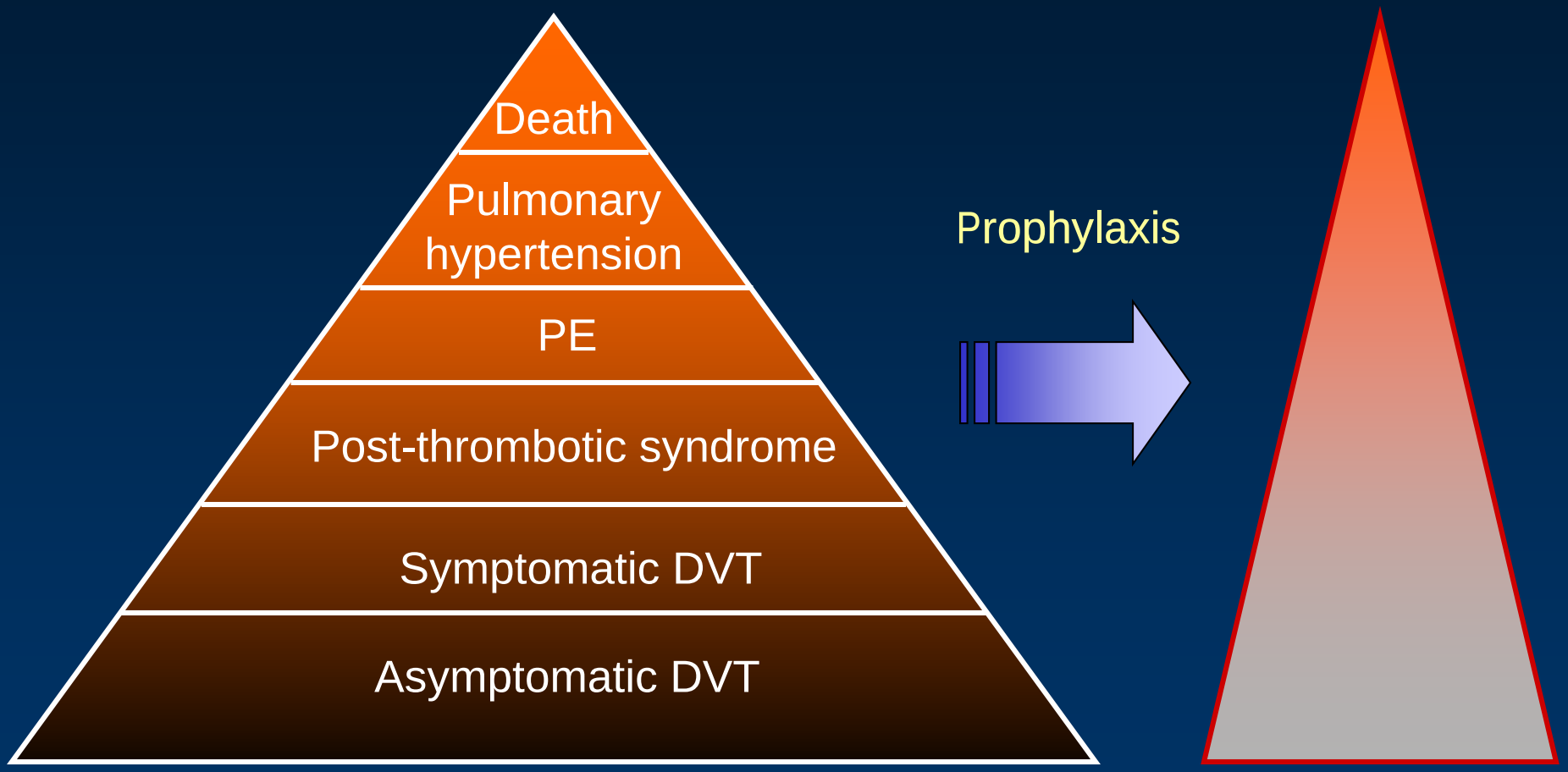
=> It represents more than the mortality related to AIDS, breast cancer and road traffic accidents combined [1-4]

1 Cohen AT et al.Thromb Haemost. 2007;98:756–64.
2. Caprini JA, Am J Surg. 2010 Jan;199(1 Suppl):S3-10.
3. Eurostat statistics on health and safety 2001. Available from: http://epp.eurostat.cec.eu.int.
4. Gerotziafas GT et al. Curr Opin Pulm Med. 2004; 10:356–65.

Effective, safe, and cost-effective VTE prophylaxis is available!

- Pharmacologic Prophylaxis reduces DVT and PE by 50-65%
- Symptomatic and Asymptomatic VTE reduced.
- Bleeding risk due to prophylaxis is rare.
- HIT
  - 2.37% with UFH (occasionally very serious)
  - .06% with LMWH
- Cost effectiveness of VTE prophylaxis has been repeatedly demonstrated.

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

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.

Hospital No. _____

Choose All That Apply

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

VTE IN JORDAN

4 YR Prospective study in inpatients

Total 217 patients:102 m,115 f

Total of 49 (22.5%) had inherited VTE

PC DEF	**17**	**(35%)**
PS DEF	**15**	**(31%)**
ATIII DEF	**10**	**(20%)**
Others	**7**	**(14%)**

AWIDI et al am j hematol
1993,44:95-100

Risks and Incidence of a First Episode of Venous Thrombosis[†]

Condition/risk factor(s)	Relative risk	Incidence, percent per year
Normal	1	0.008
Hyperhomocysteinemia	2.5	0.02
(MTHFR 677T mutation)	1	--
Prothrombin gene mutation	2.8	0.02
Oral contraceptives	4	0.03
Factor V Leiden (heterozygous)	7	0.06
Oral contraceptives plus heterozygous factor V Leiden	35	0.29
Factor V Leiden (homozygous)	80	0.5 to 1.0

[†] Adult subjects only. Data from the Leiden Thrombophilia Study.

FACTOR V LEIDEN
(APC RESISTANCE)

- **G –TO- A SUBSTITUTION AT NUCLEOTIDE 1691 IN THE GENE OF F V**
- **SINGLE AA REPLACEMENT IN plasma (ARG 506 Gln) at 1 of 3 cleavage sites in F Va molecule**
- **F V Leiden is inactivated at a rate 10 times slower**

FACTOR V LEIDEN IN JORDAN

- 400 healthy subjects
- 52(13%) had APC resistance
- 49(12.25%) were F V Leiden(DNA test)
- 42(10.5%) were heterozygs for F V Leiden
- 7(1.75%) were homozygous for F V Leiden

Awidi A et al,Thromb&haemost 1999,81(4):582-4

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

4hrs post injection blood level 0.6-1u

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

OVERLAP HEPARIN+WARFARIN

VTE - Duration of therapy ACCP Guidelines 2001

3-6 months

- 1st event with time-limited risk factor

?6 months

- 1st idiopathic

12 months-lifetime

- 1st event with*
  - Cancer until resolved
  - ACA
  - AT deficiency
- Recurrent event

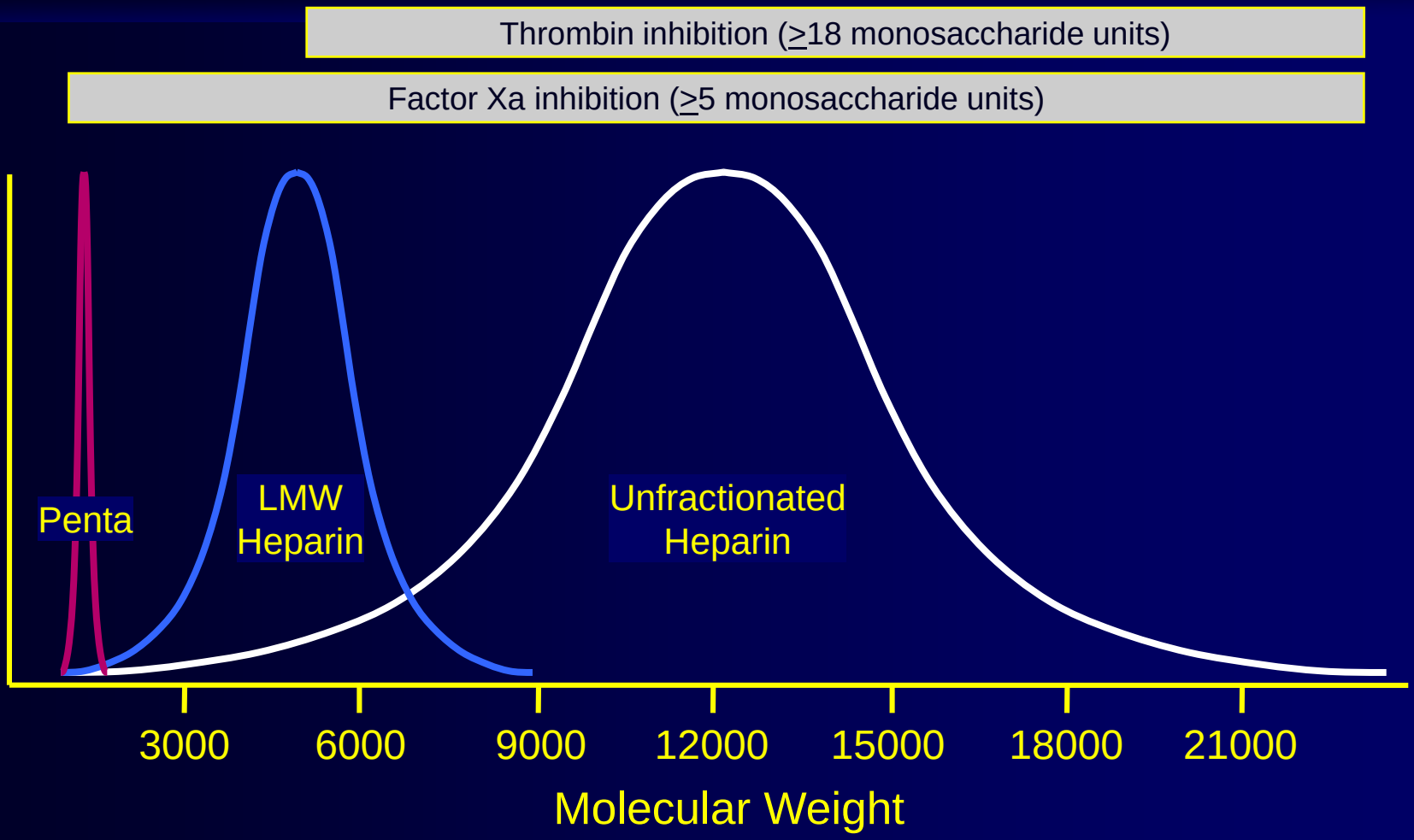
All recommendations to be individualised

*** Unclear for homozygous fVL, homocysteinemia, protein S or C deficiency**

VTE:OTHER TREATMENT MODALITIES

* THROMBOLYTIC THERAPY
  SK 250K loading>100k/hr 24-72hr(pe,dvt)
  TPA (pe) 100mg over 2hrs
* V.Thrombectomy
* IVC Filters
* Pulmonary embolectomy
* Post DVT syndrome

Heparin Preparations Used Clinically



Warfarin

Identified (1924) as a toxic substance in spoiled sweet clover that caused bleeding in cattle

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)

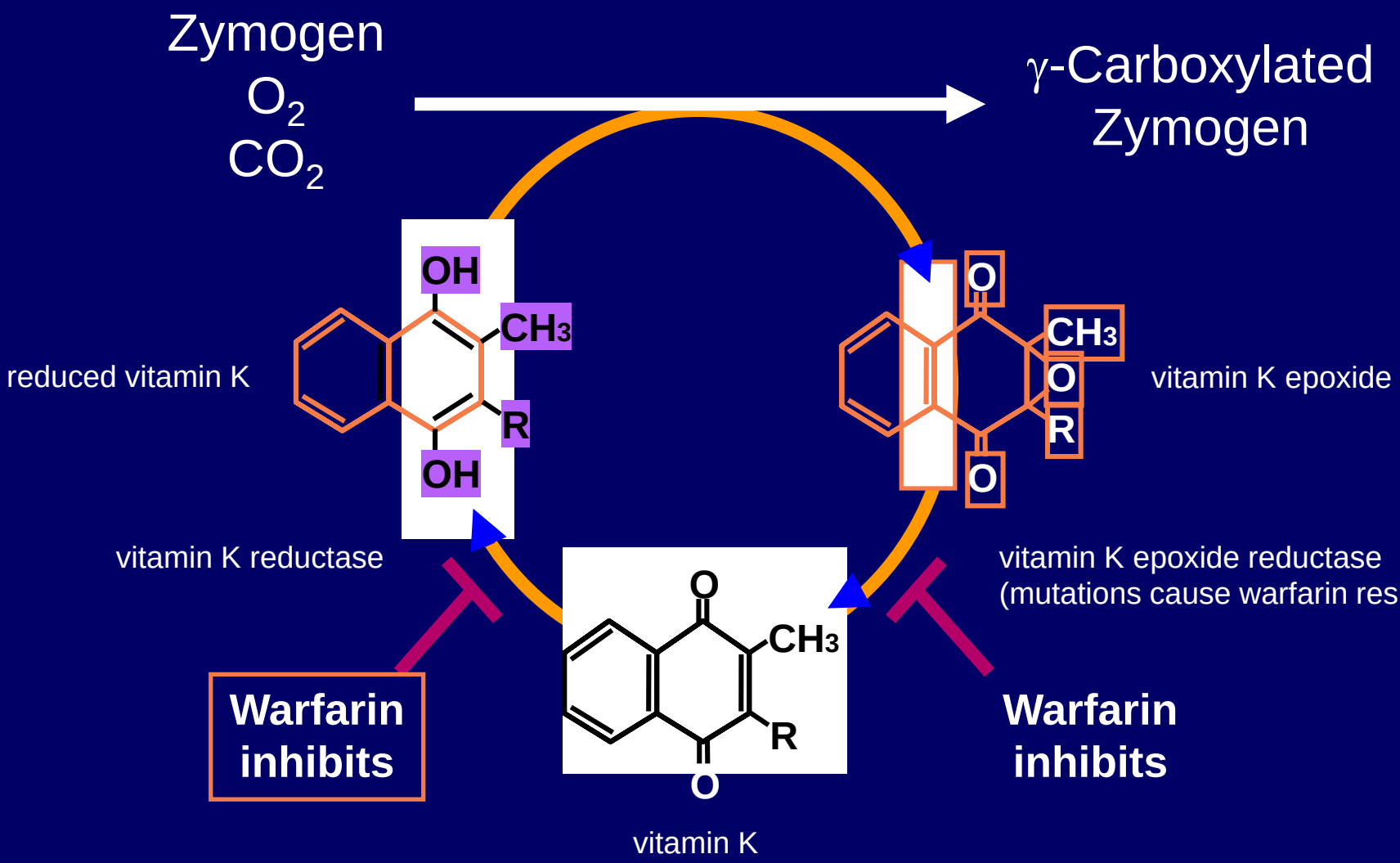
- Prothrombin
- Factor VII
- Factor IX
- Factor X

} procoagulant

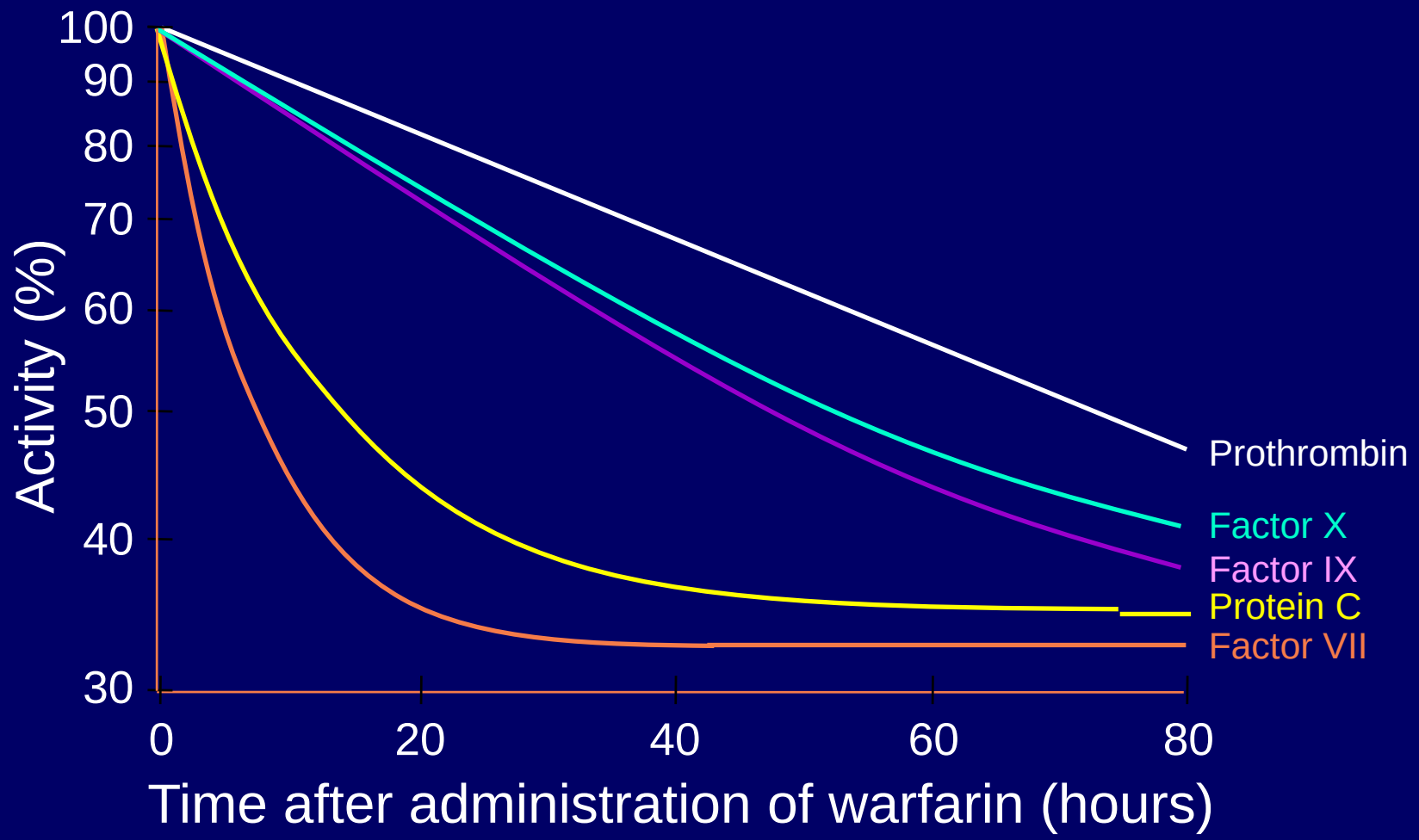
- Protein C
- Protein S

} anticoagulant

Vitamin K Cycle



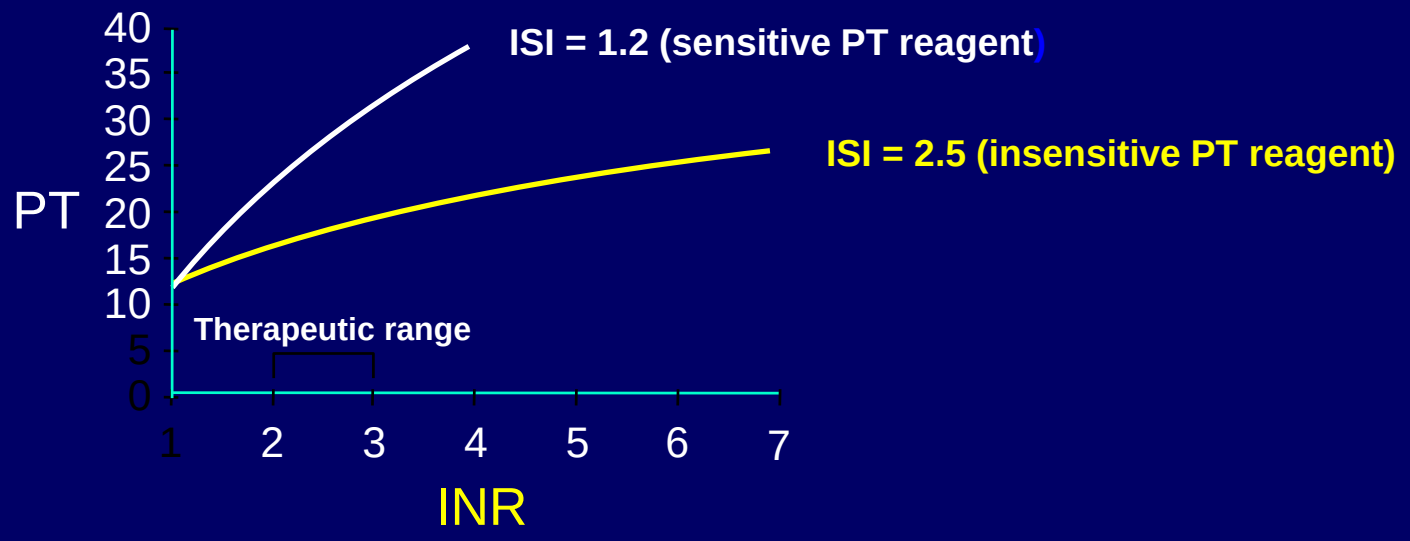
Clearance of Vitamin K-dependent Proteins



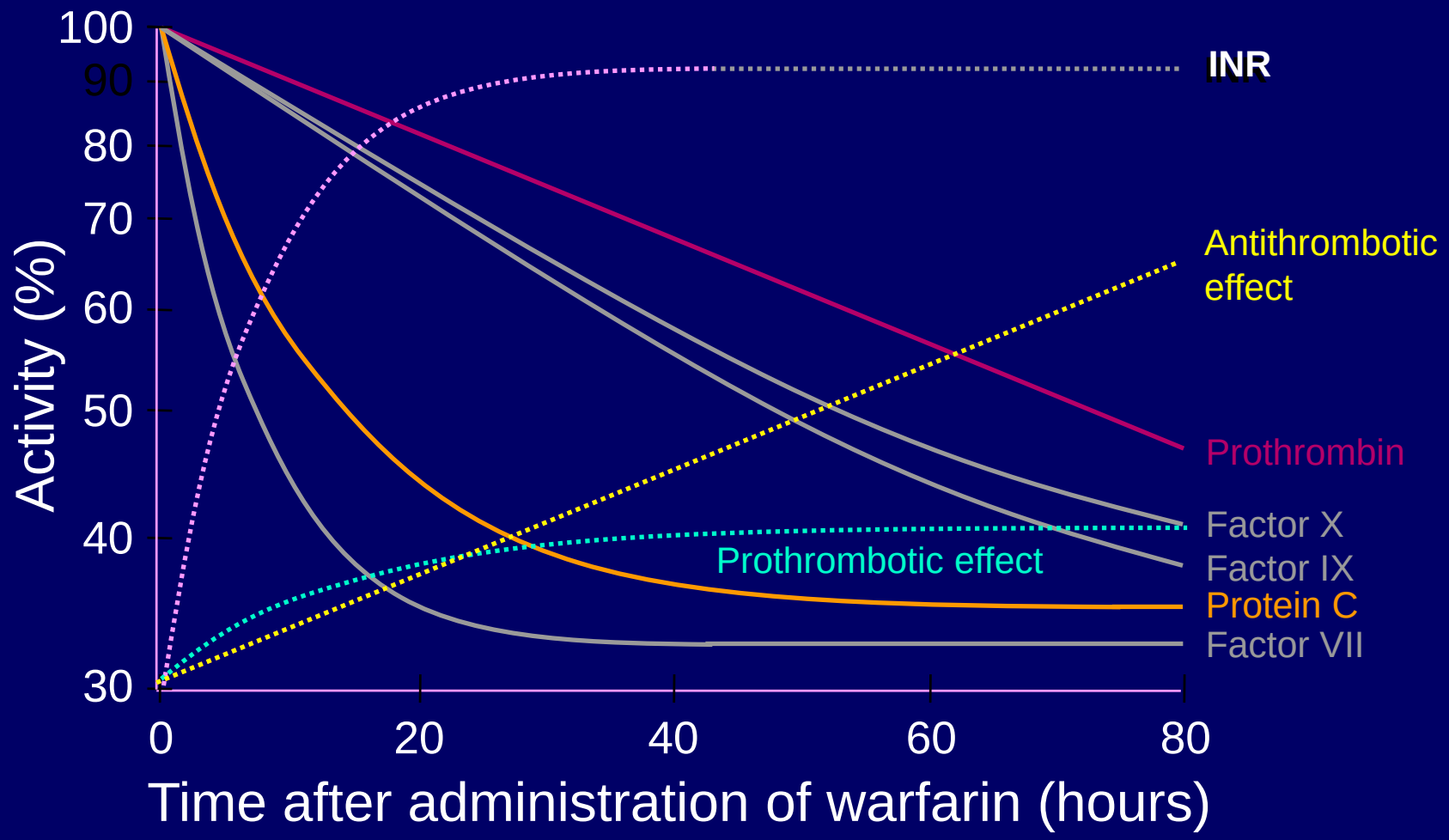
International Normalized Ratio (INR)

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

C = International Sensitivity Index



Clearance of Vitamin K-dependent Proteins



Conditions that Alter the Response to Warfarin

Compliance

Drugs
- Affect hepatic metabolism of warfarin
- Affect binding to plasma proteins

Diet
- Availability of vitamin K

Other conditions
- Nephrotic syndrome (low plasma albumin)
- Pregnancy (high levels of coagulation factors)
- Liver disease (low levels of coagulation factors)

Complications of Warfarin Therapy

Bleeding

Risk increases with INR > 4
Treated with vitamin K
or fresh-frozen plasma (immediate response)

Birth defects and abortion

Skeletal and CNS abnormalities (hypoplastic nose, flat face, altered calcification)
Contraindicated during pregnancy
(heparin may be used)

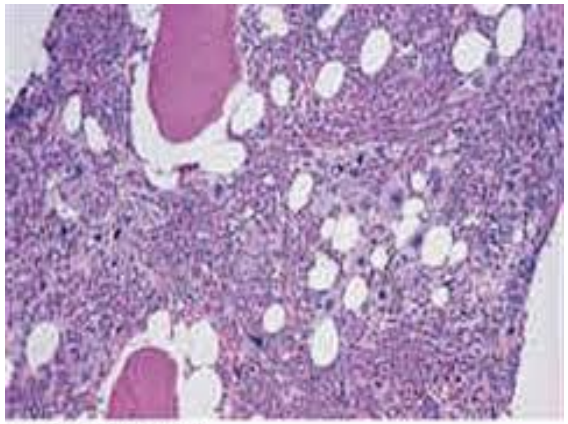
Skin necrosis

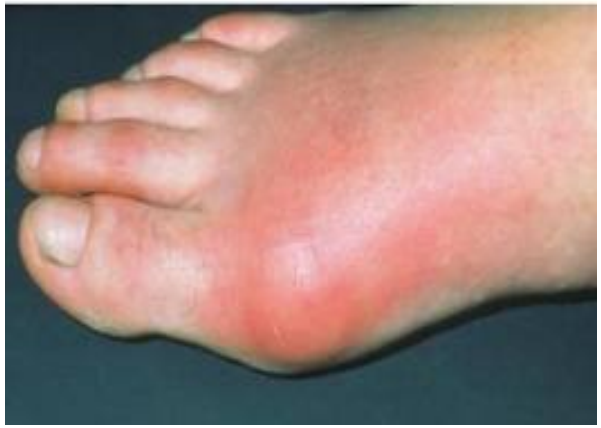
Microvascular thrombosis
In patients with heterozygous
protein C or S deficiency if a high initial dose is used or heparin overlap is inadequate

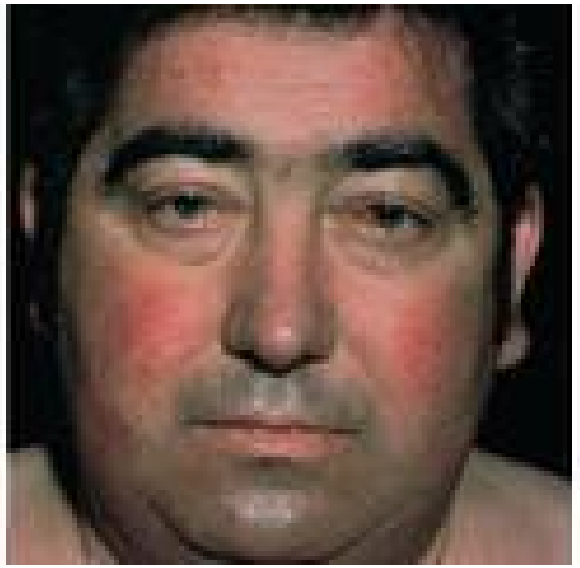
Case 8

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

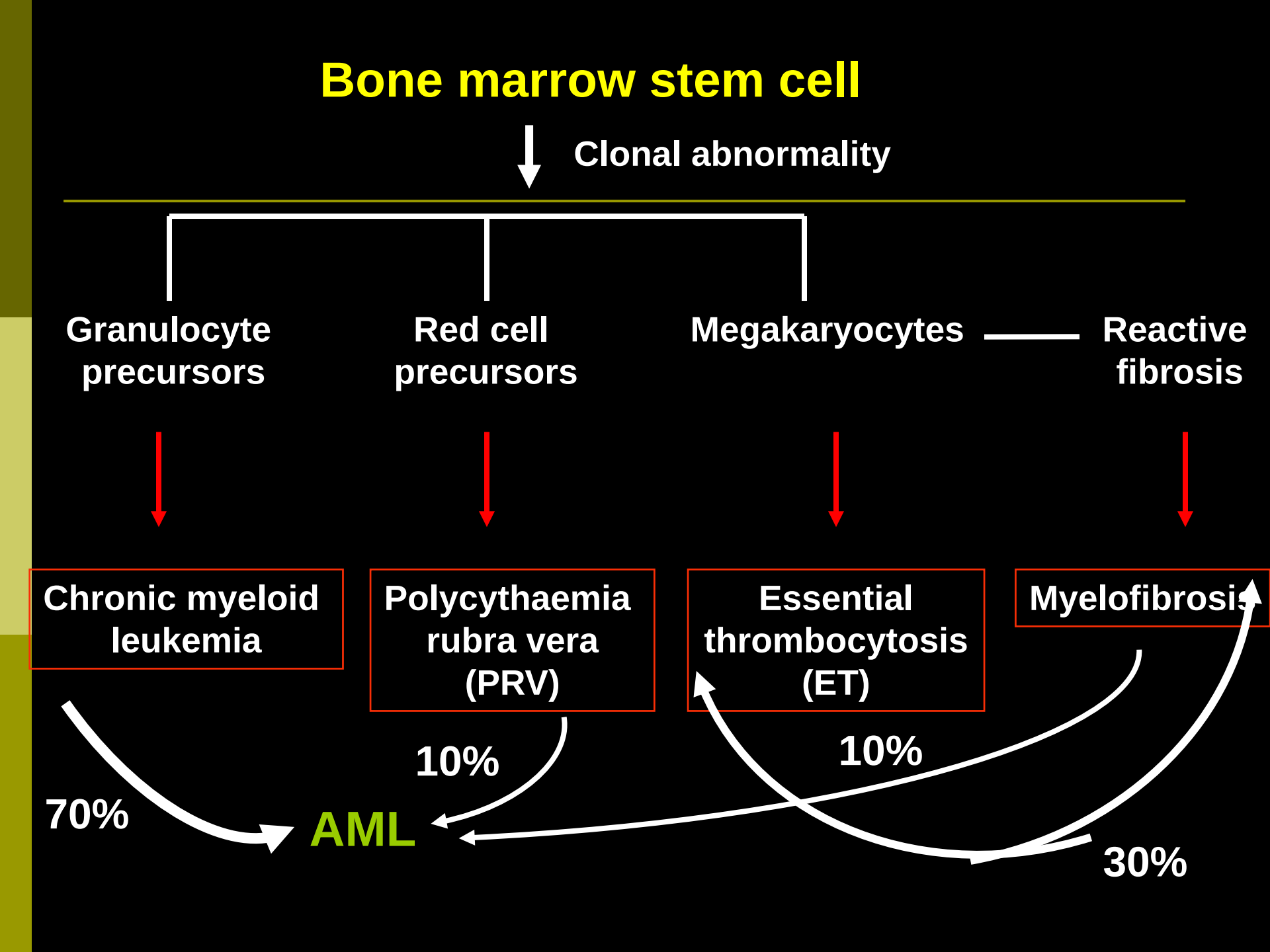
Myeloproliferative Neoplasms

Common features

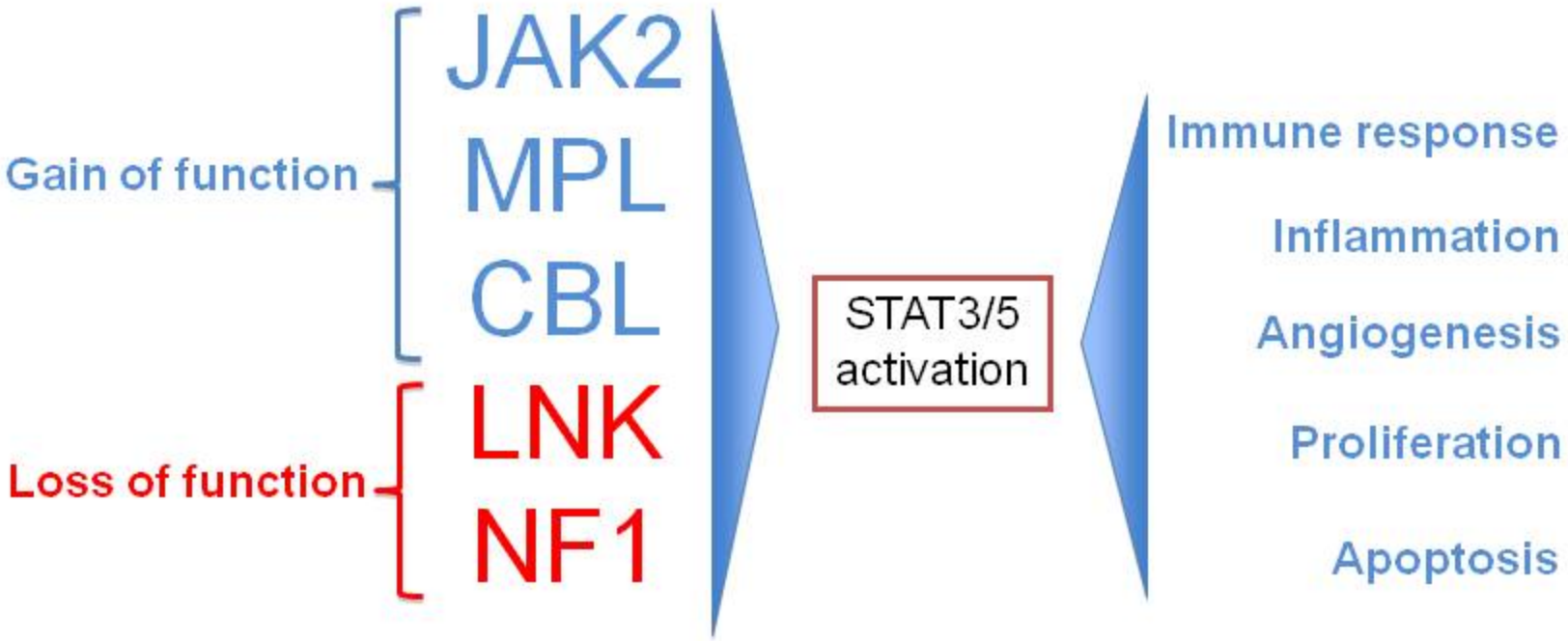
- Specific clincopathologic criteria for diagnosis and distinct diseases, have common features
- Increased number of one or more myeloid cells
- splenomegaly
- Hypercatabolism: wt loss, gout
- Clonal marrow hyperplasia without dysplasia
- Predisposition to evolve

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

Bone marrow stem cell

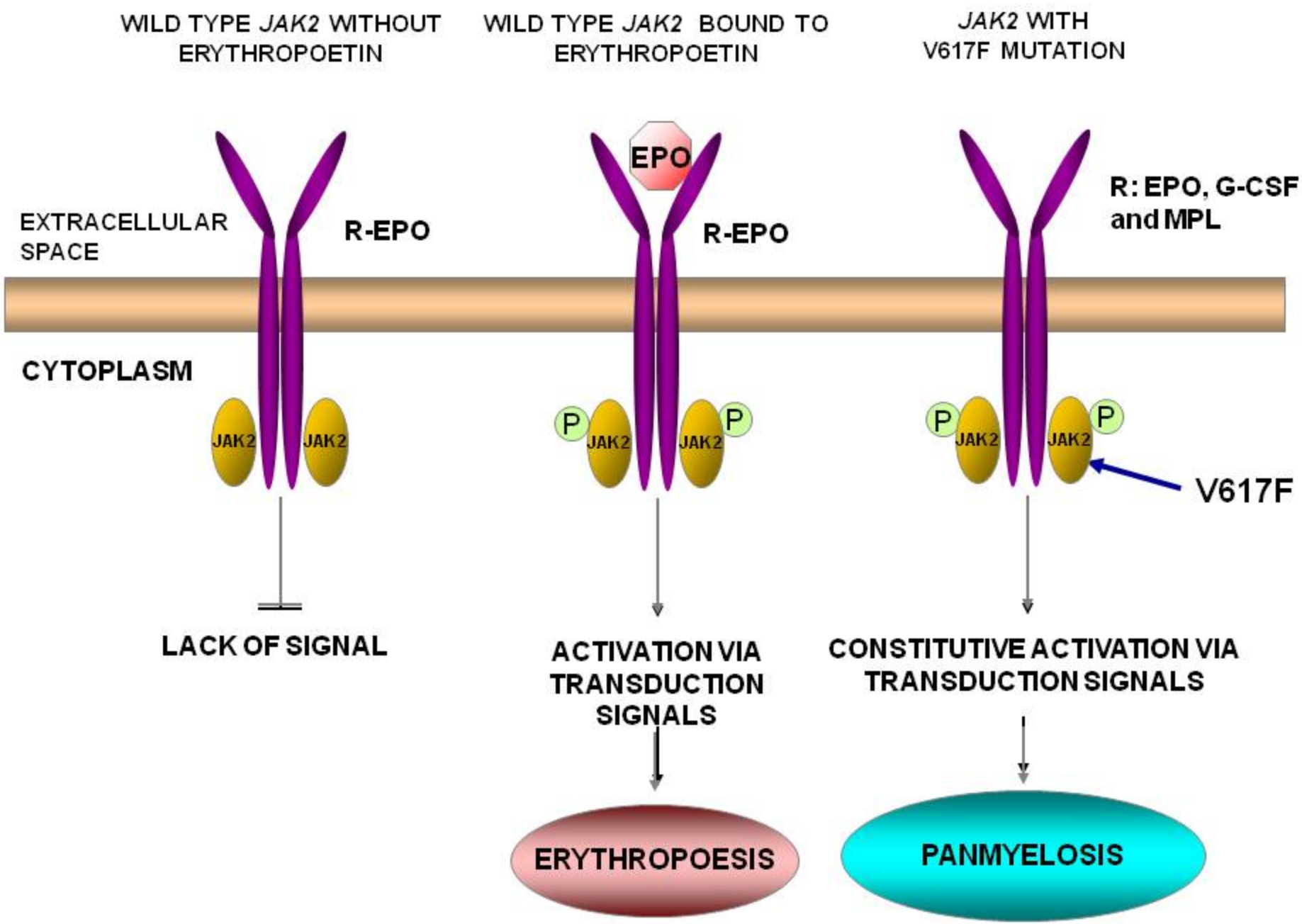


Role of mutations in chronic phase of MPN



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



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

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)

Diagnostic Criteria (Conventional): PRV

A1	Raised red cell mass
A2	Normal O2 sats and EPO
A3	Palpable spleen
A4	No BCR-ABL fusion
B1	Thrombocytosis >400 x 109/L
B2	Neutrophilia >10 x 109/L
B3	Radiological splenomegaly
B4	Endogenous erythroid colonies

A1+A2+either another A or two B establishes PV

JAK2/ serum erythropoeitin

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

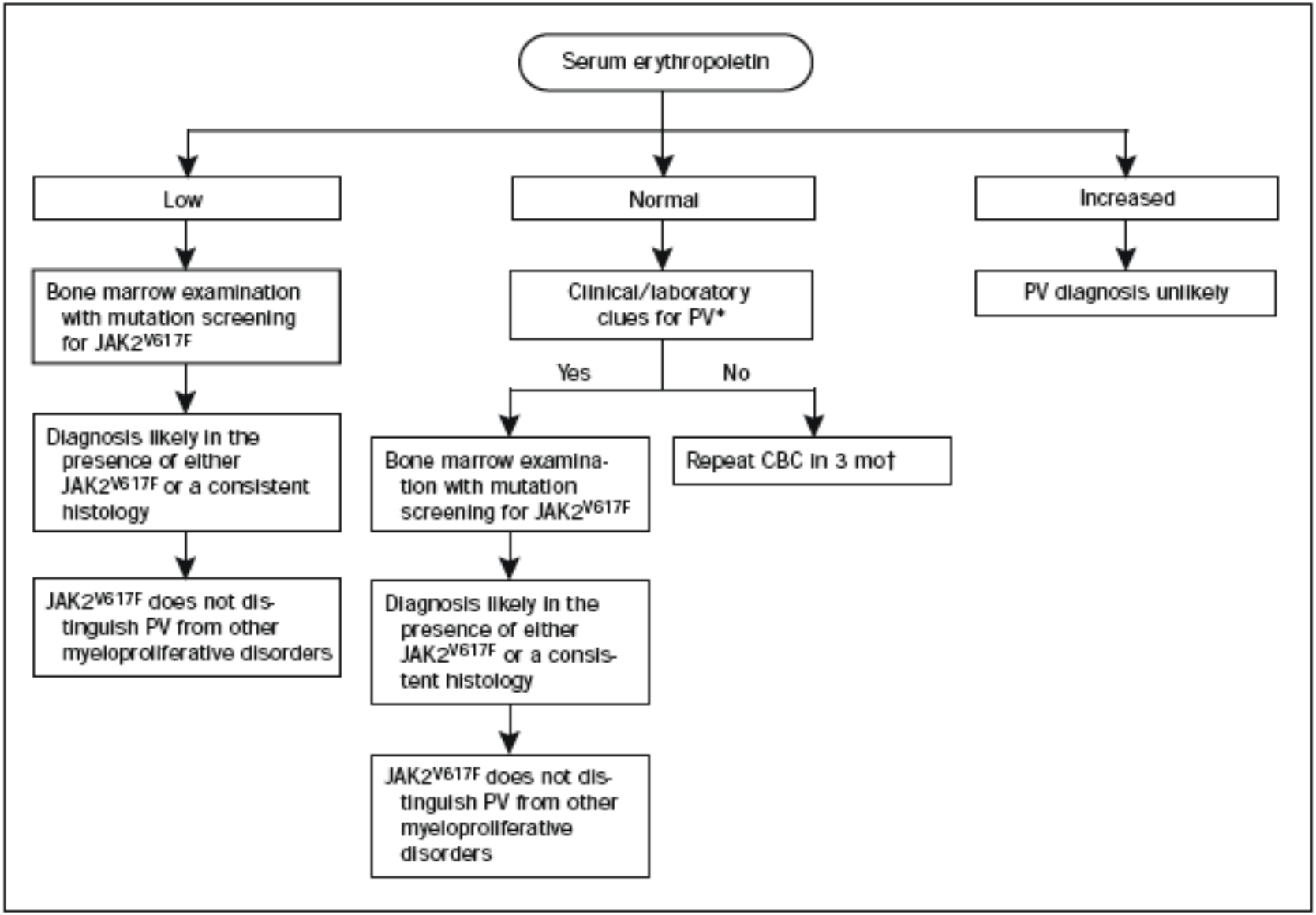


FIGURE 1. Diagnostic algorithm for polycythemia vera (PV).

*Clinical clues for PV include splenomegaly, thrombosis, aquagenic pruritus, and erythromelalgia. Laboratory clues for PV include thrombocytosis, leukocytosis, and increased leukocyte alkaline phosphatase score. Janus kinase 2 (JAK2) screening is to detect the V617F mutation that occurs in most patients with PV. BM = bone marrow; CBC = complete blood cell count; MPD = myeloproliferative disorders.

†Alternatively, one can consider mutation screening for $JAK2^{V617F}$ to help decide necessity of BM examination.

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]

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

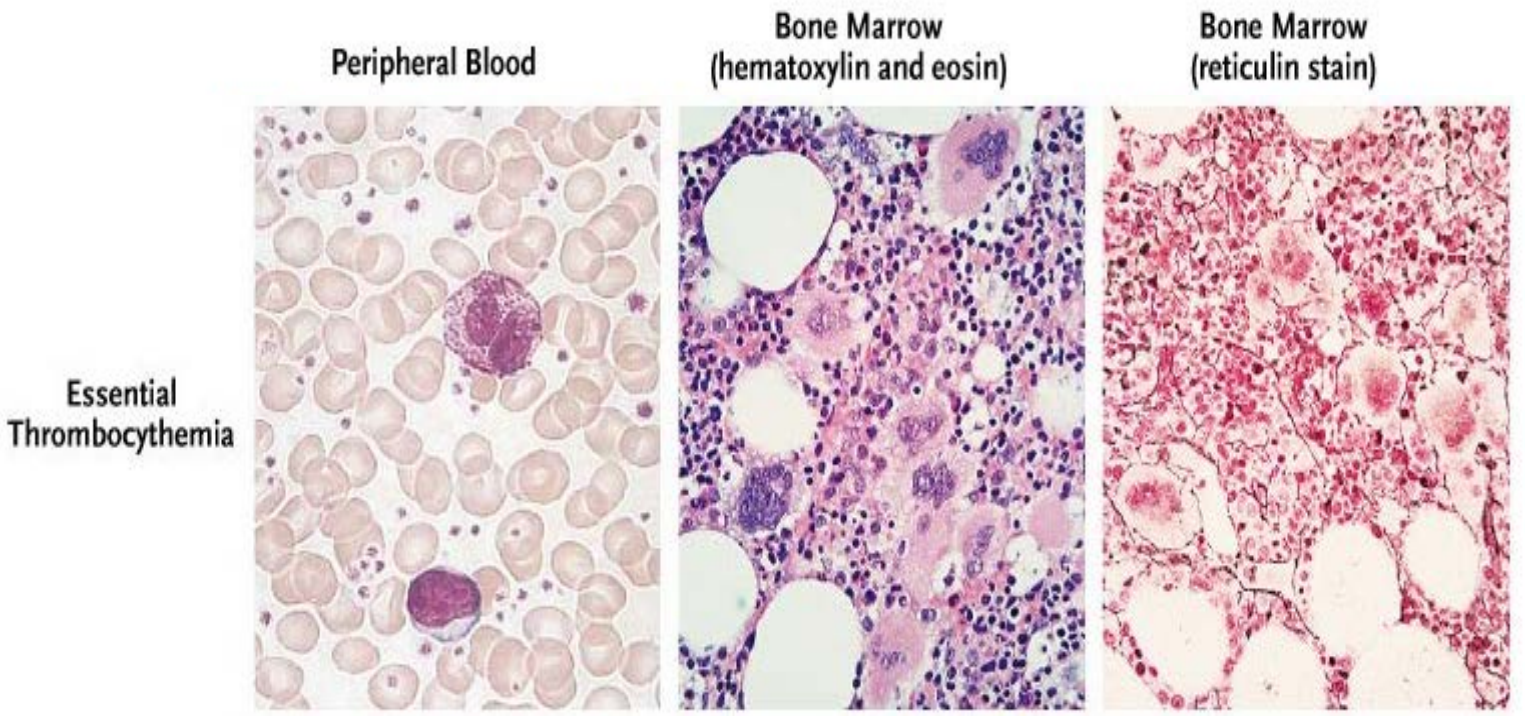
ELN recommendations: Barbui T. et al., J Clin Oncol. 2011 Jan 4. [Epub ahead of print]

Essential Thrombocythemia: 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"

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