Bleeding & Thrombotic Disorders

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Outline

I. Physiology of haemostasis

II. Clinical aspects of bleeding

III. Approach to evaluation of bleeding disorders

IV. Management options of bleeding disorders

V. Arterial thrombosis

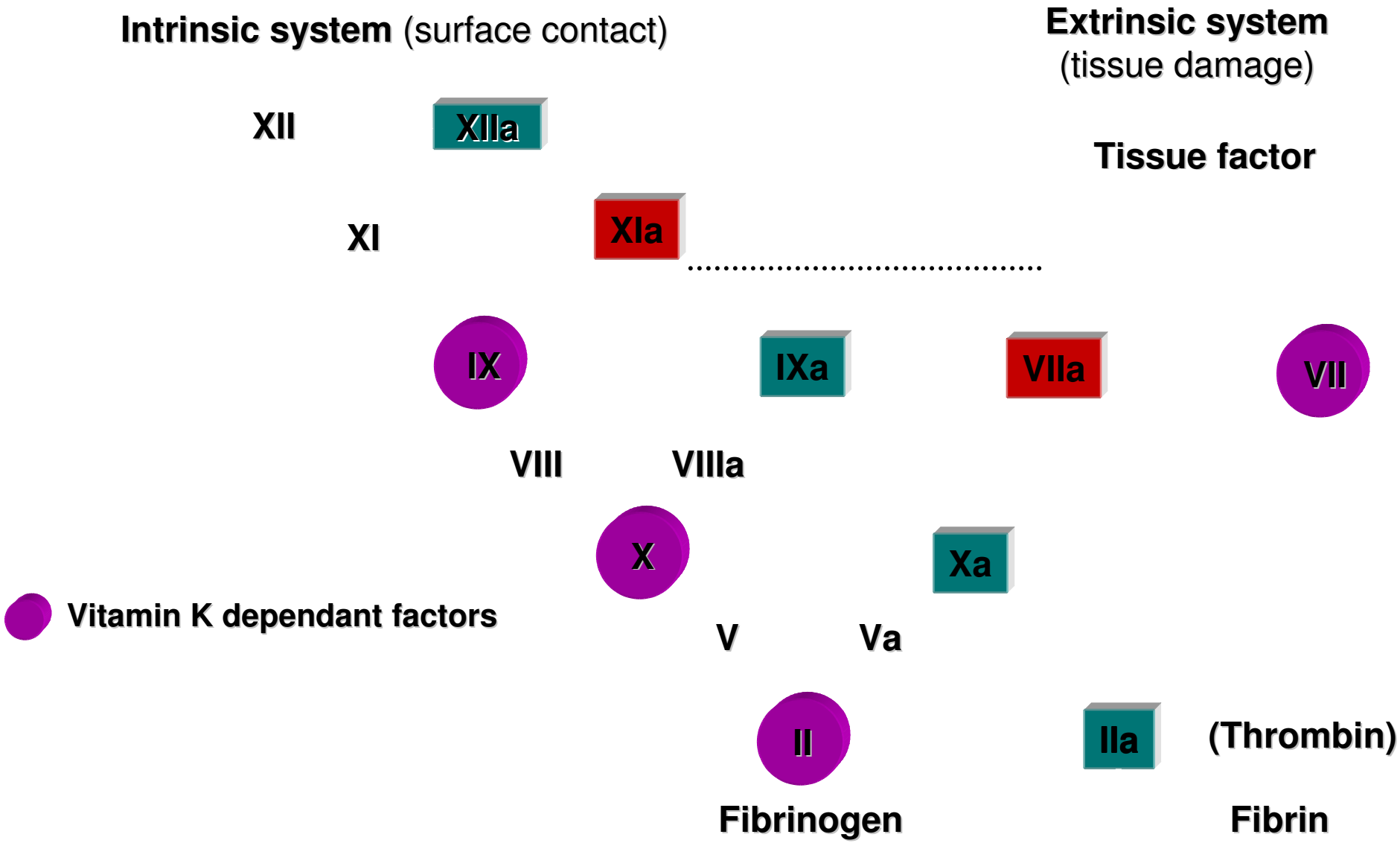
VI. Venous thrombosis

Stages of Haemostasis (凝血)

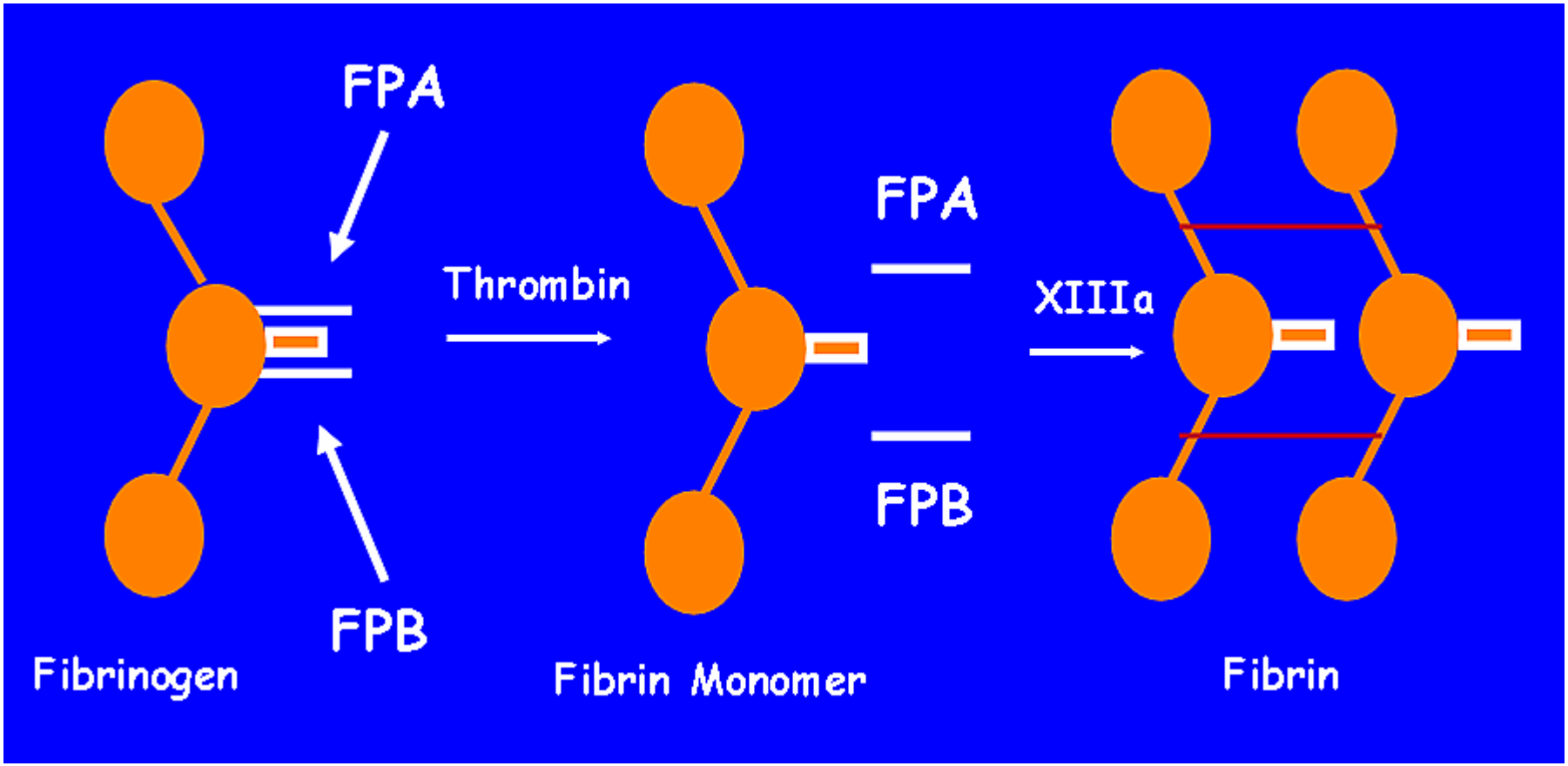
Response to vessel injury

1. Vasoconstriction (血管收縮) to reduce blood flow
2. Primary Haemostasis: platelet plug formation
   - von Willebrand factor binds damaged vessel and platelets
3. Secondary Haemostasis
   - Activation of coagulation cascade (凝血階梯)
4. Tertiary Haemostasis
   - Cross-linking of fibrin strands
   - Clot maturation and wound healing

Secondary Haemostasis: Coagulation cascade



Tertiary Haemostasis

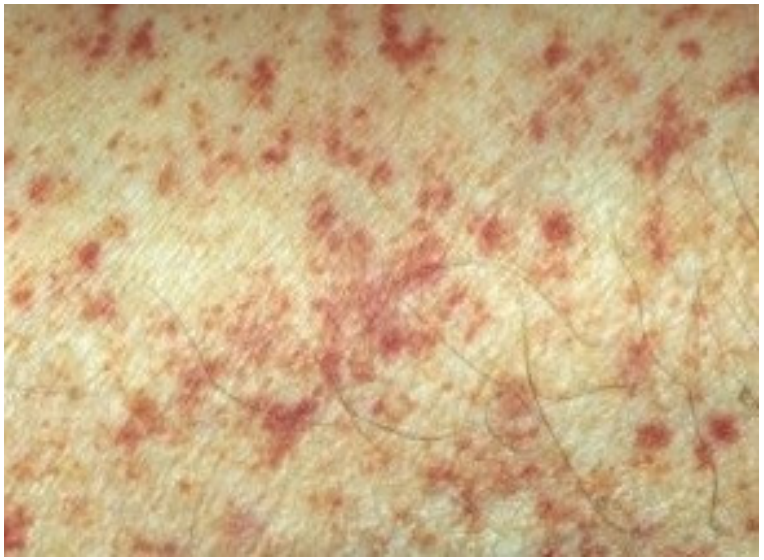


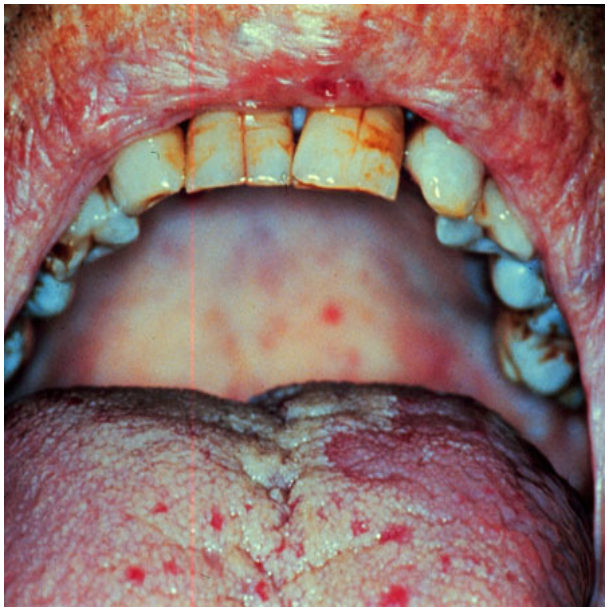
Clinical Features of Bleeding Disorders

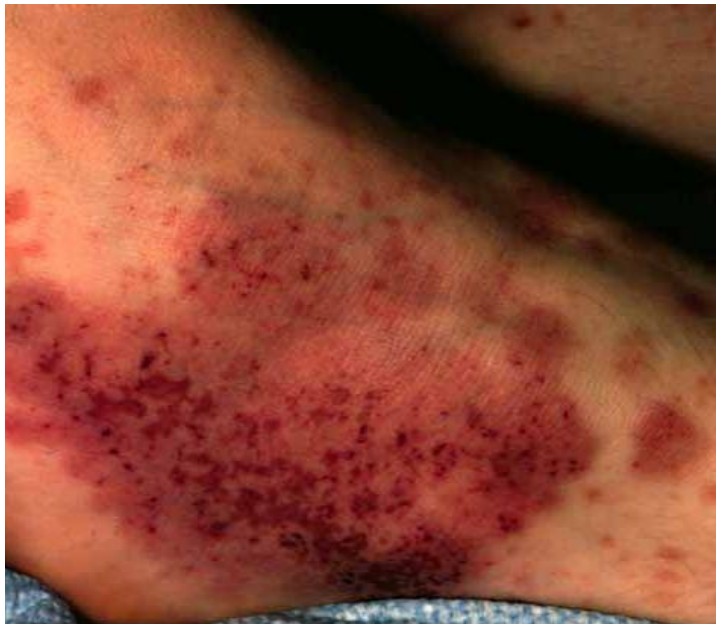
	Platelet disorders	**Coagulation factor disorders**
Site of Bleeding	Skin Mucous membrane (epistaxis, gum vaginal, GI tract)	Deep in soft tissue (joints, muscle)
Petechiae	Yes	No
Ecchymoses (bruises)	Small, superficial	Large, deep
Haemarthrosis / muscle bleeding	Extremely rare	Common
Bleeding after cuts & scratches	Yes	No
Bleeding after surgery or trauma	Immediate usually mild	Delayed (1-2 days) often severe

Petechiae (瘀點)

Typical of platelet disorders



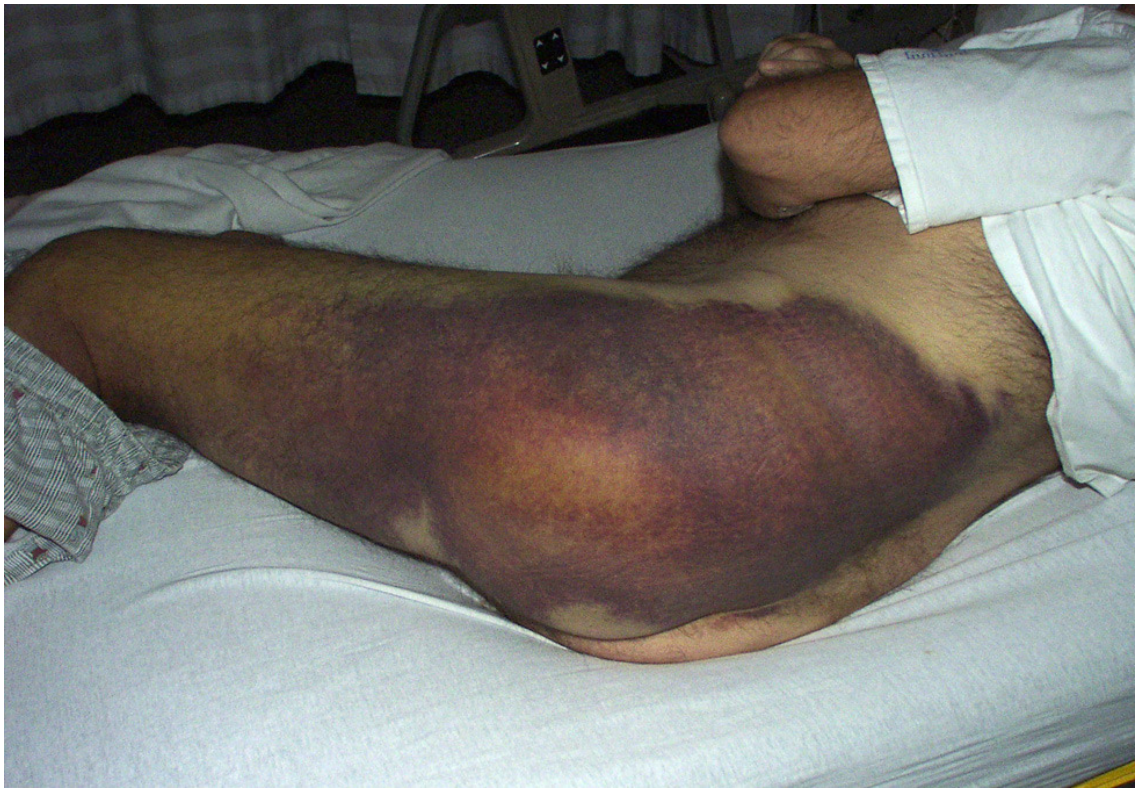


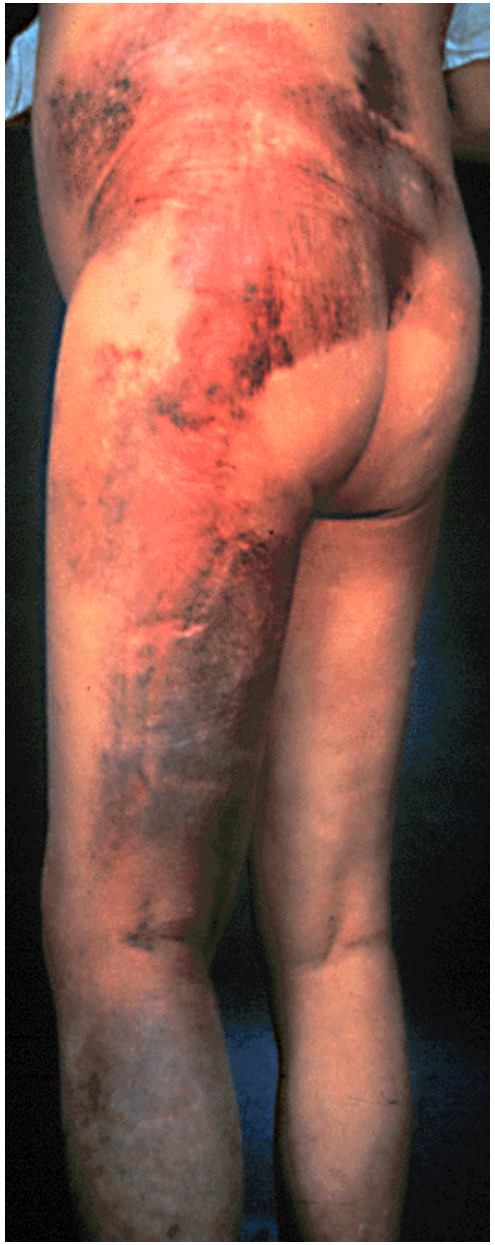


Do not blanch with pressure
(cf. angiomas 血管瘤)
Not palpable
(cf. vasculitis 血管炎)

Ecchymoses (瘀斑)

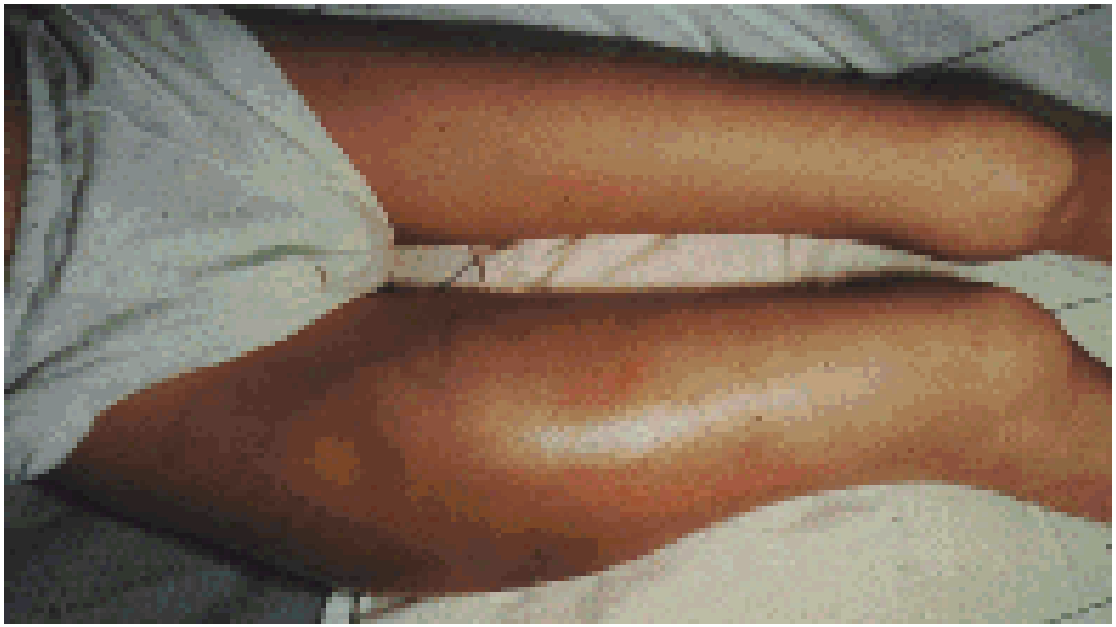
Typical of coagulation factor disorders

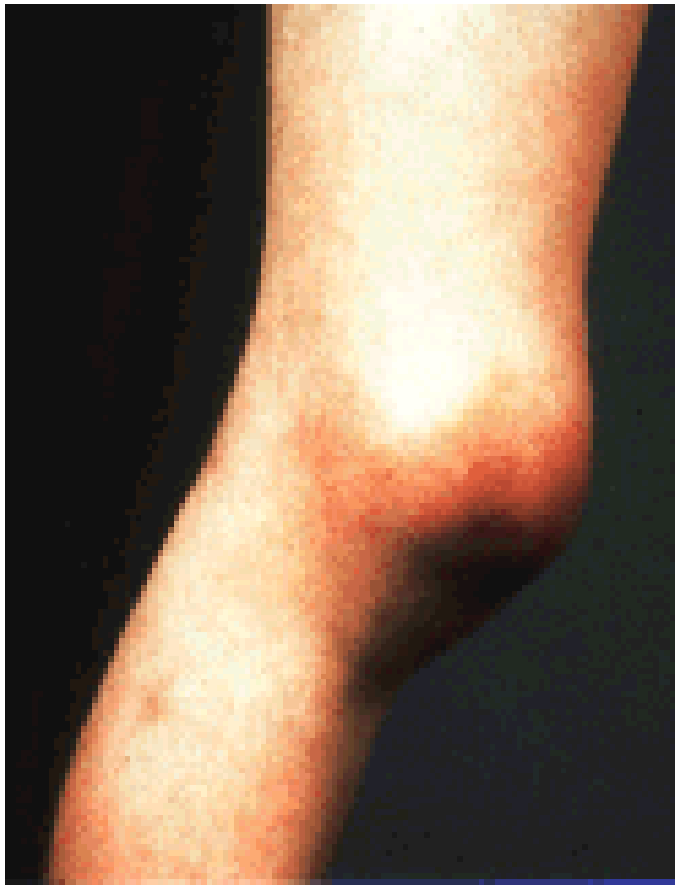




Haemarthrosis (關節積血) /Muscle Bleeding

Typical of coagulation factor disorders





Personal Bleeding History

- Childhood: excessive bleeding from simple scrapes and cuts
- Mucosal bleeding: epistaxis (鼻出血), gingival (齒齦) or haemorrhoidal (痔瘡)
- Gynaecologic: menorrhagia (經血過多), post-partum bleeding (產後血崩)
- Bleeding after surgery, dental extraction
- Haemarthrosis (關節積血)

- How easy? How frequent? Duration, amount of bleeding
- Type of insults/injuries associated with bleeding
- Transfusion requirement

- ? Non-accidental trauma

History

- Past history
  - Renal or hepatic disorders , connective tissue (結締組織) or rheumatologic disorders (風濕病), GI problems or malabsorptive state (吸收不良)

- Drug history
  - Aspirin, anticoagulant (抗凝血劑), antibiotics, etc

- Family history
  - X-linked recessive: haemophilias (血友病)
  - Autosomal dominant: von Willebrand diseases (血管性血友病. vWD)
  - Autosomal recessive: others

Physical Examination

- Size, location, and distribution of ecchymoses, hematomas, petechiae, and other areas of bleeding

- Are there signs of systemic diseases (rheumatoid arthritis 風濕性關節炎, leukaemia 白血病, liver disease, etc)
  - Evidence of chronic liver disease
  - Lymphadenopathy (淋巴結腫大), hepatosplenomegaly (肝脾腫大)

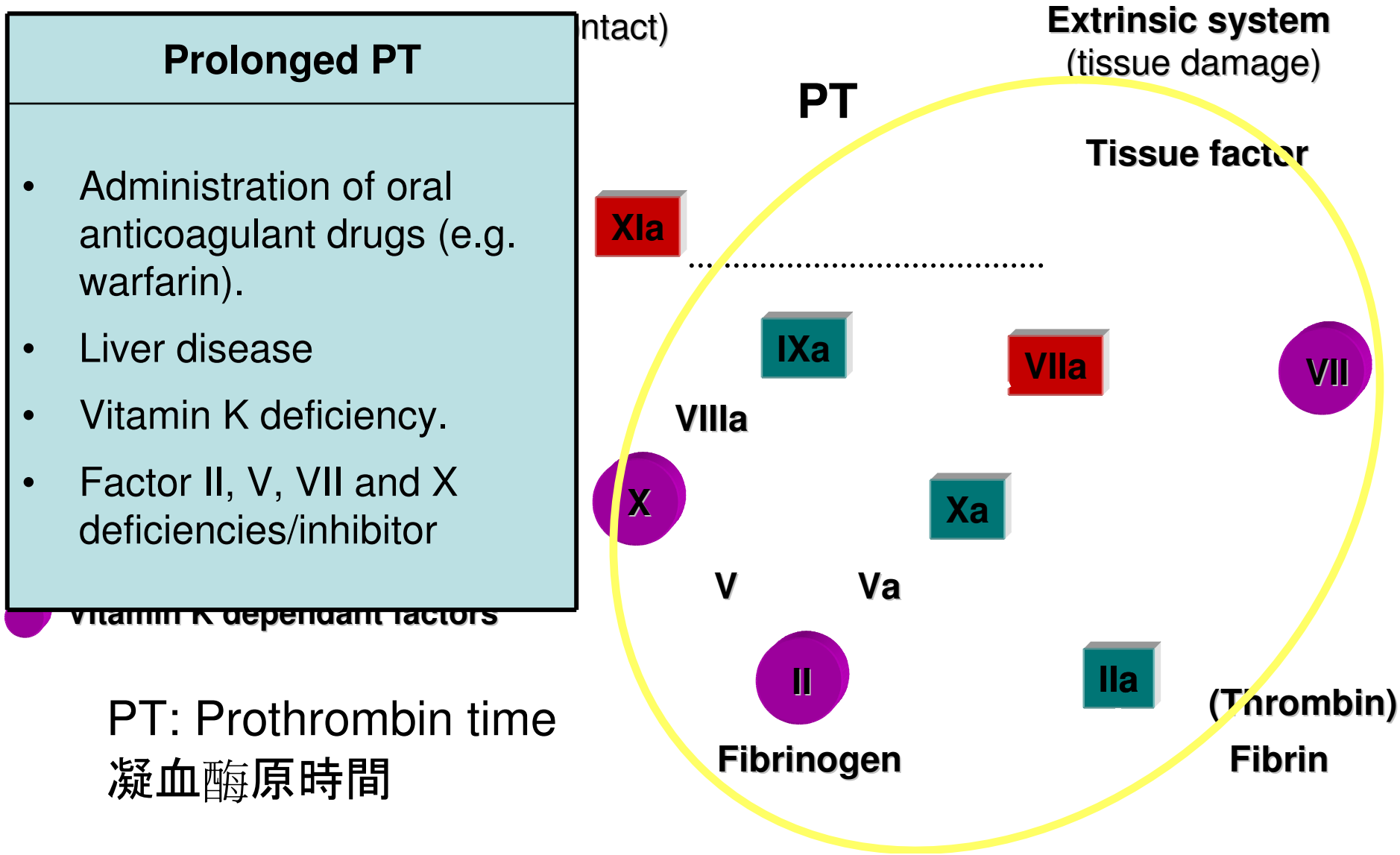
Laboratory Evaluation of Bleeding - Overview

CBC and smear	Platelet count	Thrombocytopenia
	RBC and platelet morphology	TTP, DIC, etc.
Coagulation pathways	Prothrombin time	Extrinsic/common
	Partial thromboplastin time	Intrinsic/common
pathways		
	Coagulation factor assays	Specific factor deficiencies
	50:50 mix	Inhibitors (e.g., antibodies)
	Fibrinogen assay	Decreased fibrinogen
	Thrombin time	Qualitative/quantitative fibrinogen defects
	FDPs or D-dimer	Fibrinolysis (DIC)
Platelet function	von Willebrand factor	vWD
	Bleeding time	*In vivo* test (non-specific)
	Platelet function analyzer (PFA)	Qualitative platelet and vWD
disorders		
	Platelet function tests	Qualitative platelet
disorders		

Coagulation cascade

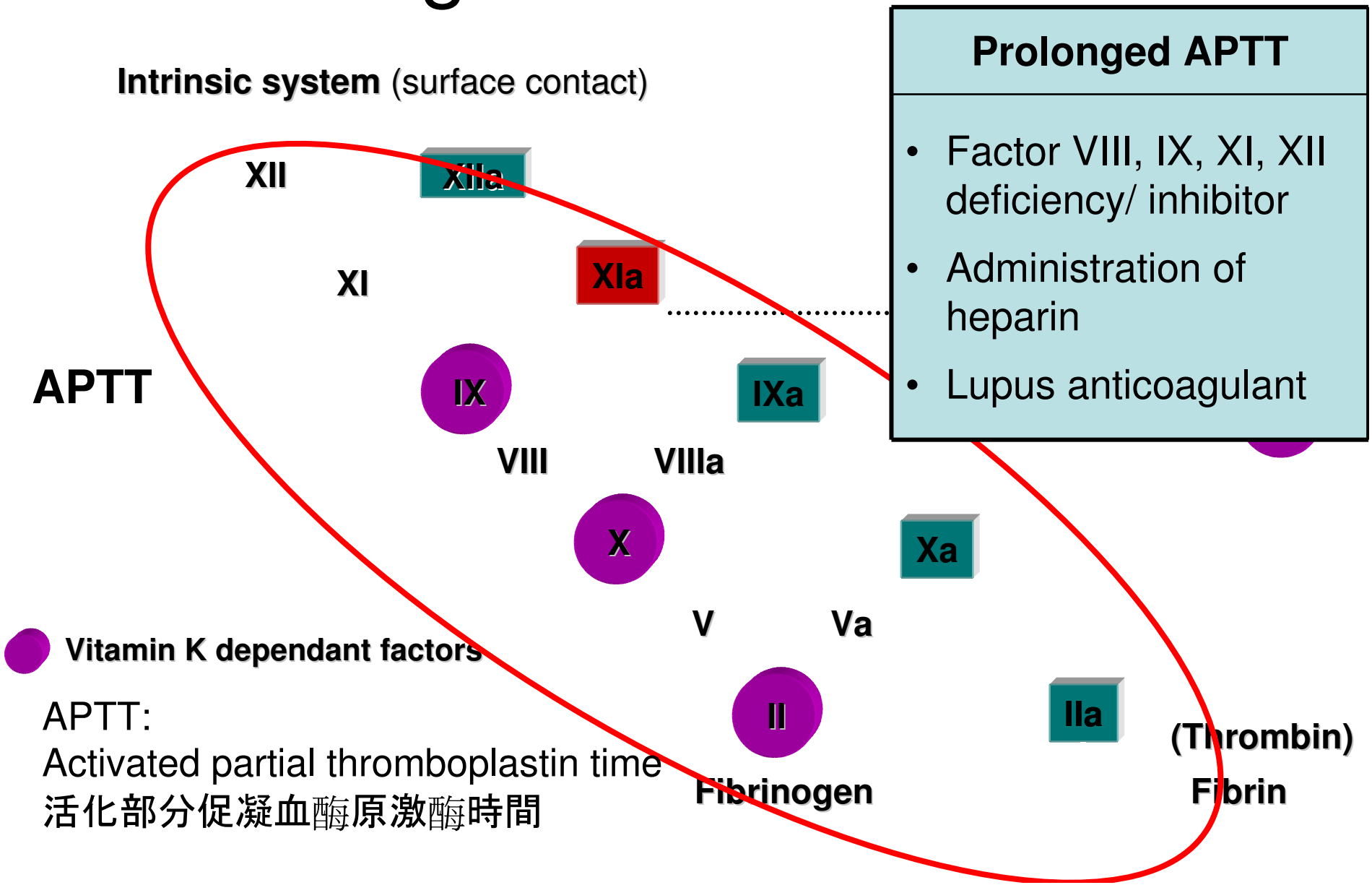
Prolonged PT

- Administration of oral anticoagulant drugs (e.g. warfarin).
- Liver disease
- Vitamin K deficiency.
- Factor II, V, VII and X deficiencies/inhibitor



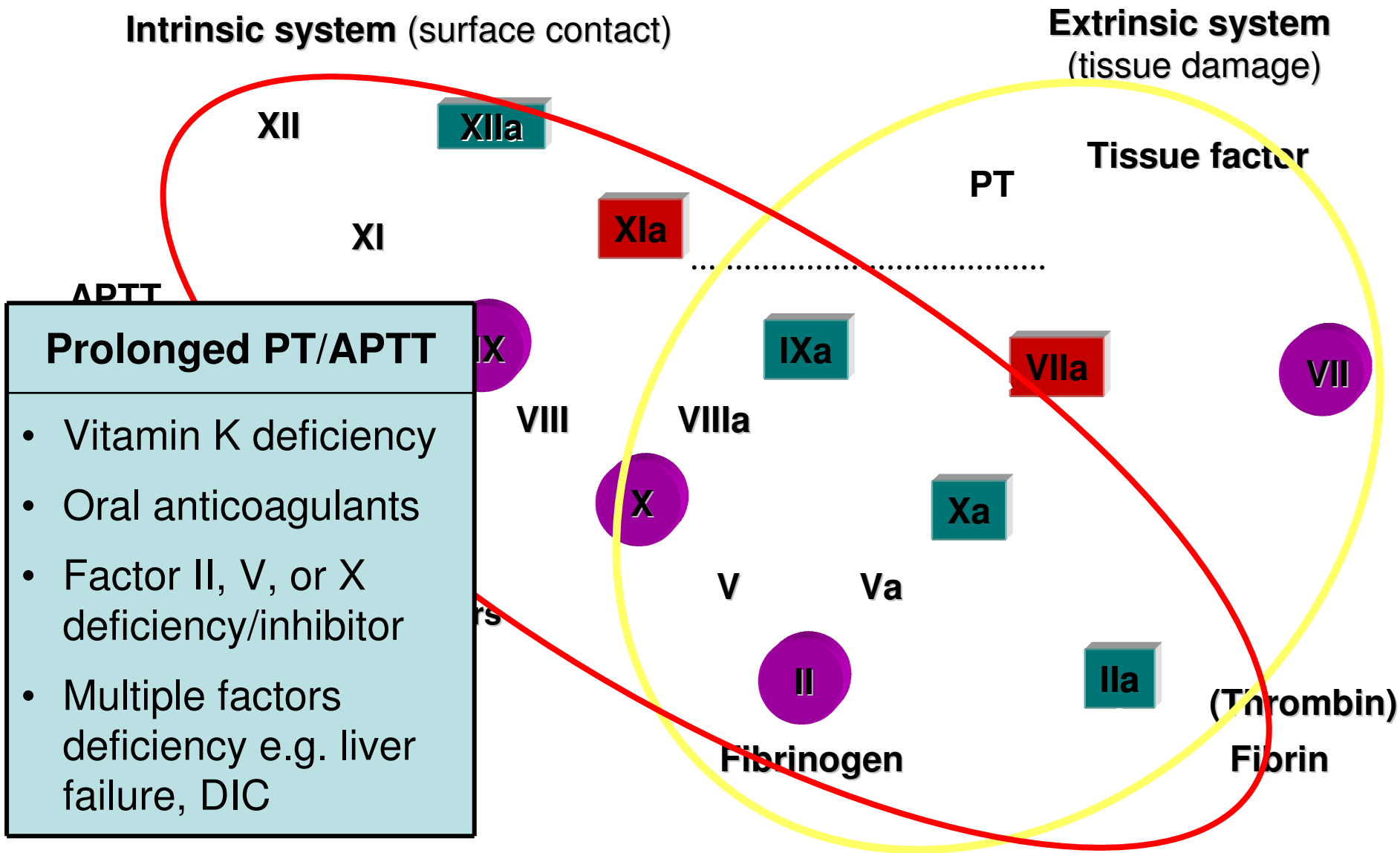
PT: Prothrombin time
凝血酶原時間

Coagulation cascade

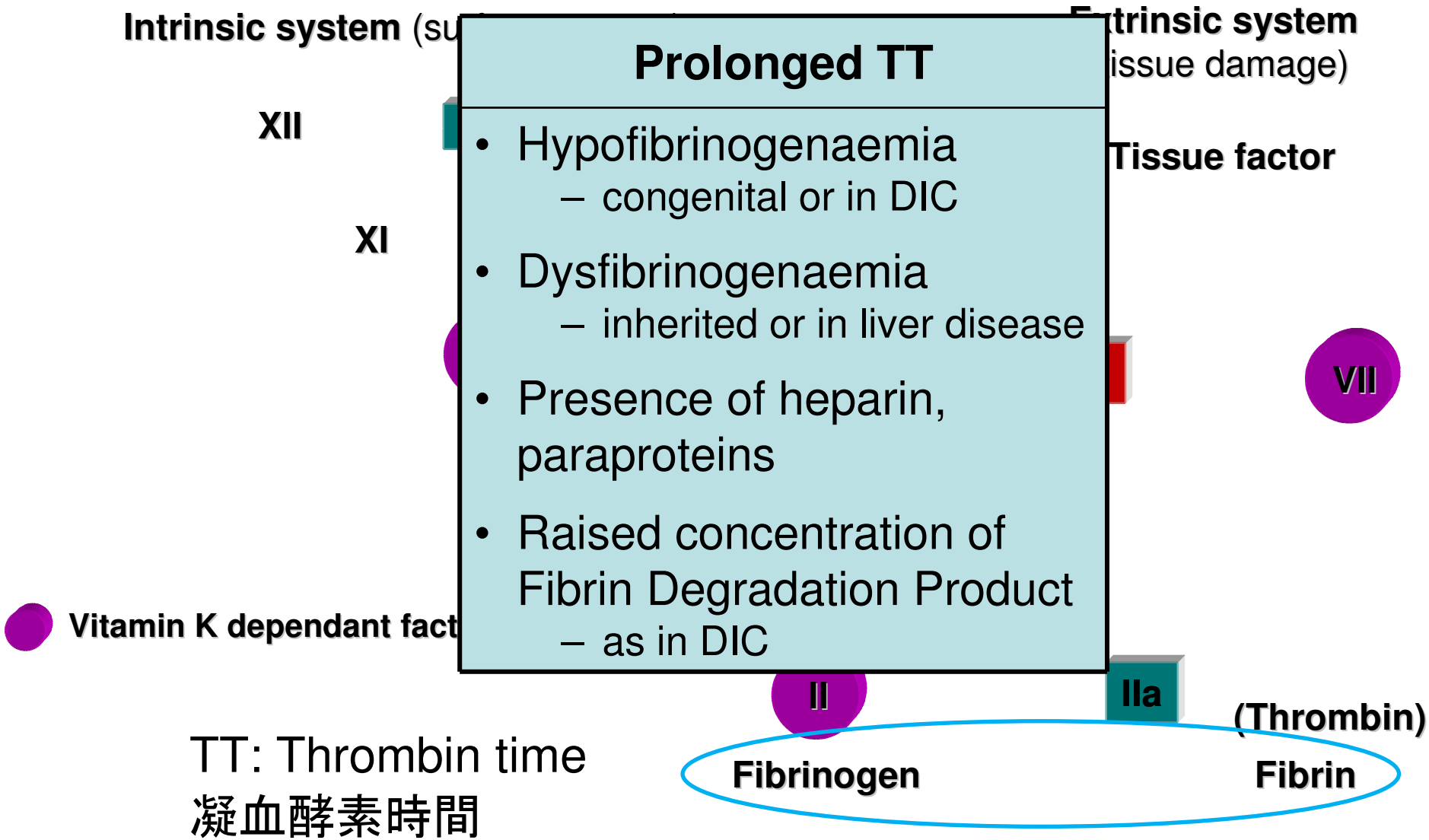


APTT:
Activated partial thromboplastin time
活化部分促凝血酶原激酶時間

Coagulation cascade



Coagulation cascade

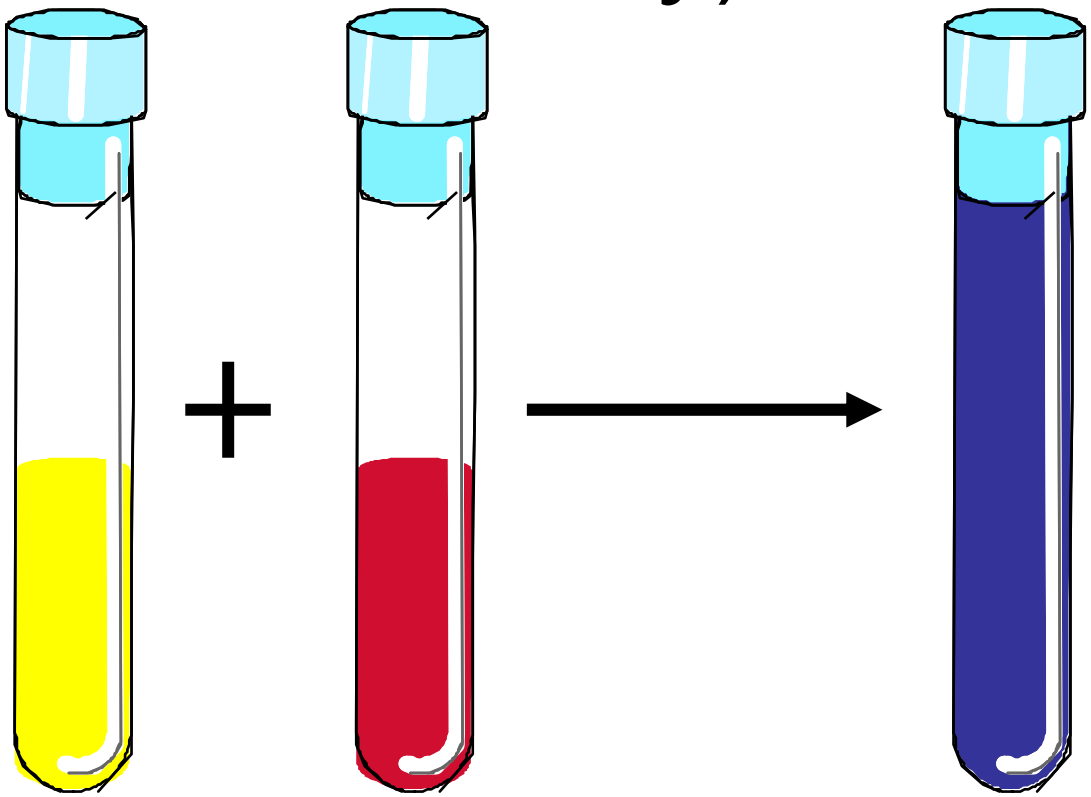


TT: Thrombin time
凝血酵素時間

Abnormal clotting profile

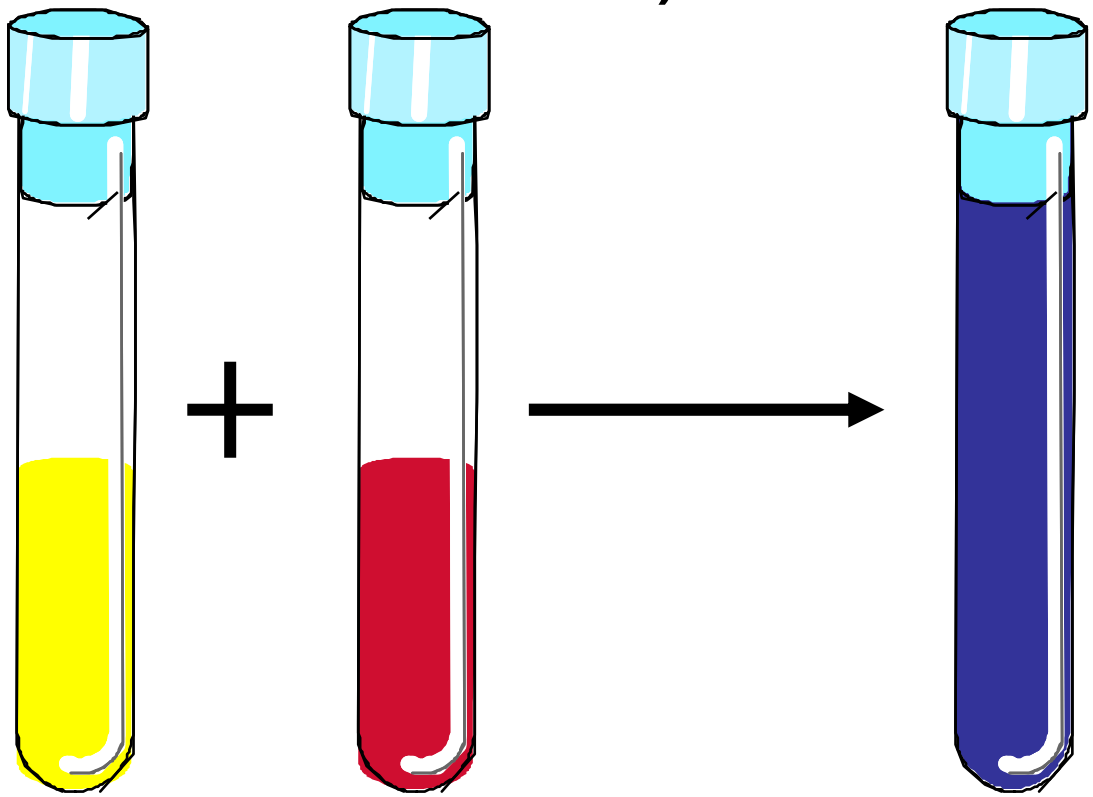
- Clotting factor deficiency
- Presence of inhibitor (抑制物)
  - antibodies which inhibit the function of the clotting factor
- A 50:50 mixture of normal and test plasma and then repeat the test

1:1 Mixing Test (Factor Deficiency)



F VIII	0%	100%	50%
APTT	120s	30s	35s

1:1 Mixing Test (Factor Inhibitor)



Inhibitor	+	-	+
APTT	120s	30s	120s

Management Options for Bleeding

- Blood product transfusion
  - Red cells
  - Fresh frozen plasma (血漿, FFP)
  - Platelet concentrate
  - Cryoprecipitate 低溫沉澱物 (contains Factor VIII, von Willebrand factor, fibrinogen)
- Factor concentrates
- Desmopressin 去氨加壓素 (DDAVP)
- Antifibrinolytic agents 抗纖維蛋白溶解劑 (e.g. tranexamic acid 氨甲環酸)
- Recombinant human factor VIIa 基因重組活化凝血因數VII

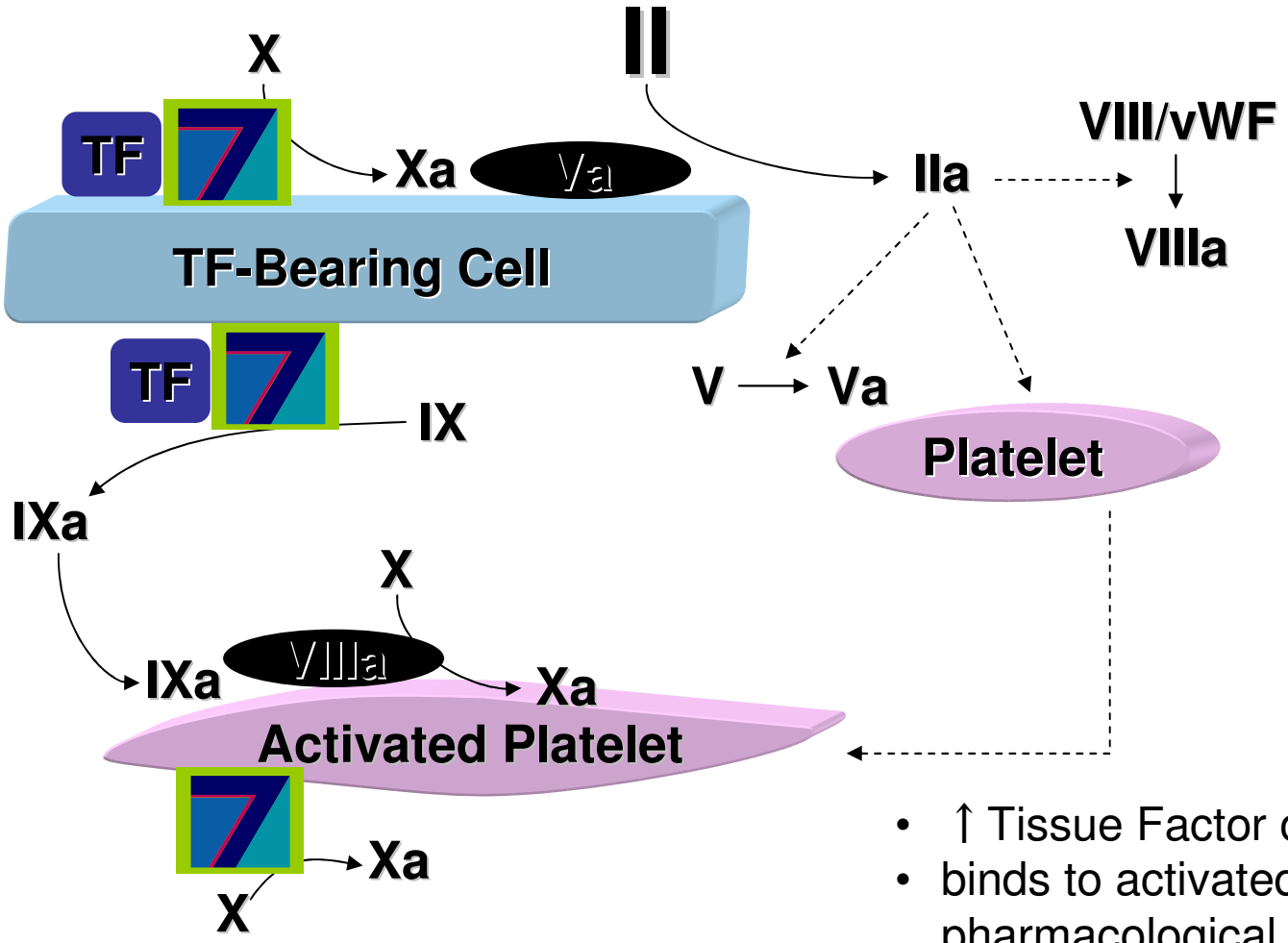
Antifibrinolytic Agents 抗纖維蛋白溶解劑

- Example: tranexamic acid 氨甲環酸
- Mechanism
  - Prevent activation plasminogen 纖維蛋白溶 原-> plasmin 纖維蛋白溶
- Uses
  - Primary menorrhagia (原發性經血過多)
  - Haemophilias (血友病), vWD for dental extractions
  - Bleeding in patients with thrombocytopenia
  - Blood loss during cardiac surgery
- Side effects
  - GI toxicity
  - Thrombus (血栓) formation

Desmopressin 去氨加壓素 (DDAVP)

- Mechanism
  - Increased release of vWF from endothelium
- Dose
  - 0.3μg/kg IV q12 hrs
  - 150mg intranasal q12hrs
- Uses
  - Most patients with von Willebrand disease
  - Mild hemophilia A
- Side effects
  - Facial flushing and headache
  - Water retention and hyponatremia

Recombinant FVIIa: Mechanism of Action



- ↑ Tissue Factor occupancy
- binds to activated platelets in pharmacological doses
- provides Factor X activation independent of Tissue Factor

Recombinant Human Factor VIIa (rFVIIa; *Novoseven®*)

- Use
  - Treatment of bleeding and prevention of bleeding in surgery in patients with Factor VIII & IX inhibitors, factor VII deficiency (approved indications)
  - Bleeding with other clotting disorders
  - CNS bleeding, post-operative bleeding, etc

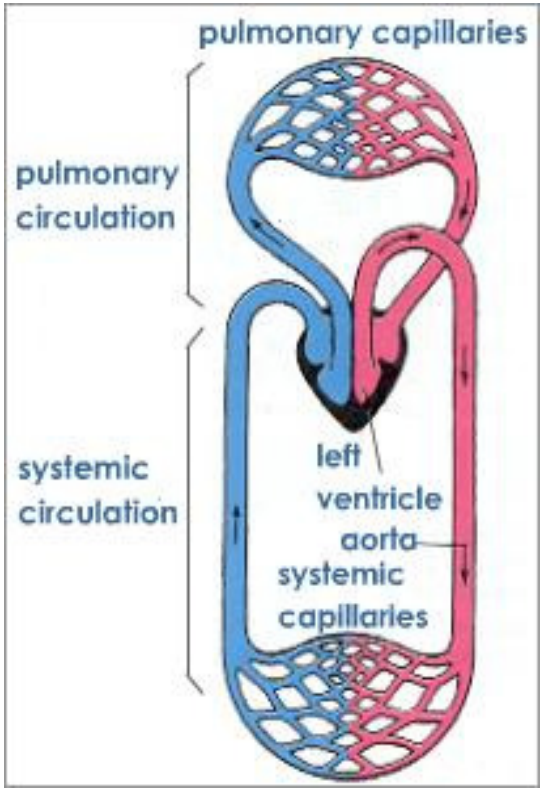
- Dose
  - 90 µg/kg IV q 2 hr
  - “Adjust as clinically indicated”
  - Range: 35 and 120 µg/kg
  - Very expensive

Mechanism of Clot Formation

Venous thrombosis

靜脈栓塞

- heavily dependent on excessive thrombin generation from soluble coagulation factors
- Anticoagulation is the key to effective treatment and prevention

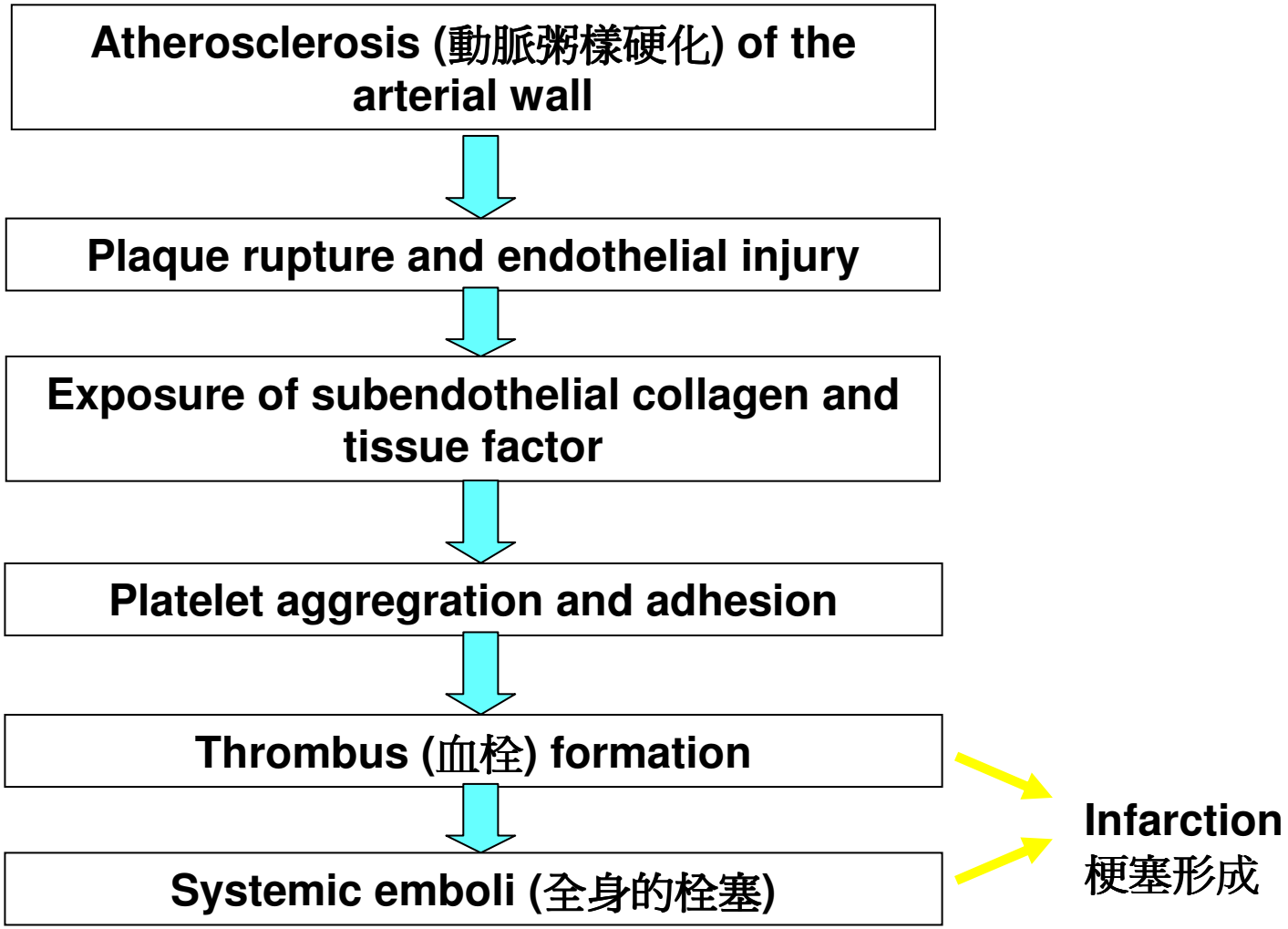


Arterial thrombosis

動脈栓塞

- dominated by platelets interacting with damaged endothelium
- Anti-platelet drug is the mainstay of treatment and prevention

Arterial Thrombosis

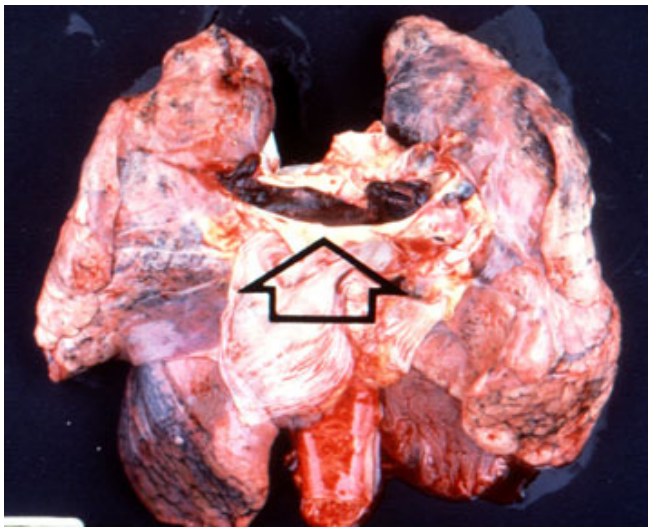


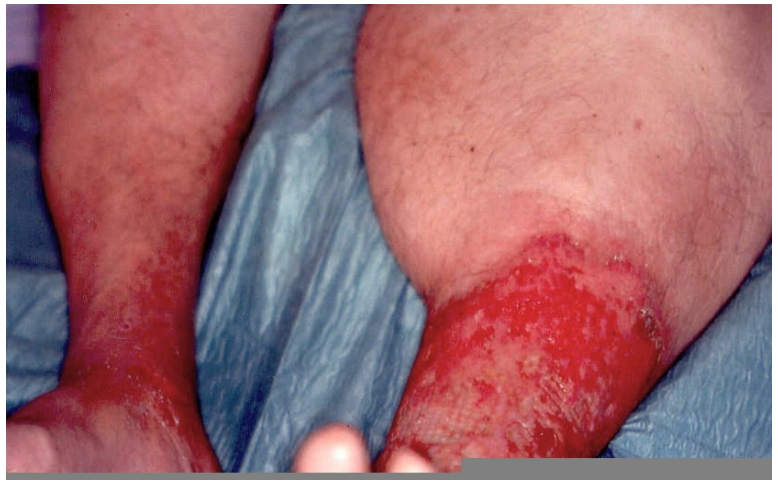
Risk factors of arterial thrombosis (artherosclerosis)

- Positive family history
- Male sex
- Smoker
- Hypertension 高血壓
- Diabetes mellitus 糖尿病
- Hyperlipidaemia 高血脂症
- Gout 痛風
- Polycythaemia 紅血球增多症
- Hyperhomocysteinaemia 高血高半胱胺酸
- Low serum folate, vitamin B12 and B6, etc

Venous thromboembolism 靜脈血栓栓塞 (VTE)

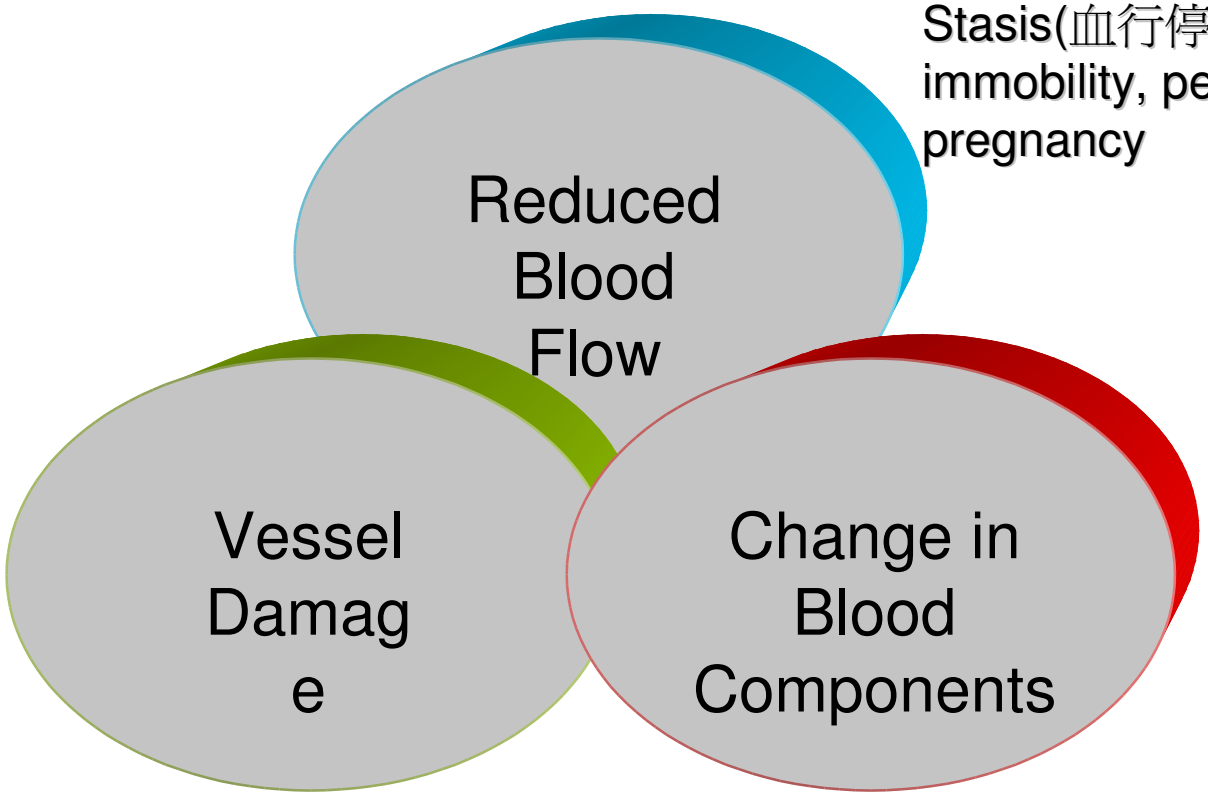
- Deep vein thrombosis (深靜脈栓塞症) and pulmonary embolism (肺栓塞)
- Massive pulmonary embolism causes up to 10% of all hospital deaths
- Complications of VTE
  - Death (1% of VTE fatal)
  - Post-thrombotic syndrome
  - Recurrent VTE
  - Complication of therapy





Venous thrombosis

Virchow's triad for venous thromboembolism:



Stasis(血行停滞): post-operation, immobility, pelvic obstruction, pregnancy

smoking, hypertension, DM, hyperlipidaemia

Hypercoagulability (凝固性過高): hereditary protein C, protein S or anti-thrombin deficiency, factor V Leiden, prothrombin mutation, OCP/HRT, malignancy, lupus anticoagulant (狼瘡抗凝物), polycythaemia

Risk Factors for VTE

Transient/Provoked/Secondary

- Surgery
- Trauma (major or lower-extremity injury)
- Acute medical illness
- Immobilization
- Oestrogen therapy (OCP/HRT)
- Pregnancy and puerperium
- Prolonged air travel

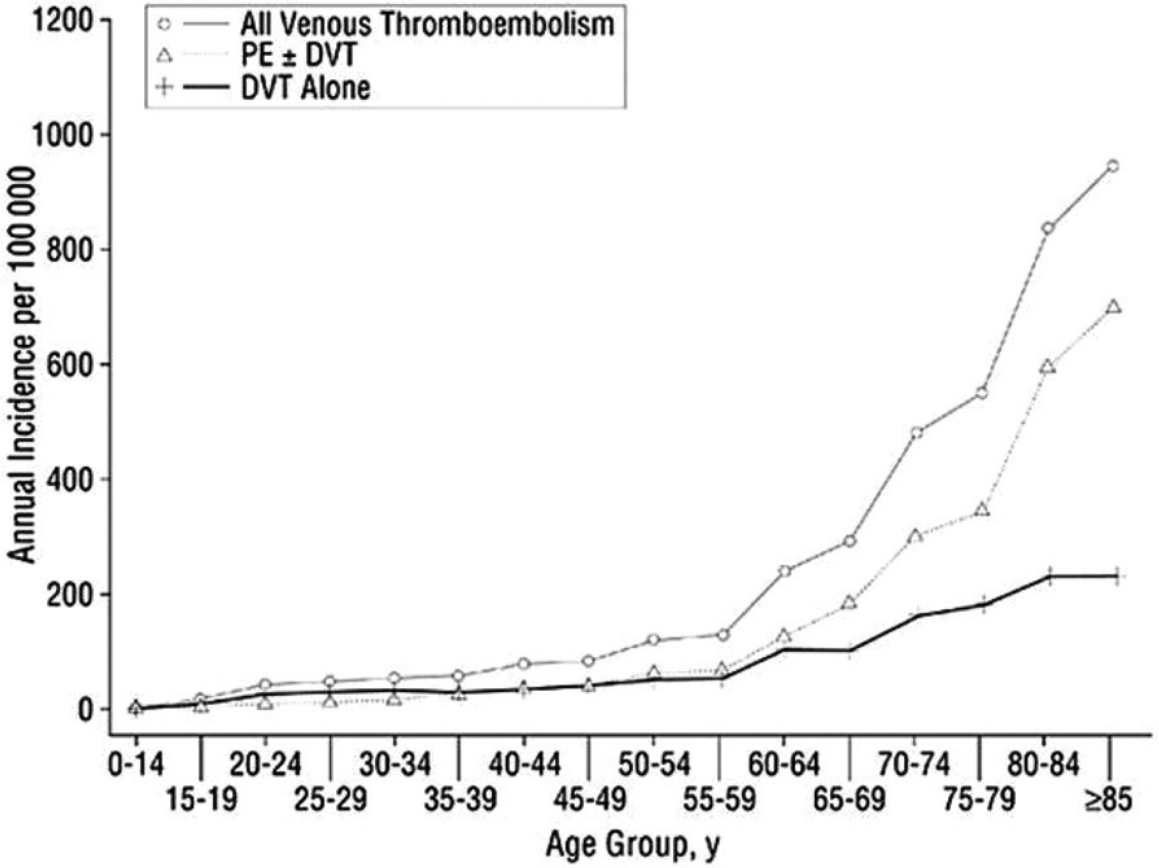
Persistent

- Obesity
- Chronic medical illness
  - cancer and its therapy
  - inflammatory bowel disease
  - nephrotic syndrome
  - myeloproilferative neoplasms / parocysmal nocturnal haemoglobinuria
- Paralysis
- Hereditary disorders
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin III deficiency
  - Factor V leiden
  - Prothrombin G20210A variant
- Antiphospholipid syndrome

Idiopathic/unprovoked
原發的

Incidence of VTE

- VTE is common in Caucasians
- Estimated annual incidence 1.24 to 2.93 per 1000 in the general population



Oger E. Thromb Haemost 2000, White RH, et al Ann Intern Med 1998, Silverstein R, et al. Blood 2007

Incidence of DVT

- Incidence of DVT in the general HK population estimated as ~17 per 100,000
- Incidence of 2/1000 pregnancy similar to Caucasian population
- A retrospective autopsy study of PE in Chinese patients in a university hospital in HK between 1964 to 1995 revealed a steady increase in the prevalence of fatal PE from 0.21% to 4.7%
- Incidence of VTE in Chinese is expected to increase with time

Liu HS, et al. HKMJ 2002; Chan LY, et al. Obstet Gynecol 2001; Chau KY, et al. Pathology 1991 & 1997

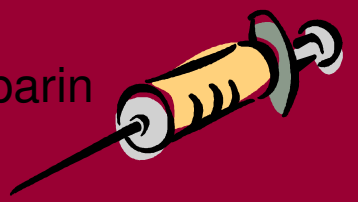
Prevalence of Hereditary Thrombophilia
(遺傳性高血栓形成傾向)

Defect	General population	Unselected thrombosis	Selected thrombosis	Relative Risk
Anti-thrombin	0.02%	0.5-1%	4-7%	X 20-50
Protein C	0.2-0.3%	3%	6-9%	X 10-15
Protein S	?	1-2%	3-13%	> X 2
Factor V Leiden	2-15% (Caucasians)	20-50%	>50%	Hetero. X3-8 Homo. X80
Prothrombin G20210A	2% (N. Europe)	6%		X 5
Dysfibrinogen-aemia		0.8%		

Management of Acute VTE

Initial Therapy

Parenteral administration of heparin
- Unfractionated heparin
- Low-molecular-weight heparin
- Fondaparinux



≥ 5 days

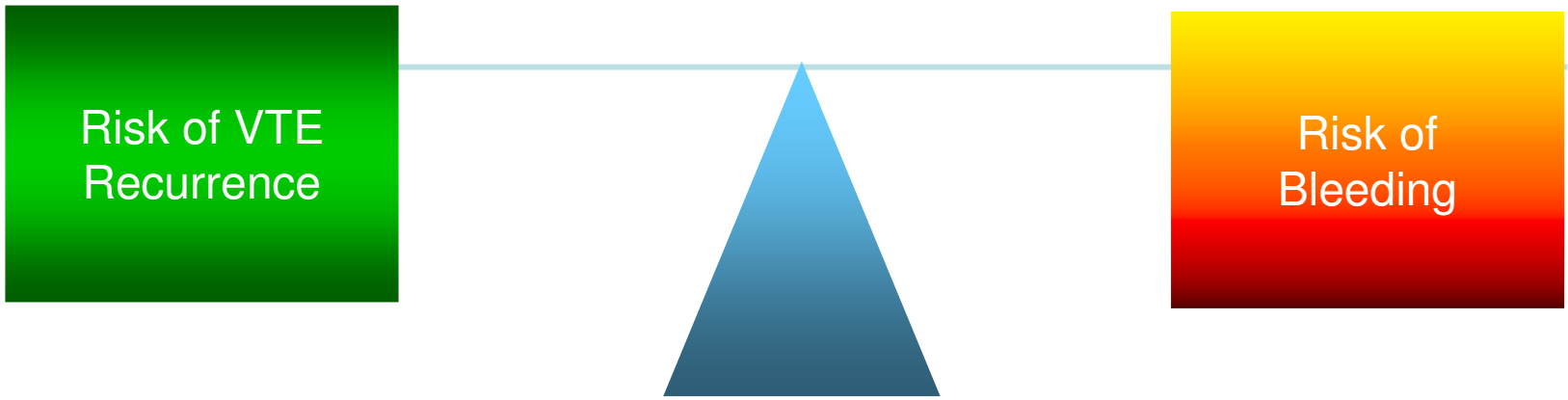
Secondary Prevention

Oral vitamin K antagonists

for a certain period
usually 3 to 12 months
or even longer

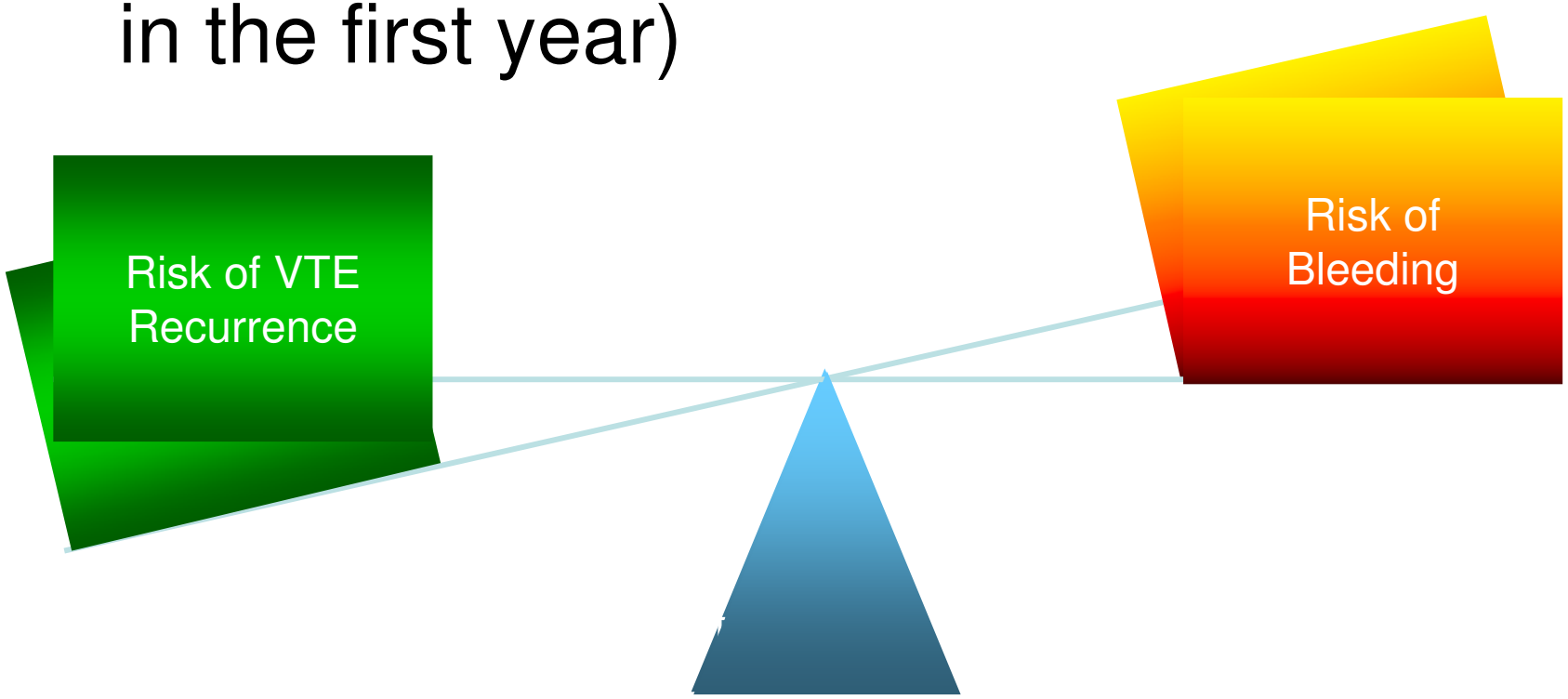
What is the optimal duration of anticoagulation treatment?

- Balance the benefit and risk of anticoagulation
- Risk of Bleeding: 2-12% in controlled studies
- Not every patient with VTE has the same recurrence risk



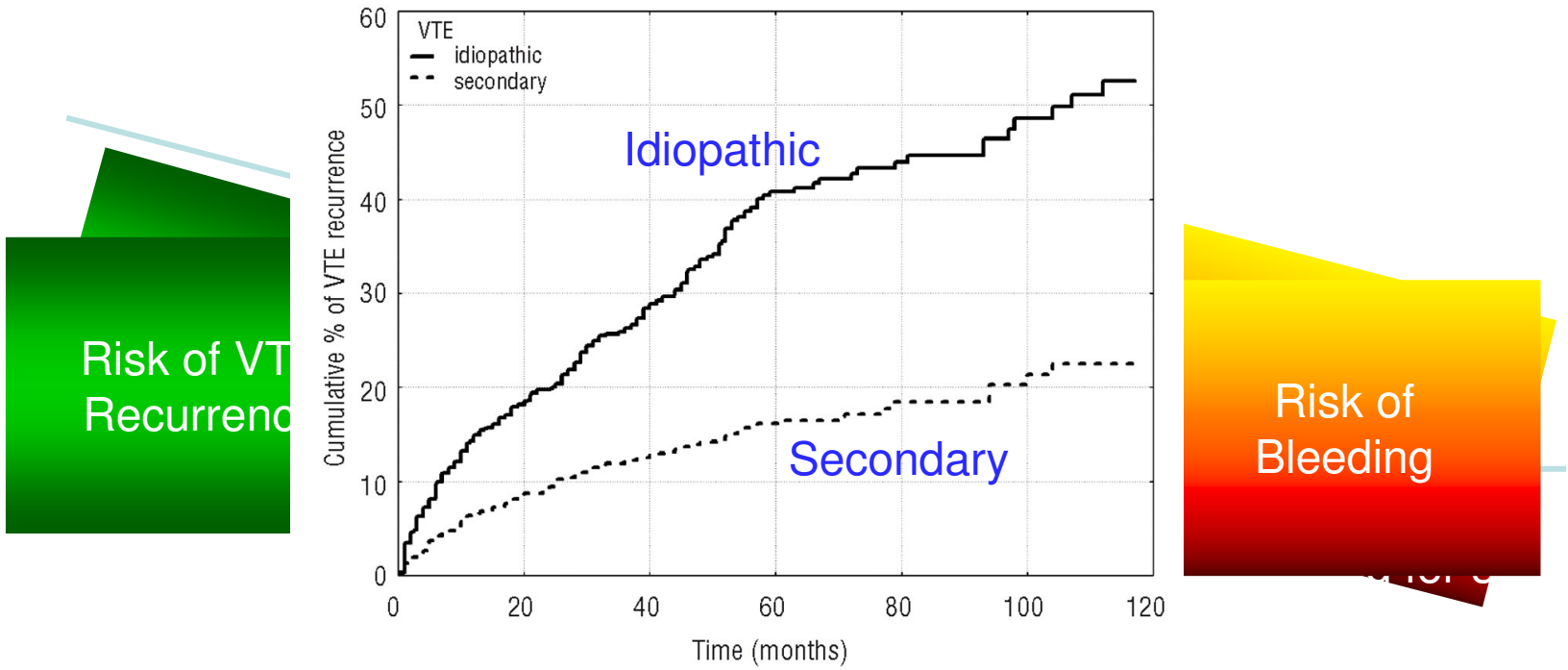
If VTE is associated with a major non-reversible risk factor

- e.g. active cancer
- very high risk of recurrence if anticoagulant therapy is stopped (≥ 15% in the first year)

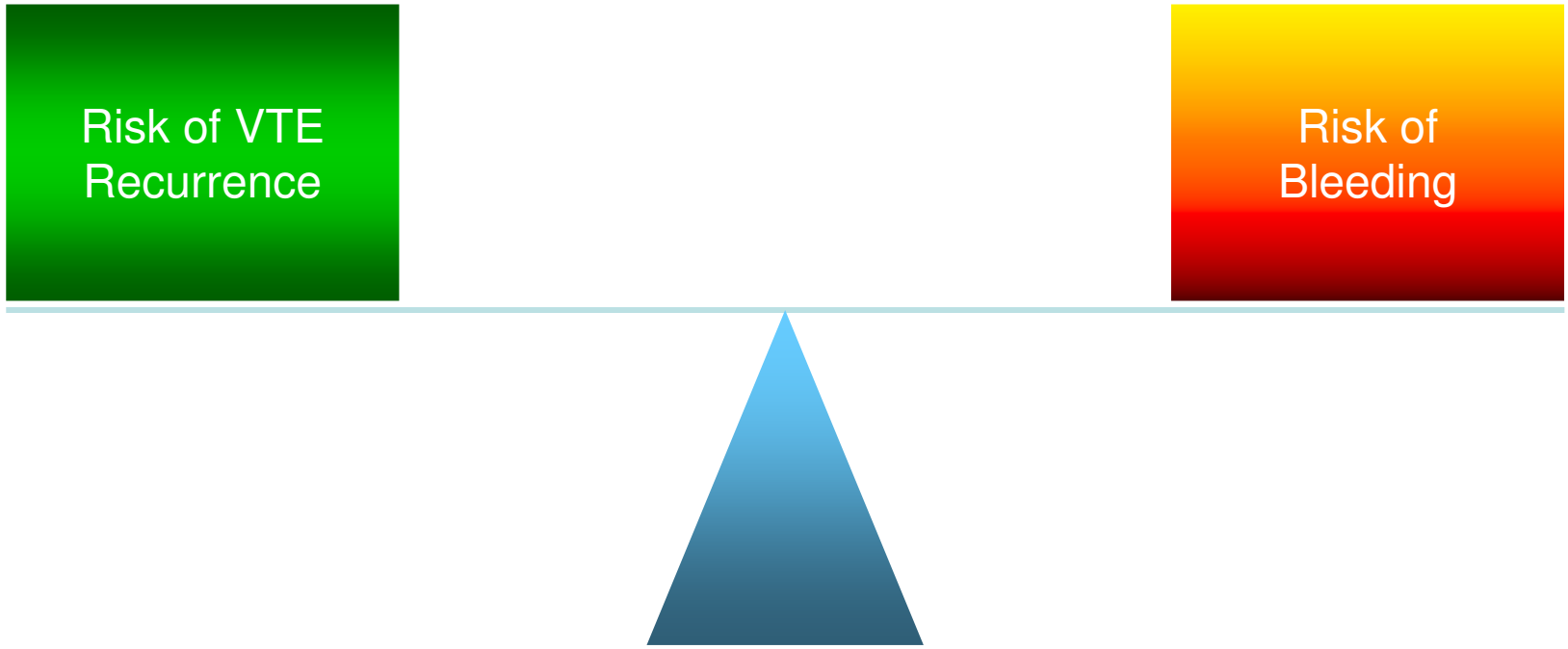


If VTE is associated with a major reversible risk factor

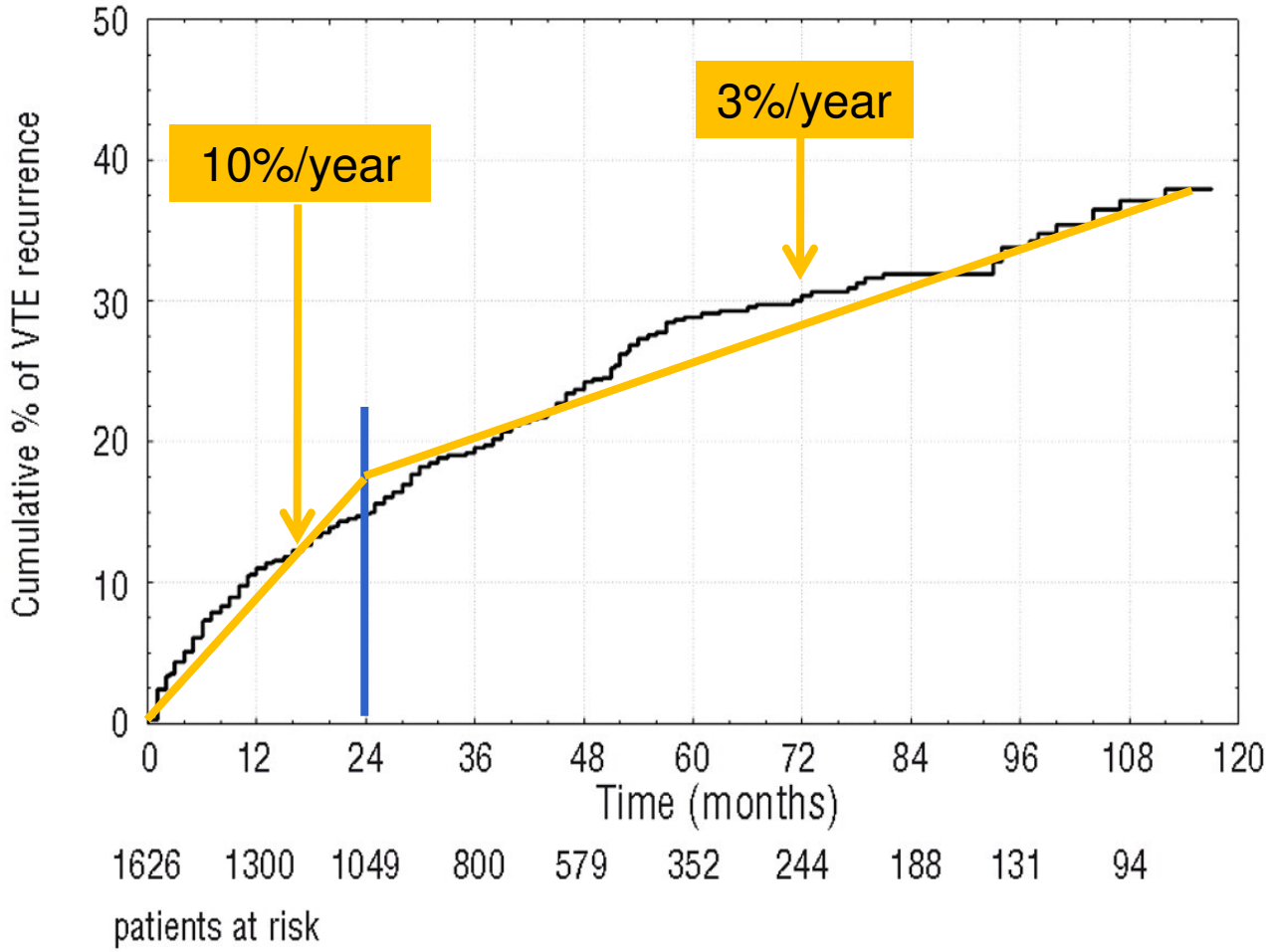
- e.g. recent surgery, immobilization, trauma, pregnancy, OCP use
- very low risk of recurrence if anticoagulant therapy is stopped (≤ 3% in the first year)



How about in patients with an episode of idiopathic VTE?



Risk of recurrent VTE after stopping anticoagulation



Prandoni, P. et al. Haematologica 2007;92:199-205

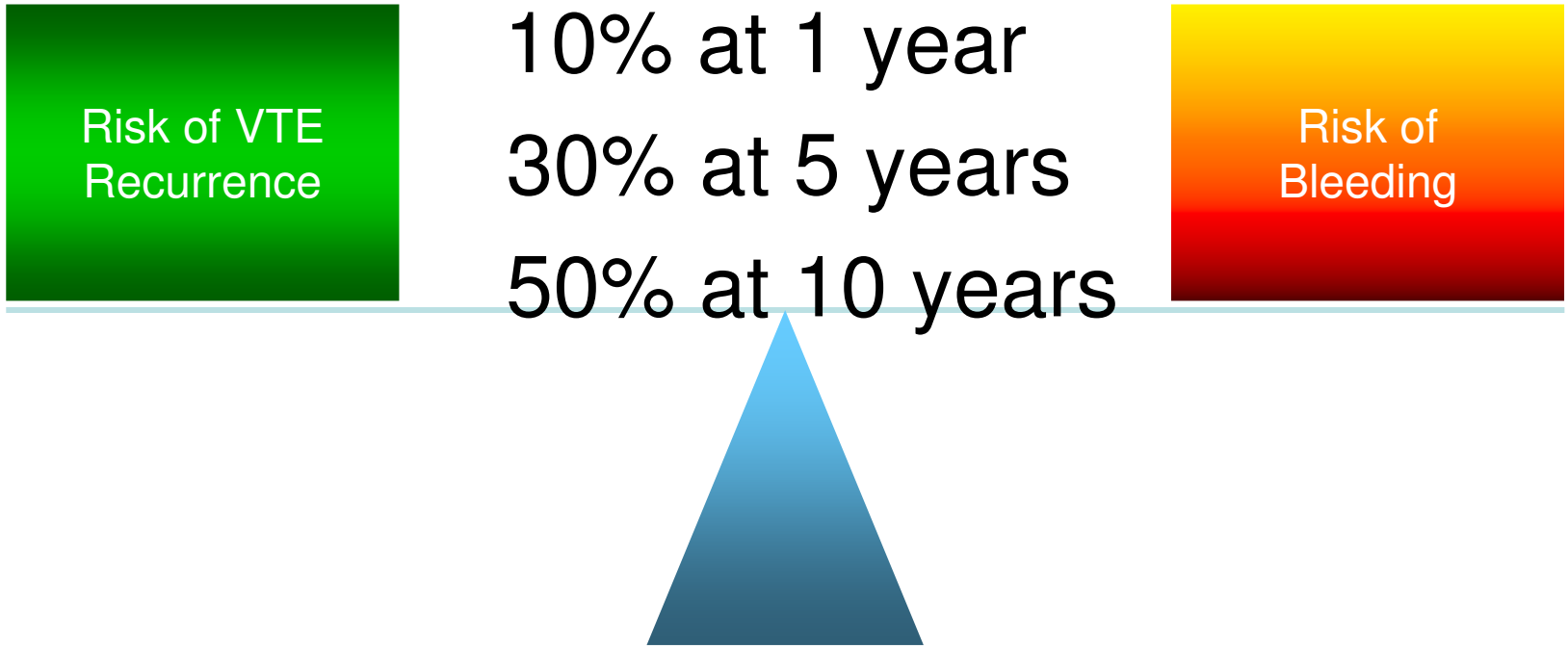
How about in patients with an episode of idiopathic VTE?

Cumulative risk of recurrence

10% at 1 year

30% at 5 years

50% at 10 years



Proposed Duration of Anticoagulation

Indication	8th ACCP guidelines[1]	BTS guidelines[2]
First episode of DVT/PE secondary to a transient risk factor	3 months (Grade 1A)	4-6 weeks (Grade A)
First episode of idiopathic (unprovoked VTE)	At least 3 month (Grade 1A) After 3 months, evaluate risk-benefit ratio of long term treatment (Grade 1C). In case of favorable risk-benefit ratio, long-term treatment (Grade 1A)s	3 months (Grade A)
Other (recurrent, active cancer, …)#	Long term (Grade 1A)	At least 6 months (Grade C)

All recommendations are subject to modification by individual characteristics including patient preference, age, co-morbidity, bleeding risk, and likelihood of recurrence

#Proper duration of therapy is unclear in first event with homozygous factor V Leiden, homocystinemia, deficiency of protein C or S, or multiple thrombophilias, and in recurrent events with reversible risk factors. Long term anticoagulation is suggested in high risk thrombophilias (e.g. antithrombin deficiency, antiphospholid syndrome)

AACP = American College of Chest Physicians; BTS, British Thoracic Society

[1]Kearon C, et al. Chest 2008, [2]Thorax. 2003

Individualized Treatment of Idiopathic Proximal DVT or PE

- Patients should receive 3 months of anticoagulation to treat the acute event
- Then a decision should be made to either stop treatment or to continue it indefinitely
- With the option of subsequently stopping treatment if the patient's risk of bleeding becomes excessive or if the patients decline anticoagulation

Extension of Anticoagulation beyond 3-6 months

- Recurrent VTE

  Risk (%/year) ~ 8%

  Case fatality rate (4-12%) 0.3 – 1%

- Bleeding

  Risk (%/year) ~ 2 – 6%

  Case fatality rate (10%) 0.2 – 0.6%

Douketis JD et al. Ann Int Med 2007
Linkins LA et al. Ann Int Med 2003

Factors associated with higher risk of recurrence, adding benefit to long-term treatment

- Second or subsequent idiopathic event
- Positive D-dimer after withdrawing therapy
- Antithrombin III deficiency
- Antiphospholipid syndrome
- Residual venous thrombous on ultrasound (difficult to standardize)
- Male gender
- Older age
- Pulmonary embolism
- Persistent pulmonary hypertension
- Established post-thrombotic syndrome

Factors associated with higher risk of bleeding, favour stopping anticoagulation

- Age > 75
- Previous GI bleeding (especially if cause not reversible)
- History of non-cardioembolic stroke
- Chronic renal or hepatic failure
- Concomitant anti-platelet therapy
- Other serious acute or chronic illness
- Persistently poor anticoagulant control
- Poor compliance with anticoagulant monitoring

Kearon C, et al. Chest 2008

When to test for thrombophilia?

- Young age
- Positive family history
- Recurrent VTE
- Unusual sites – e.g., mesenteric (腸繫膜), cerebral (大腦的)
- Idiopathic (原發的) ?

- Anti-thrombin III, protein S, protein C should be done 4 weeks after cessation of anticoagulation

Screening for Cancer in Patients with Idiopathic VTE

- ~ 10% of patients who present with an idiopathic or unprovoked VTE are diagnosed with cancer within the next 1 to 2 years
- Clinicians should maintain a low threshold of suspicion for malignancy in patients with an unprovoked VTE
- A thorough history, physical examination, routine blood tests (CBC, RFT, LFT, LDH), and chest X-ray detected many of the cancers
- Additional diagnostic testing should be guided by any abnormal findings gleaned from the initial clinical or laboratory data

Rosovsky R et al. Hematology 2010

Anticoagulants

- Unfractionated (UFH) heparin 肝素
- Low-molecular weight heparin 低分子肝素
- Warfarin 華法林
- New agents:
  - Dabigatran
  - Rivaroxaban

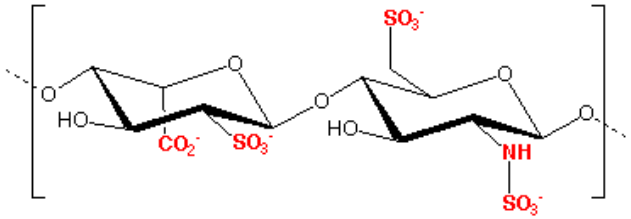
Indications for anticoagulants

- Venous thromboembolic disease
  - Treatment & prophylaxis
- Atrial fibrillation (心房纖顫)
- Heart valve prostheses (機械心瓣)
- Mural thrombosis (壁的血栓)
- Acute coronary syndrome
- Post-thrombolytic therapy for myocardial infarction

Heparin

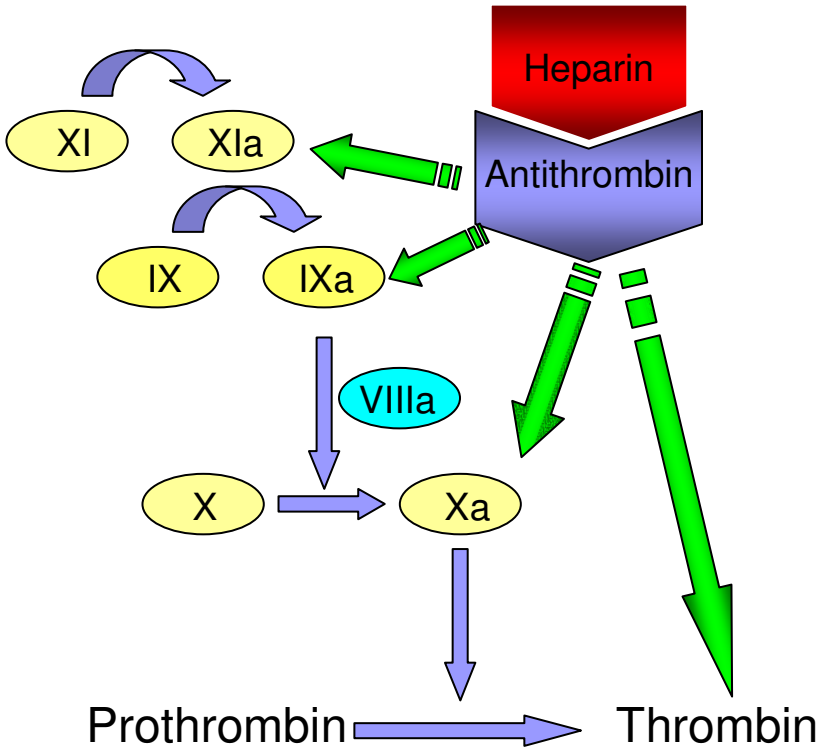
- Acidic mucopolysaccharide
  - Unfractionated/standard: molecular weight 15,000 – 18,000
  - Low molecular weight: MW 2000-10,000, produced by enzymatic or chemical depolymerization of unfractionated heparin

- Not absorbed by GI tract, needs to be given by parenteral routes



Mode of action

Unfractionated heparin (UFH)



Low molecular weight heparin (LMWH)

- **Greater ability to inhibit factor Xa than to inhibit thrombin**
- **Less interaction with platelet function**

UFH also impairs platelet function

How to use UFH?

- Initial loading dose (bolus injection): 80-100 units/kg
- Continuous infusion of about 15-22 units/kg/hr
- To maintain APTT at 2-2.5 times the control or baseline value
- Monitor APTT every 4-6 hours after change in dosage, every 6-12 hours in stable condition
- Dose titration may be difficult

Comparison of unfractionated heparin (UFH) and low molecular heparin (LMWH)

	UFH	LMWH
Mean molecular weight in kilodaltons (range)	15 (4-30)	4.5 (2-10)
Anti-Xa: anti-IIa	1:1	2:1 to 4:1
Inhibits platelet function	Yes	No
Bioavailability (生物利用度)	50%	100%
Half-life: intravenous subcutaneous	1 hr 2 hr	2 hr 4 hr
Elimination	Kidney and liver	Kidney
Monitoring	APTT	Xa assay (rarely needed)
Frequency of heparin-induced thrombocytopenia (HIT)	High	Low
Osteoporosis (骨質疏鬆)	Yes	Less frequent

Vitamin K Antagonist

- Derivatives of coumarin or indandione
- Warfarin (a coumarin) is most commonly used
- Vitamin K antagonists
- Block the γ-carboxylation of glutamic acid residues of vitamin K dependent clotting factors (II, VII, IX, X) → reduce their biological activity
- Take a few days after initiation of treatment to achieve biological effects

Warfarin

Advantages

- Wide range of conditions (AF, DVT, heart valves, children, breast feeding, anti-phospholipid syndrome)
- Been around for 50+ years
- Interactions etc well defined
- Low cost
- Reliable performance

Problems

- Narrow therapeutic range
- Bleeding risk especially with overdose
- Drug/herb interactions
- Food interactions
- Regular monitoring of INR and dose titration required (inconvenience and costly)

At least 50% of patients with AF who are candidates for anticoagulant therapy do not receive such treatment

Side effects of warfarin

- Haemorrhage
- Hypersensitivity reaction
- Skin necrosis (皮膚壞死)
- Liver dysfunction, jaundice (黃疸)

- Warfarin is teratogenic (畸胎形成) and can cross placenta. It should be avoided in pregnancy and heparin is preferred.

Warfarin verus New Oral Anticoagulants

	Warfarin	Dabigatran etexilate	Rivaroxaban
Target	Vit K epox reduc	Thrombin	Factor Xa
Oral bioavailability	99%	6-7%	60-80%
T (max)	72-96 hour	2 hour	2.5 – 4 hour
Half-life	40 hours	14-17 hours	5-9 hours healthy 9-13 hours elderly
Monitoring	INR adjusted	Not needed	Not needed
Administration	Daily	Daily or BD	Daily or BD
Metabolism / Elimination	Cytochrome P450	80% renal, 20% biliary	66% renal, 33% biliary
Antidote or treatment of bleeding	Vitamin K + FFP, APCC or rFVIIa	Standard of care (plasma of factor replacement, rVIIa)	Standard of care (plasma of factor replacement, rVIIa)
Assay	PT/INR	Ecarin clotting time	Anti-factor Xa, PiCT®, HepTest®
Drug Interactions	CYP 2C9, 1A2 and 3A4	Potent P-gp inhibitors/inducers; PPIs ↓absorption	Potent P-gp inhibitors/inducers; CYP3A4 inhibitors

Advantages of New Oral Anticoagulants

- No coagulation monitoring required
- Low potential for drug/food/alcohol interaction
- Fixed dosing and predictable response
- Potential to replace warfarin in the future

Potential Drawbacks of New Anticoagulants

- Lack of easily available monitoring assay
  - Cannot easily monitor compliance (依從性)
  - Cannot easily titrate dose or assess treatment failure
- Lack of an antidote (解毒劑)
- No evidence-based reversal strategy (逆轉策略) or evidence-based bleeding management plan is available for a bleeding patient taking these drugs
- Cost-effectiveness (成本效益) uncertain
- Lack of data in other indications, such as anti-phospholipid syndrome, metallic heart valves, etc.