ANTICOAGULANTS

Haemostasis

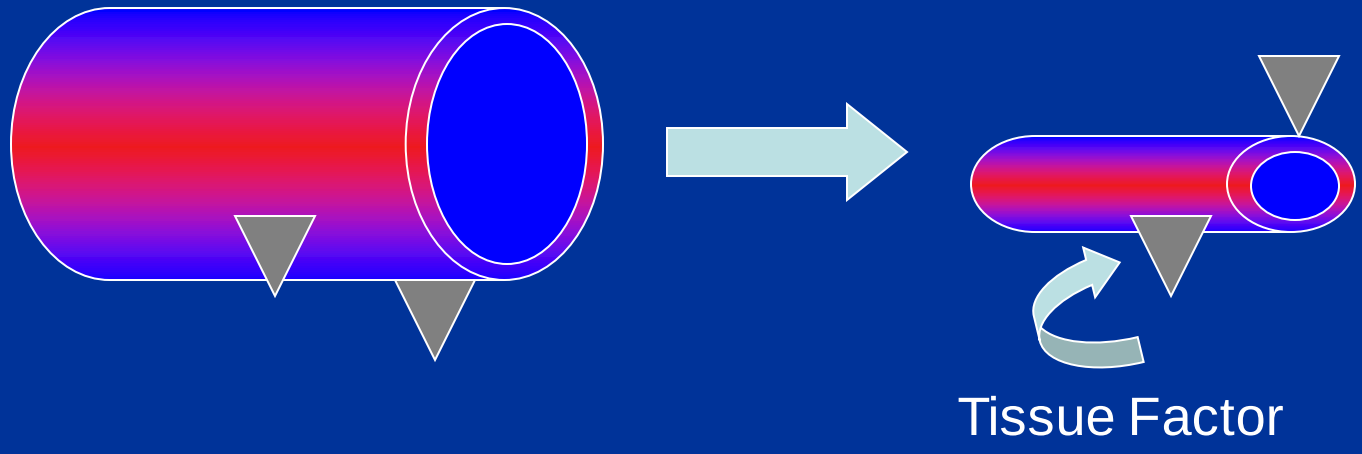
Arrest of blood loss from damaged blood vessels

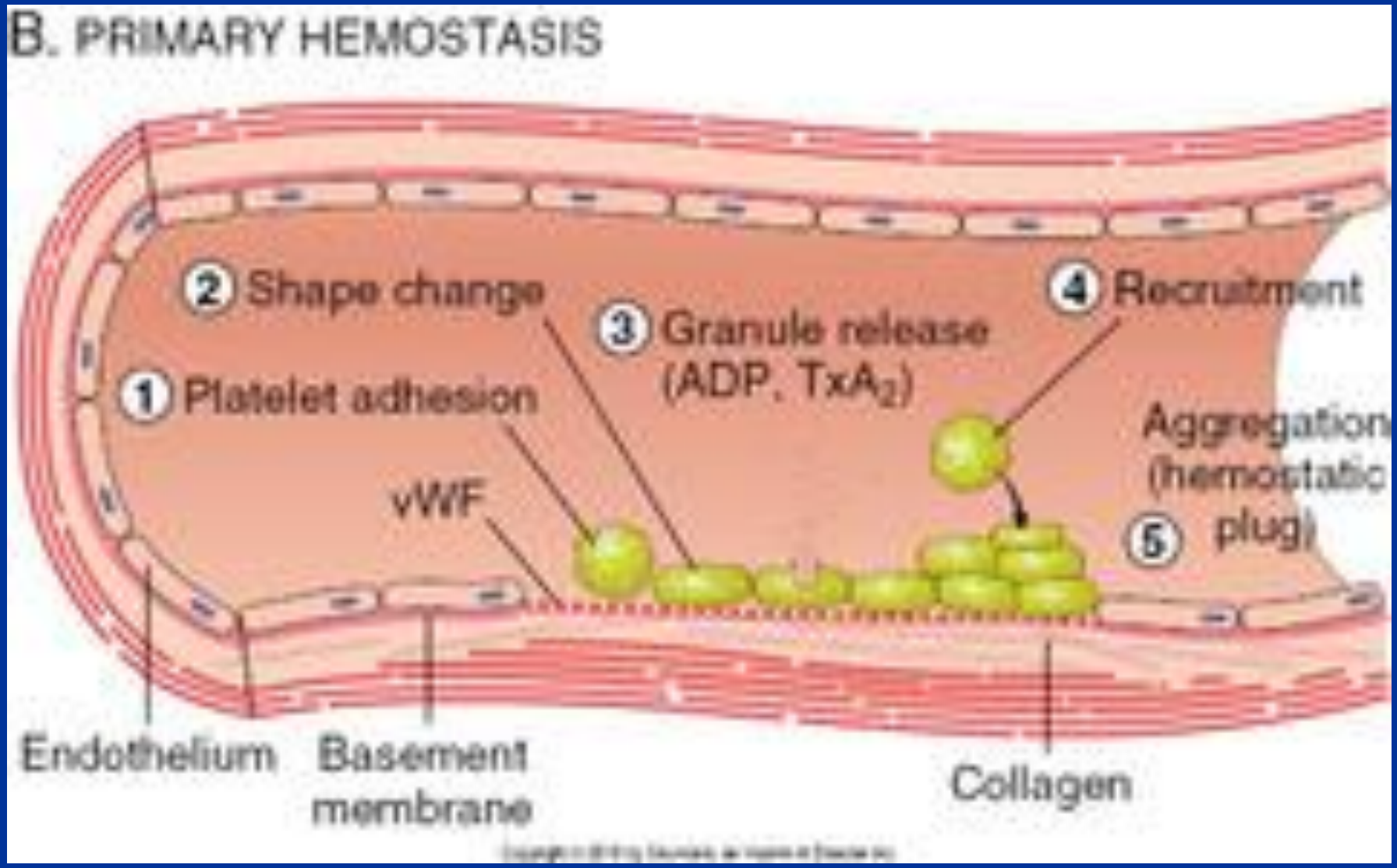
Blood Clotting

- **Vascular Phase**
- **Platelet Phase**
- **Coagulation Phase**
- **Fibrinolytic Phase**

Vascular Phase

- **Vasoconstriction**
- **Exposure to tissues activate Tissue factor and initiate coagulation**

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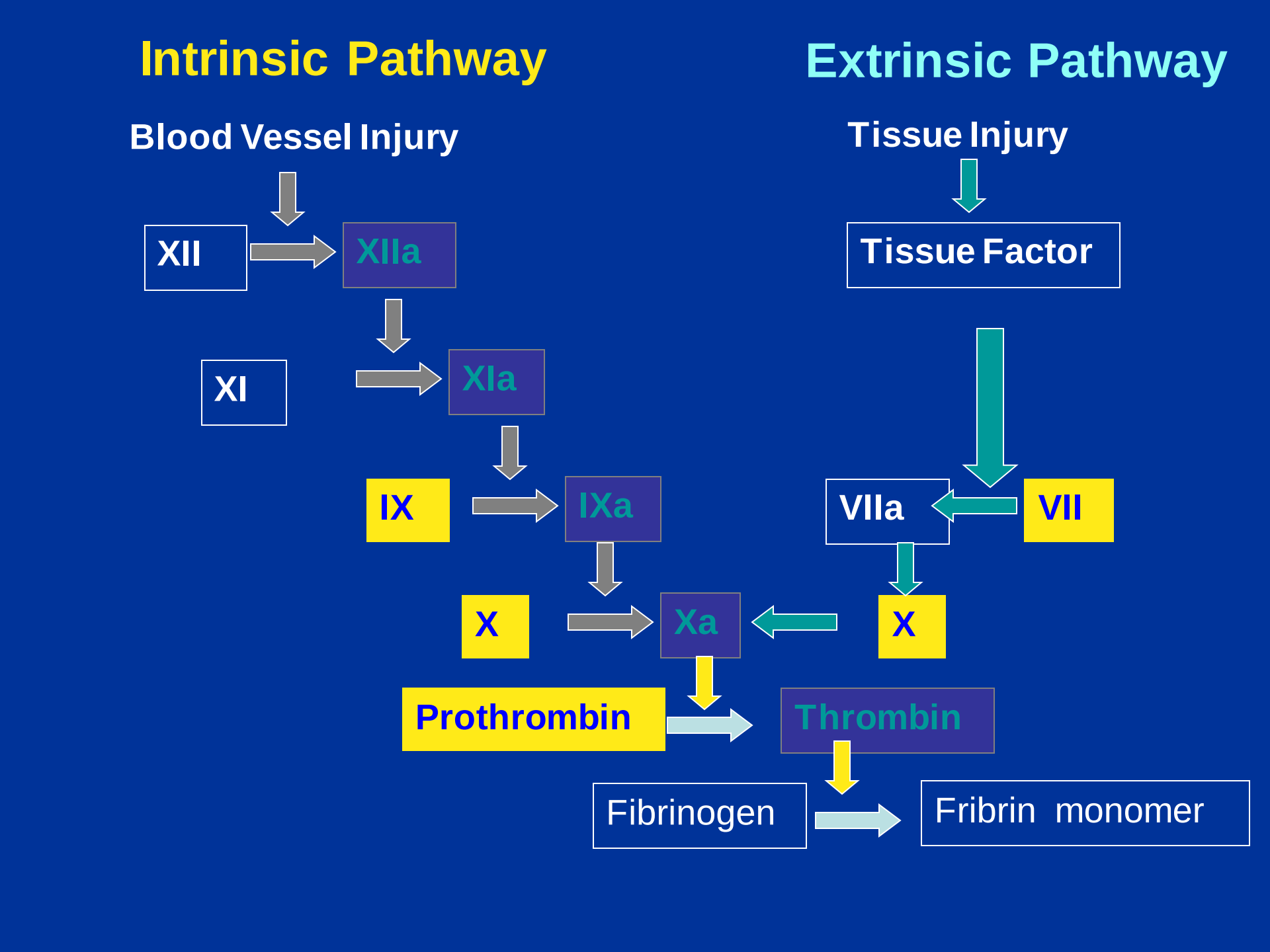
2 Shape change
3 Granule release
(ADP, TxA2)
4 Recruitment
1 Platelet adhesion
Aggregation
(hemostatic
plug)
5
vWF
Endothelium
Basement
membrane
Collagen

Coagulation Phase

- Two major pathways
  - Intrinsic pathway
  - Extrinsic pathway
- Both converge at a common point
- 13 soluble factors are involved in clotting
- Normally inactive and sequentially activated


Intrinsic Pathway
Extrinsic Pathway
Blood Vessel Injury
Tissue Injury
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XIIa
Tissue Factor
XI
XIa
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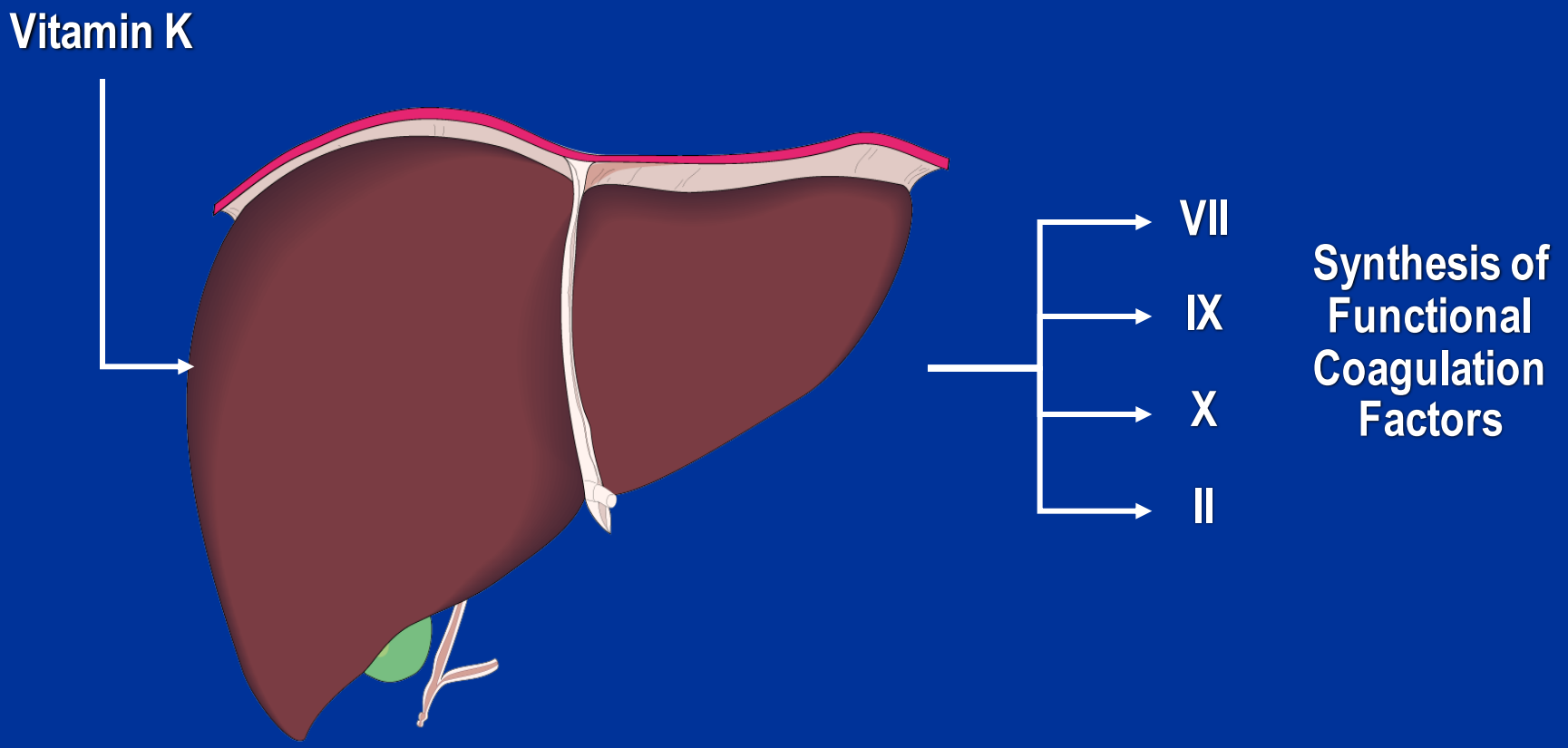
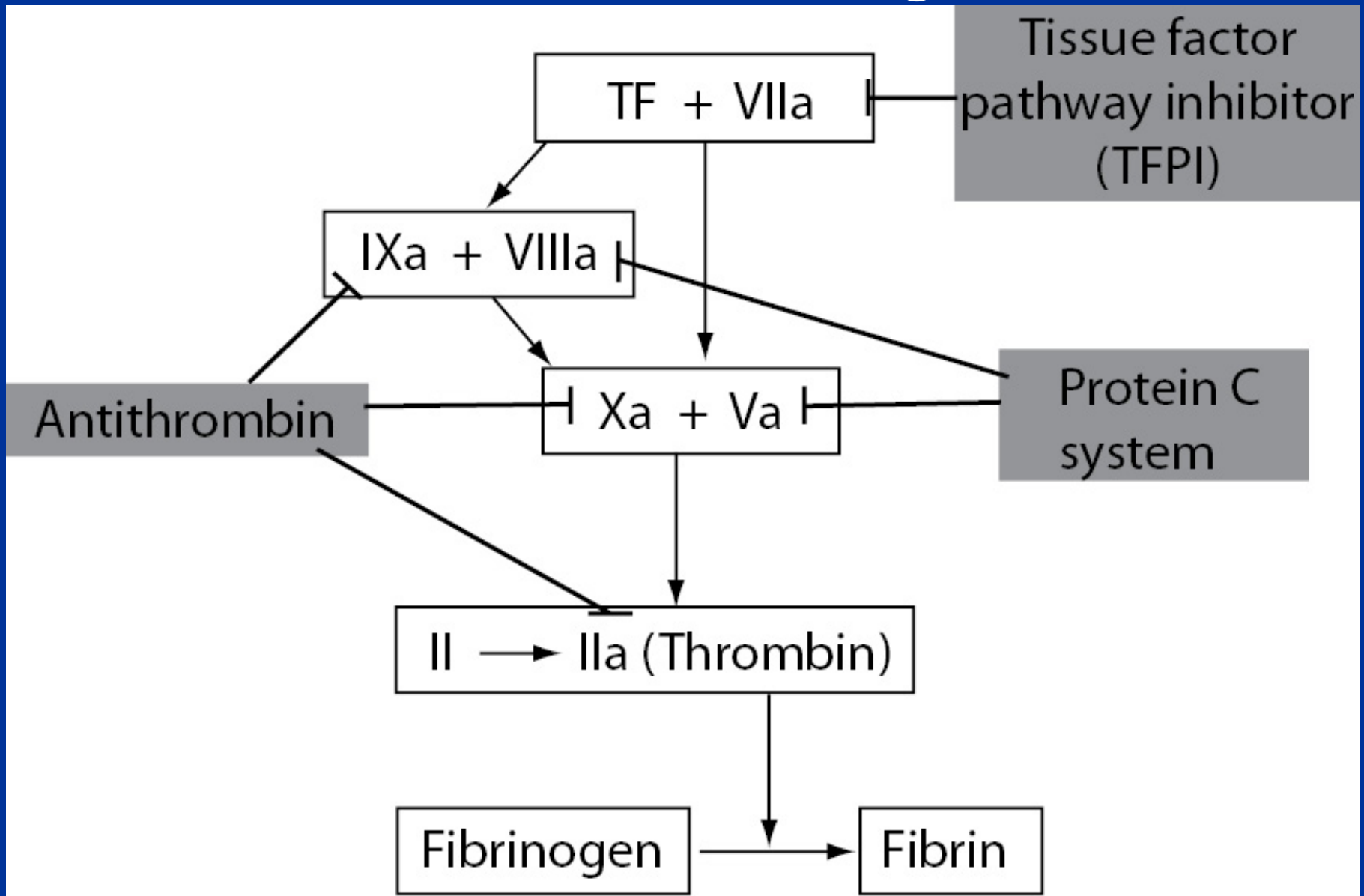
IXa
VIIa
VII
X
Xa
X
Prothrombin
Thrombin
Fibrinogen
Fribrin monomer

Vitamin K-Dependent Clotting Factors

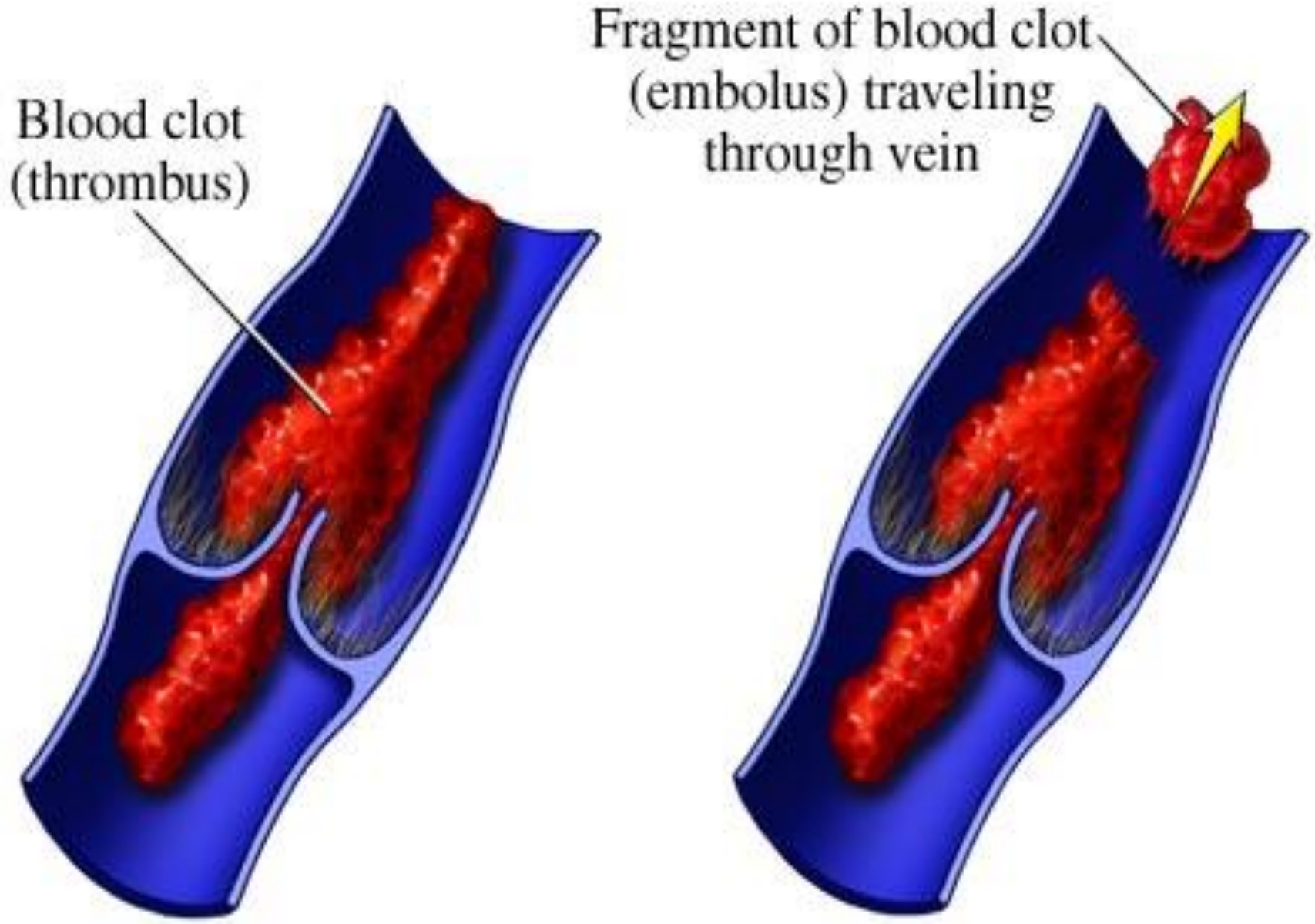


Natural anti- coagulant



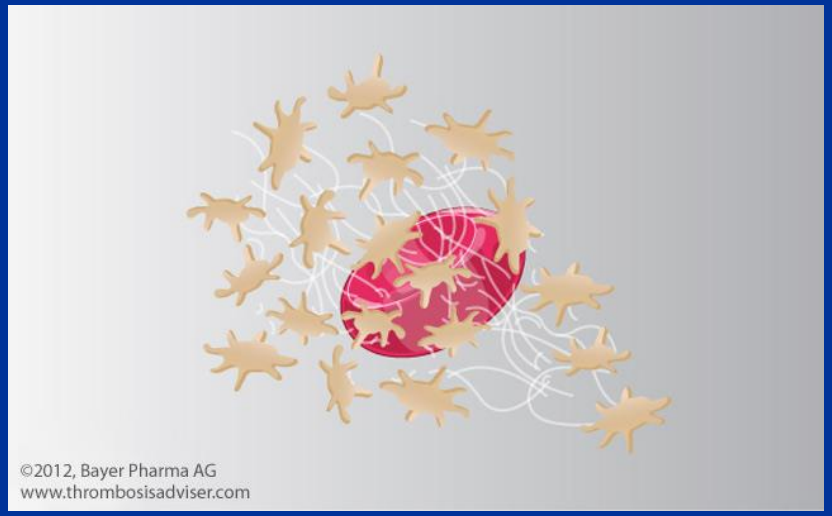
Thrombosis

Pathological formation of haemostatic plug within the vasculature in the absence of bleeding


Blood clot
(thrombus)
Fragment of blood clot
(embolus) traveling
through vein

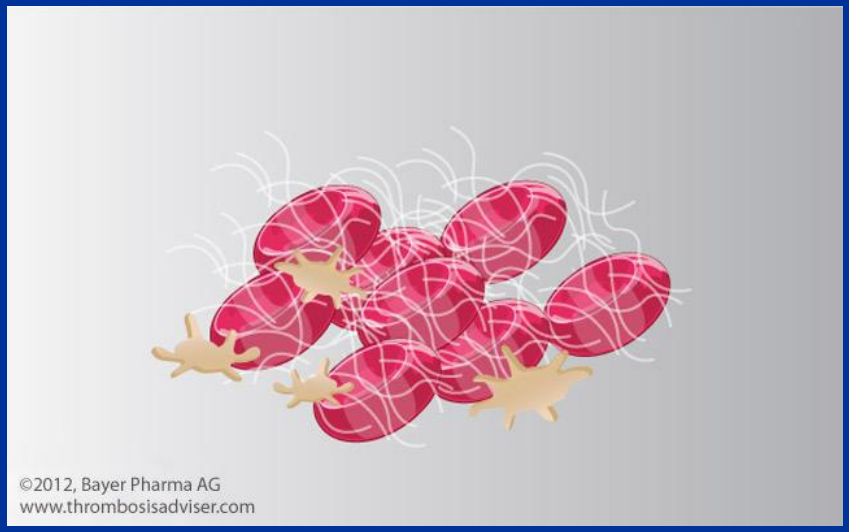
Arterial

- White
- Platelet and WBC
- With atheroscerosis
- Causes ischemia



Venous

- Red
- White head and red tail
- Embolus



Drugs effect ;

Drugs influencing coagulation

- fibrin formation → Anticoagulants
- Platelet function → Antiplatelet drugs
- Fibrinolysis → Thrombolytic drugs

Drugs influencing coagulation

- Anticoagulants
- Antiplatelet drugs
- Thrombolytic drugs

Anticoagulants

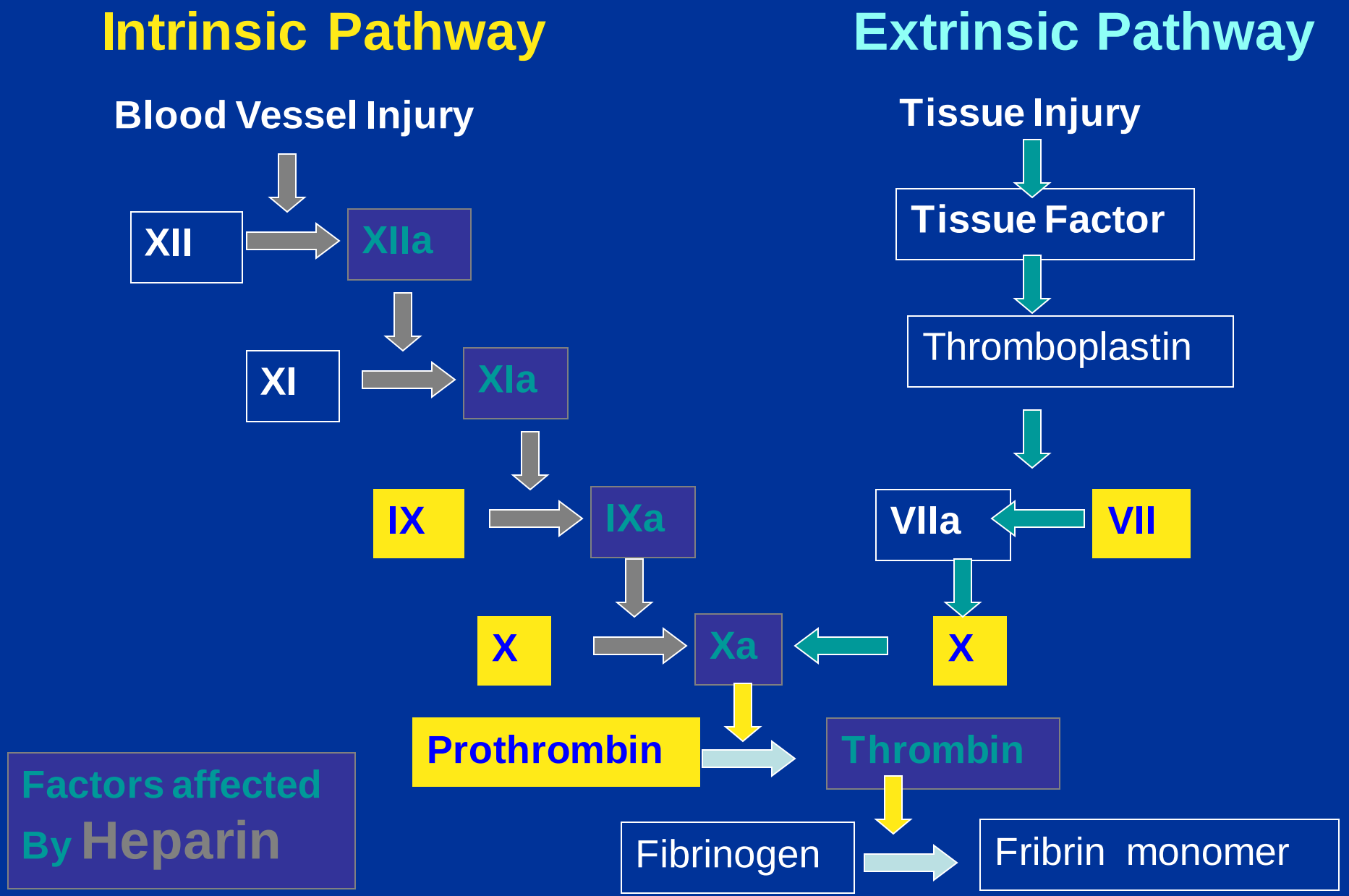
- Antithrombin activators
- Direct thrombin inhibitors
- Direct Factor Xa inhibitors
- Drugs that oppose action of Vitamin K

Anticoagulants

- Antithrombin activators
  - Heparin / LMWH
  - Synthetic pentasaccharide analogues
- Direct thrombin inhibitors
- Direct Factor Xa inhibitors
- Drugs that oppose action of Vitamin K

Heparin

- Heterogeneous mixture of branched glycosaminoglycans
- Potentiates the inhibition of IIa, IXa, Xa, XIa, XIIa by AT
- Binds to AT through a unique pentasaccharide sequence leading to a conformational change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Blood Vessel Injury
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XIIa
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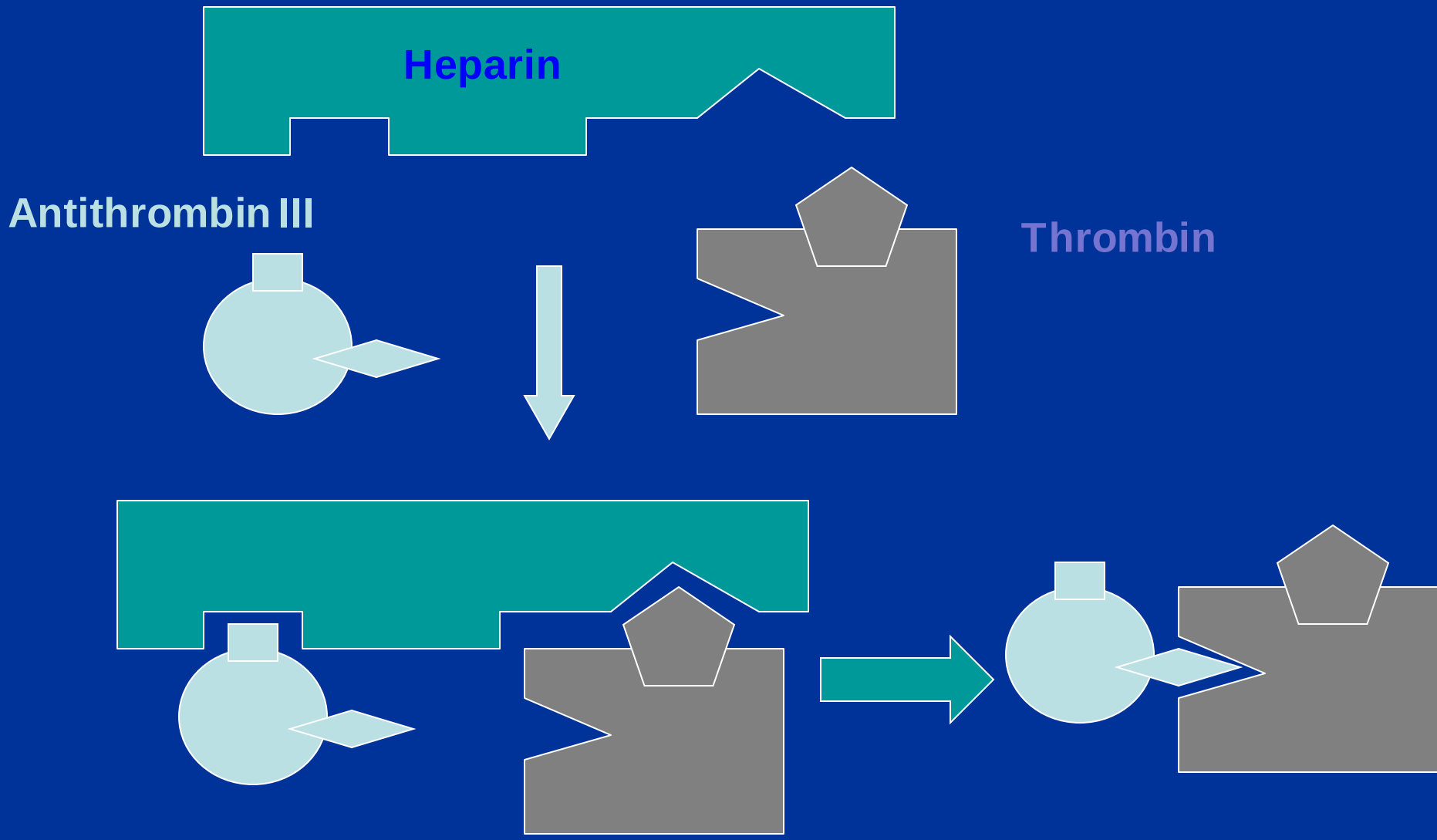
IXa
Tissue Factor
Thromboplastin
VIIa
VII
X
Xa
X
Prothrombin
Thrombin
Fibrinogen
Fribrin monomer
Factors affected
By Heparin

Heparin mechanism of action



Heparin

- Given s.c. or i.v.
- Binds to plasma proteins, endothelial cells & macrophages
- Elimination
  - Depolymerisation in endothelial cells & macrophages (rapid, saturable)
  - Renal (slow, non-saturable) and RES

Heparin: variable anticoagulant effect

- Variable protein binding
- Clearance varies with chain length

- Therefore, anticoagulant response monitored by **activated partial thromboplastin time** (APTT)
- Target 1.5 – 2.5 times control

Heparin: clinical uses

- Venous thrombosis ± embolism
- Acute coronary syndromes
- Arterial thrombosis
- Extracorporeal devices (e.g. haemodialysis)

Heparin: adverse effects

- Bleeding
- Heparin-induced thrombocytopenia (HIT)
  - Immune-mediated
- Osteoporosis

Low-molecular-weight heparins (LMWHs)

- Derived from UFH by chemical or enzymatic depolymerization
- Molecular weight 2000 – 9000
- About 15 monosaccharide units per molecule

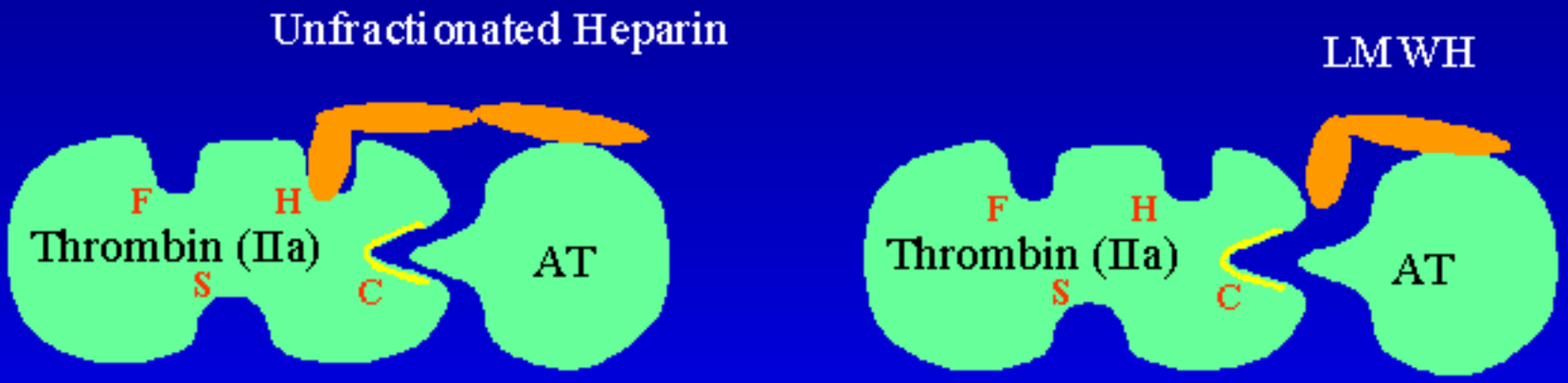
Differences in Mechanism of Action

- Any size of heparin chain can inhibit the action of factor Xa by binding to antithrombin (AT)

- In contrast, in order to inactivate thrombin (IIa), the heparin molecule must be long enough to bind both antithrombin and thrombin

- Less than half of the chains of LMWH are long enough

Differential inhibitory activity against factor Xa and IIa activity



By binding to AT, most UH and LMWH can inhibit Xa activity. Fewer than half the chains of LMWH are of sufficient length to also bind factor IIa, therefore has decreased anti-IIa activity.

Advantages of LMWH over UH

- **No need for laboratory monitoring**
  - when given on a weight-adjusted basis, the LMWH anticoagulant response is predictable and reproducible
- **Higher bioavailability** - 90% vs 30%
- **Longer plasma half-life**
  - 4 to 6 hours vs 0.5 to 1 hour
  - renal (slower) vs hepatic clearance

Advantages of LMWH over UH

- **Less inhibition of platelet function**
  - potentially less bleeding risk, but not shown in clinical use
- **Lower incidence of thrombocytopenia and thrombosis (HIT syndrome)**
  - less interaction with platelet factor 4
  - fewer heparin-dependent IgG antibodies

Monitoring of LMWH

- Unnecessary in majority of patients
- May be useful in specific instances
  - renal insufficiency (creatinine >2.0 mg/dl)
  - obese patients with altered drug pK
  - major bleeding risk factors

LMWHs

- Dalteparin
- Enoxaparin
- Tinzaparin

Synthetic pentasaccharide analogues

	Bioavailability(s.c.)	elimination	half life (h)
LMWH	80-90%	renal	4
Fondaparinux	100%	renal	17
Idraparinux	100%	renal	80

Anticoagulants

- Antithrombin activators
- Direct thrombin inhibitors
- Direct Factor Xa inhibitors
- Drugs that oppose action of Vitamin K

Direct thrombin inhibitors

- Recombinant hirudins
- Bivalirudin
- Ximelagatran / Melagatran
- Dabigatran

Recombinant hirudins

- Given i.v. , s.c.
- Elimination renal
- Half life 1-2 h

Bivalirudin

- Given i.v.
- Elimination renal & hepatic
- Half life 25 min

Ximelagatran

- Promising oral direct thrombin inhibitor
- Converted to the active form melagatran in vivo
- No dosing problems
- No monitoring needed.
- Recent atrial fibrillation study showed it to possibly be superior to warfarin.

Dabigatran

- Given orally
- Elimination renal
- Half life 12 h
- Substrate for P-glycoprotein in kidney, GIT

Anticoagulants

- Antithrombin activators
- Direct thrombin inhibitors
- Direct Factor Xa inhibitors
- Drugs that oppose action of Vitamin K

Apixaban

- Direct Factor Xa inhibitor
- Oral bioavailability 60%
- Half life 12 h
- Elimination hepatic > renal

Rivaroxaban

- Direct Factor Xa inhibitor
- Oral bioavailability 80%
- Half life 7-11 h
- Elimination renal > hepatic

Anticoagulants

- Antithrombin activators
- Direct thrombin inhibitors
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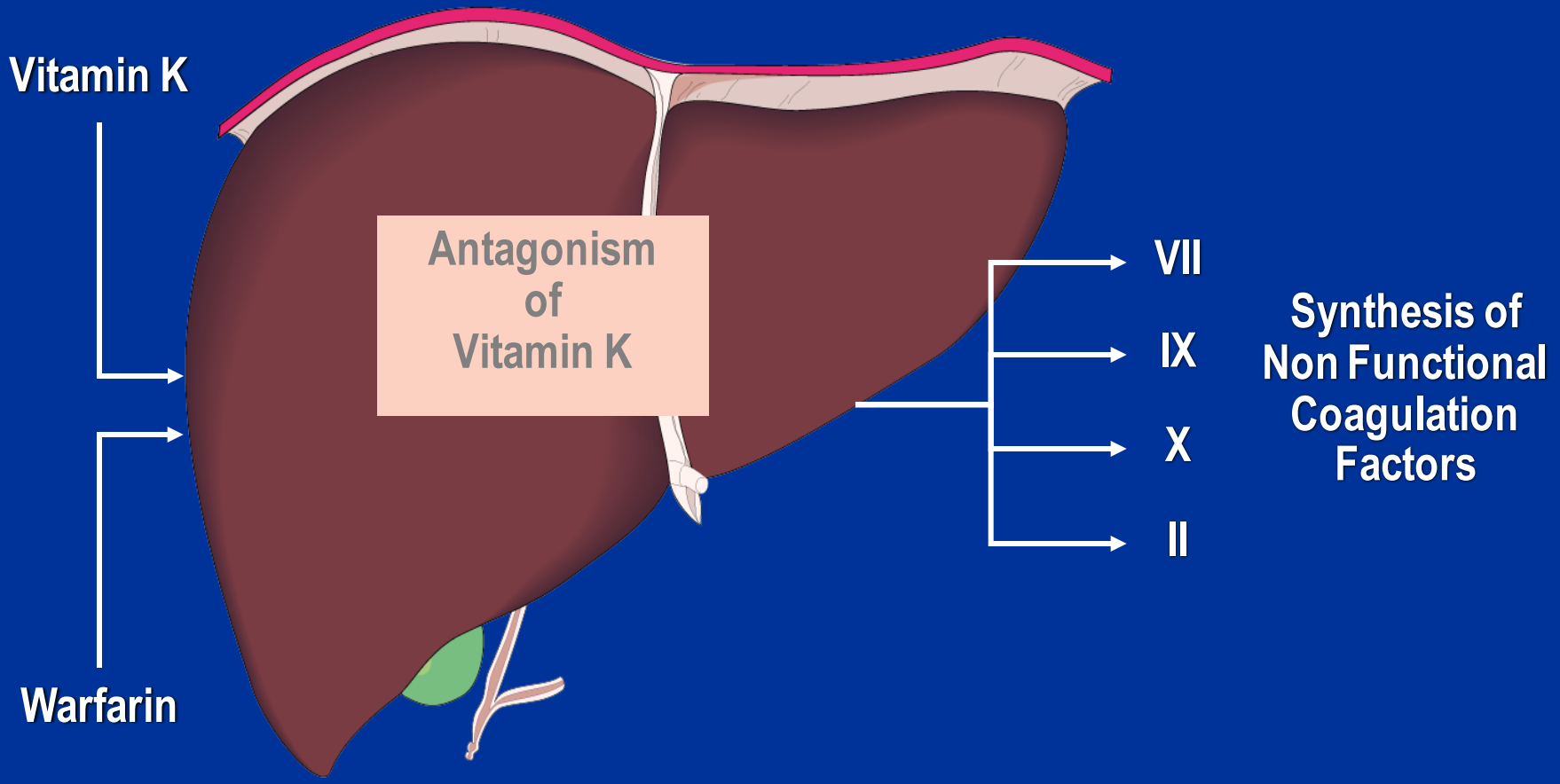
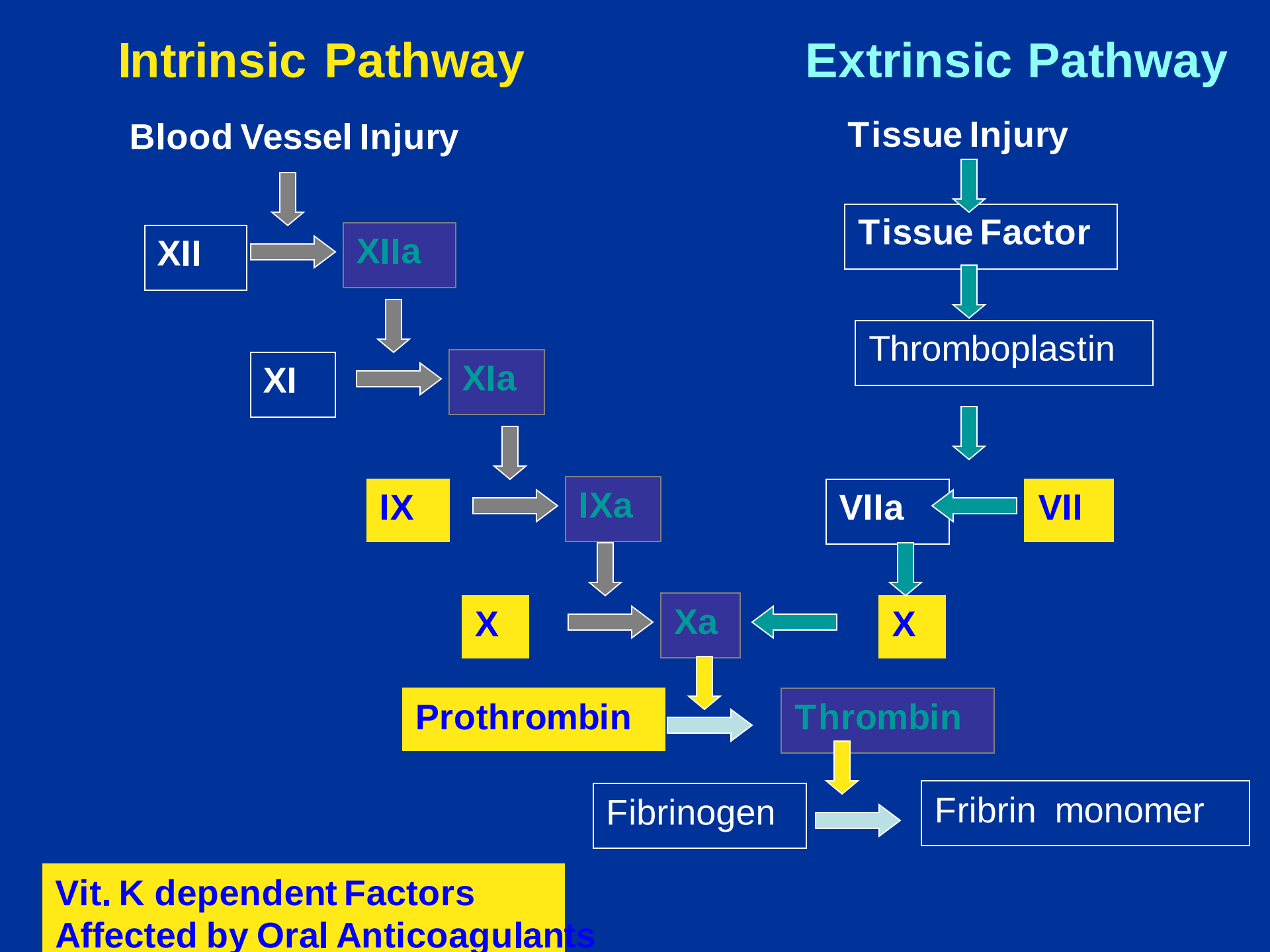
Warfarin

Reduces the post-translational carboxylation of glutamate residues of factors II, VII, IX, X

Warfarin Mechanism of Action

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VIIa
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Thrombin
Fibrinogen
Fribrin monomer
Vit. K dependent Factors
Affected by Oral Anticoagulants

Warfarin

- Anticoagulant effect seen after 2-3 days
- Monitored by international normalized ratio (INR)

- Well absorbed form GIT
- Highly protein bound
- Metabolised by CYP-450

Warfarin cont

- Clearance is slow - 36 hrs

- Can cross placenta - do not use during pregnancies

Drug interaction- with Warfarin

Category	Mechanism	Representative Drugs
Drugs that Increase Warfarin Activity	Decrease binding to Albumin	NSAID,
	Inhibit hepatic metaboli;	Cimetidine, antifungals
	Decrease synthesis of Clotting Factors	Antibiotics (oral)

Drug interaction with Warfarin cont:

Drugs that promote bleeding ↑	Inhibition of platelets	NSAID, Aspirin
	Inhibition of clotting Factors	heparin
Drugs that decrease Warfarin activity ↓	Induction of metabolizing Enzymes	Barbiturates Griseofulvin
	Promote clotting factor Synthesis	Vitamin K
	Reduced absorption	cholestyramine colestipol

Warfarin: adverse effects

- Bleeding
- Rashes
- Alopecia
- Teratogenicity

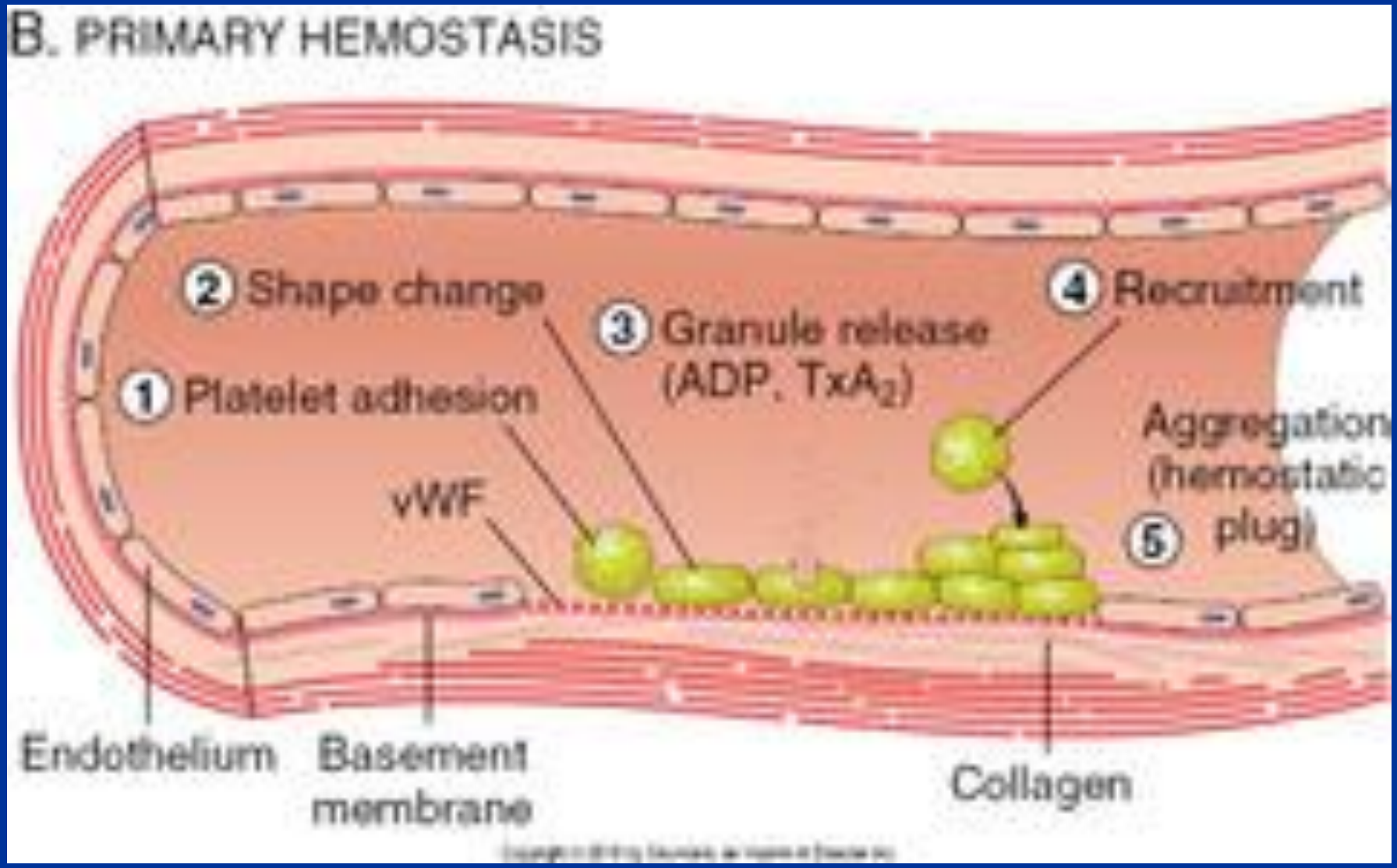
Reversing action of warfarin

- Plasma
  - Rapid but short-lasting
- Vitamin K
  - Not rapid, but lasts 1-2 weeks. Do not use if wishing to restart warfarin within next week.

Drugs influencing coagulation

- Anticoagulants
- Antiplatelet drugs
- Thrombolytic drugs

Antiplatelet drugs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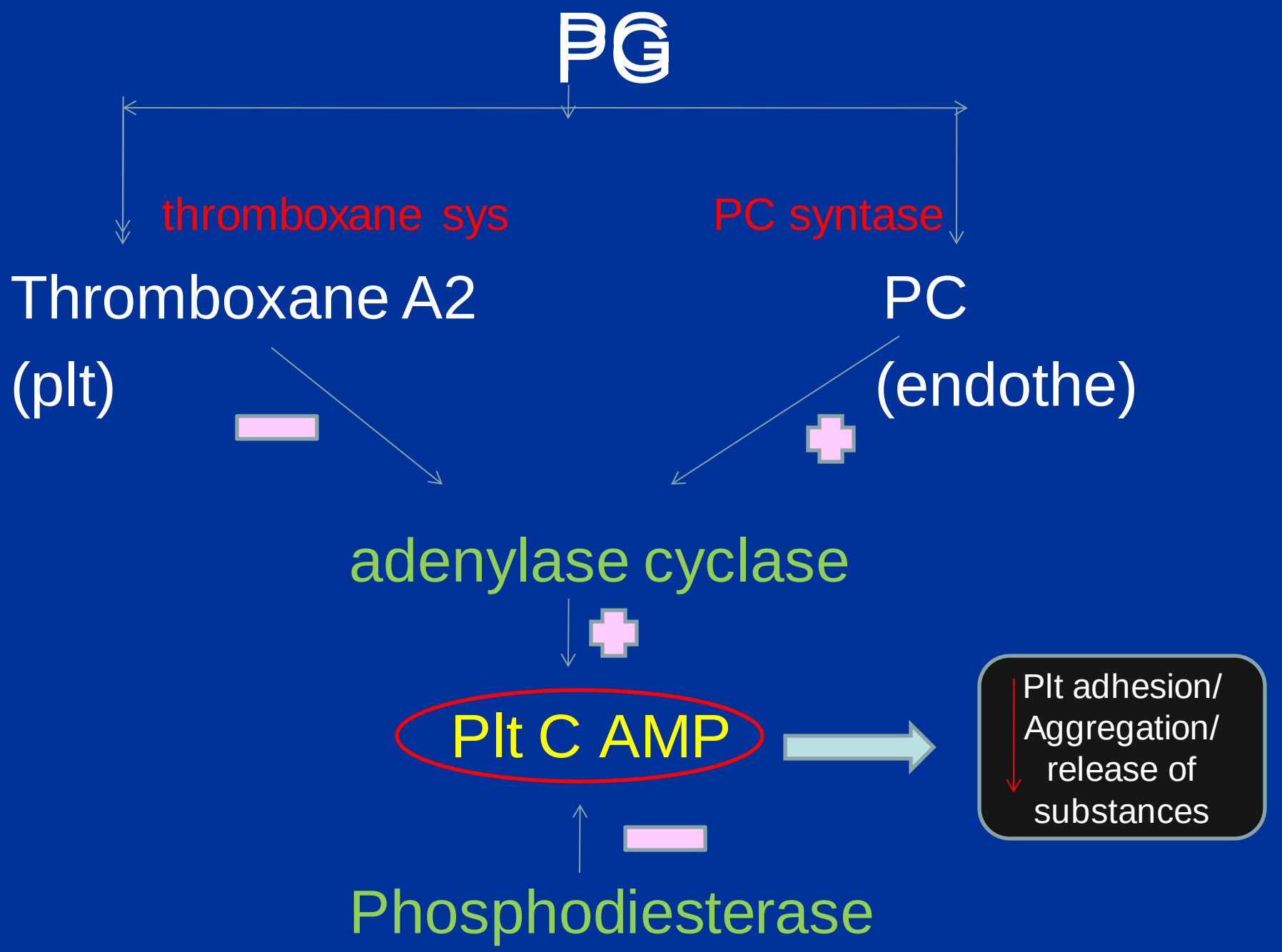
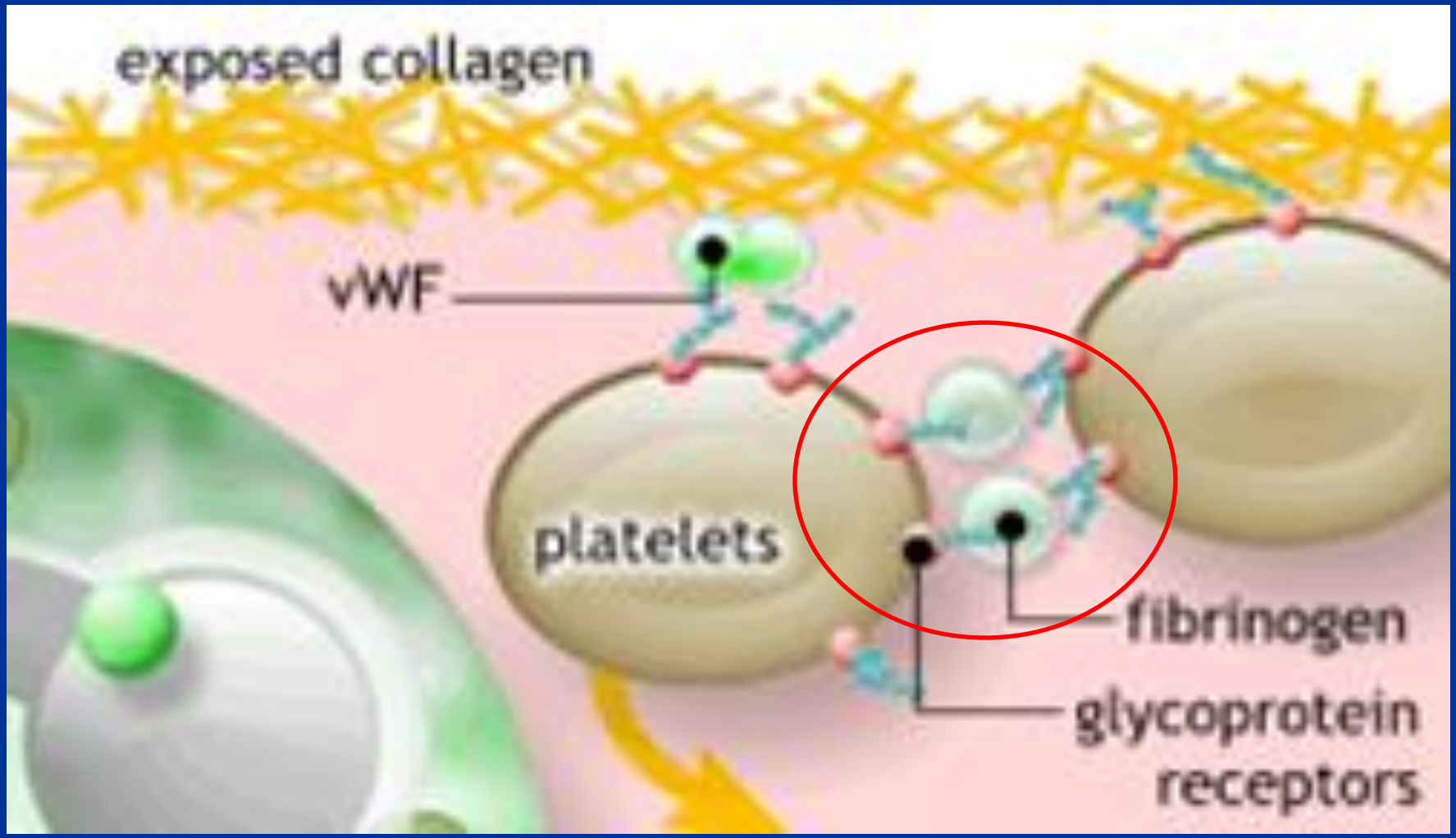

PG
thromboxane sys
PC syntase
Thromboxane A2
(plt)
PC
(endothe)
adenylase cyclase
Plt C AMP
Plt adhesion/
Aggregation/
release of
substances
Phosphodiesterase


exposed collagen
vWF
platelets
fibrinogen
glycoprotein
receptors

Antiplatelet drugs

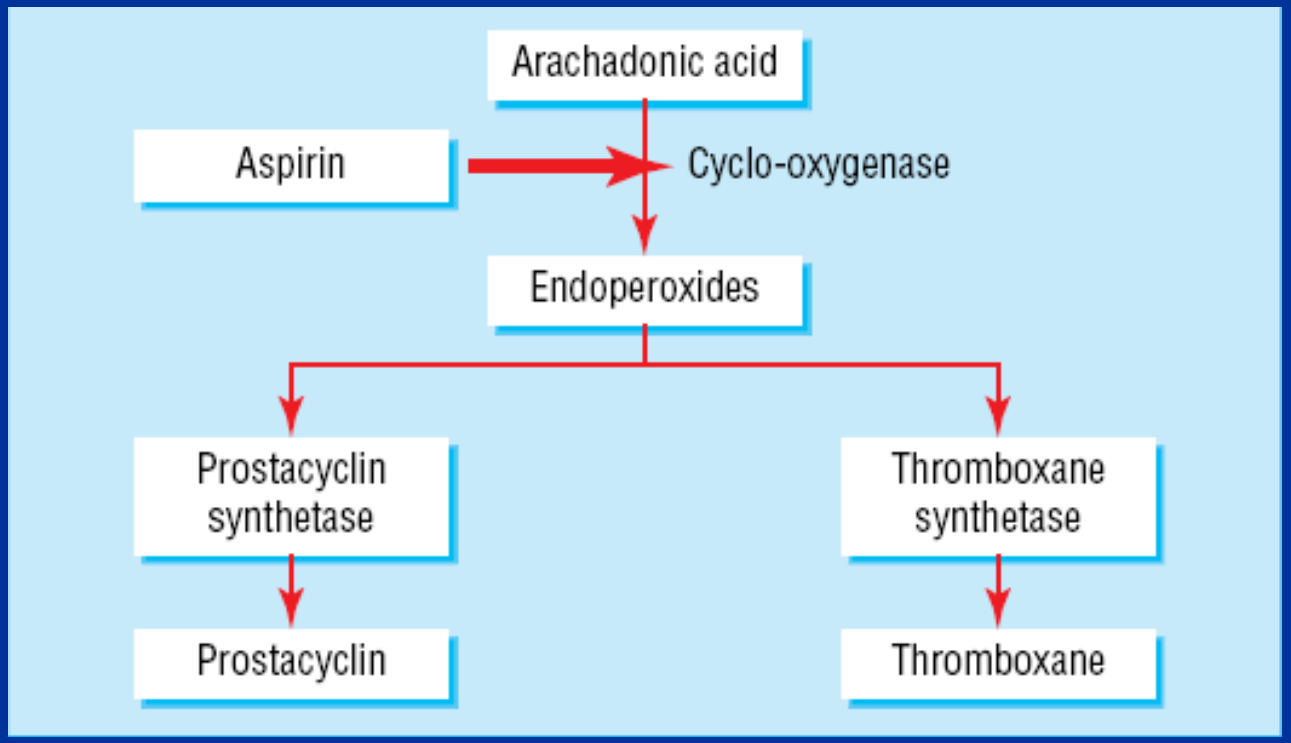
- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
- Glycoprotein IIb/IIIa receptor antagonists

Antiplatelet drugs

- COX inhibitors
  - Aspirin
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
- Glycoprotein IIb/IIIa receptor antagonists

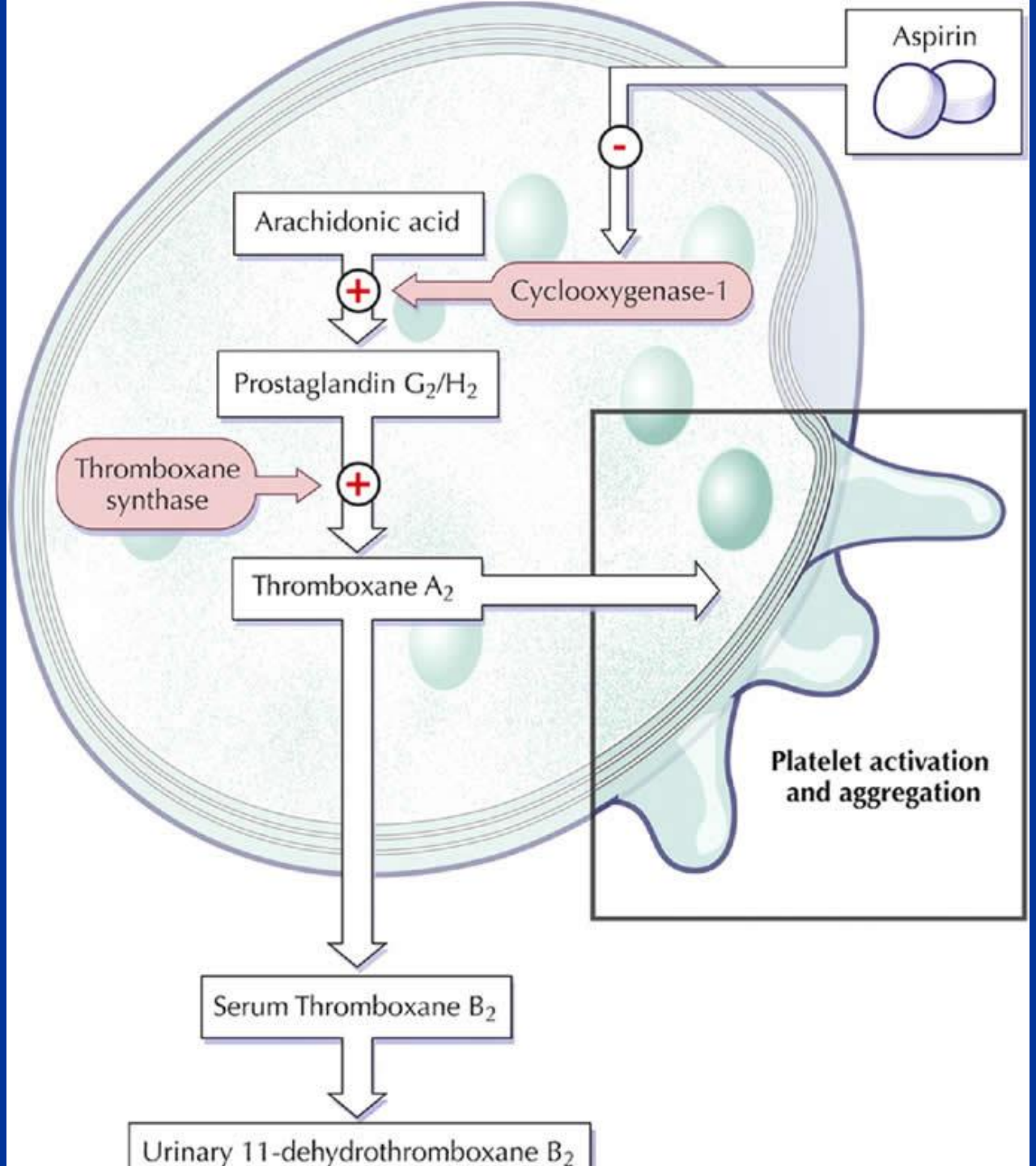
Aspirin

- Irreversible acetylation of cyclo-oxygenase-1 in platelets



endothelium

platelet


Aspirin
-
Arachidonic acid
+
Cyclooxygenase-1
Prostaglandin G_2/H_2
Thromboxane synthase
+
Thromboxane A_2
Platelet activation and aggregation
Serum Thromboxane B_2
Urinary 11-dehydrothromboxane B_2

Aspirin cont;

- Prevents platelet aggregation /adhesion

- Clinical use - prevents arterial thrombus
  - Myocardial infarction (MI)
  - stroke
  - heart valve replacement and shunts

Aspirin cont;

- Low doses (75 – 300 mg)
- Rapidly absorbed from GIT
- Absorption delayed with enteric-coated formulations
- Hydrolysed by esterases in GI mucosa & liver

Prophylactic use of Aspirin

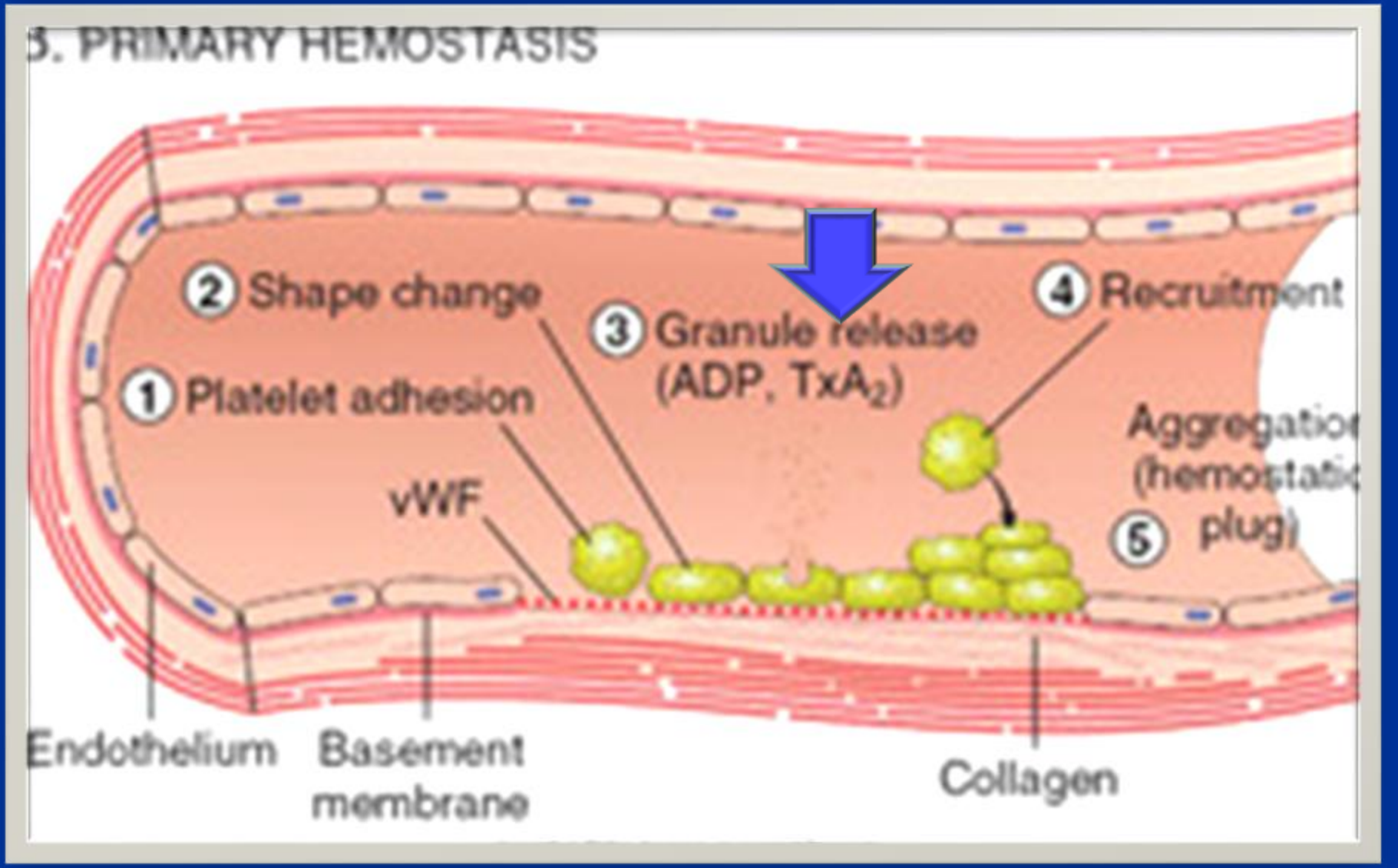
- Low dose daily.
- Prevents ischemic attack and MI

Antiplatelet drugs

- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
  - Clopidogrel, Prasugrel, Ticagrelor
- Phosphodiesterase inhibitors
- Glycoprotein IIb/IIIa receptor antagonists

Thienopyridines

- Ticlopidine
- Clopidogrel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5 plug)
Endothelium
Basement
membrane
Collagen

Clopidogrel

- Slightly more effective than aspirin
- Additive effect to aspirin

Use

- MI
- Stroke

Ticlopidine

- Slow onset of action - 3-7 days

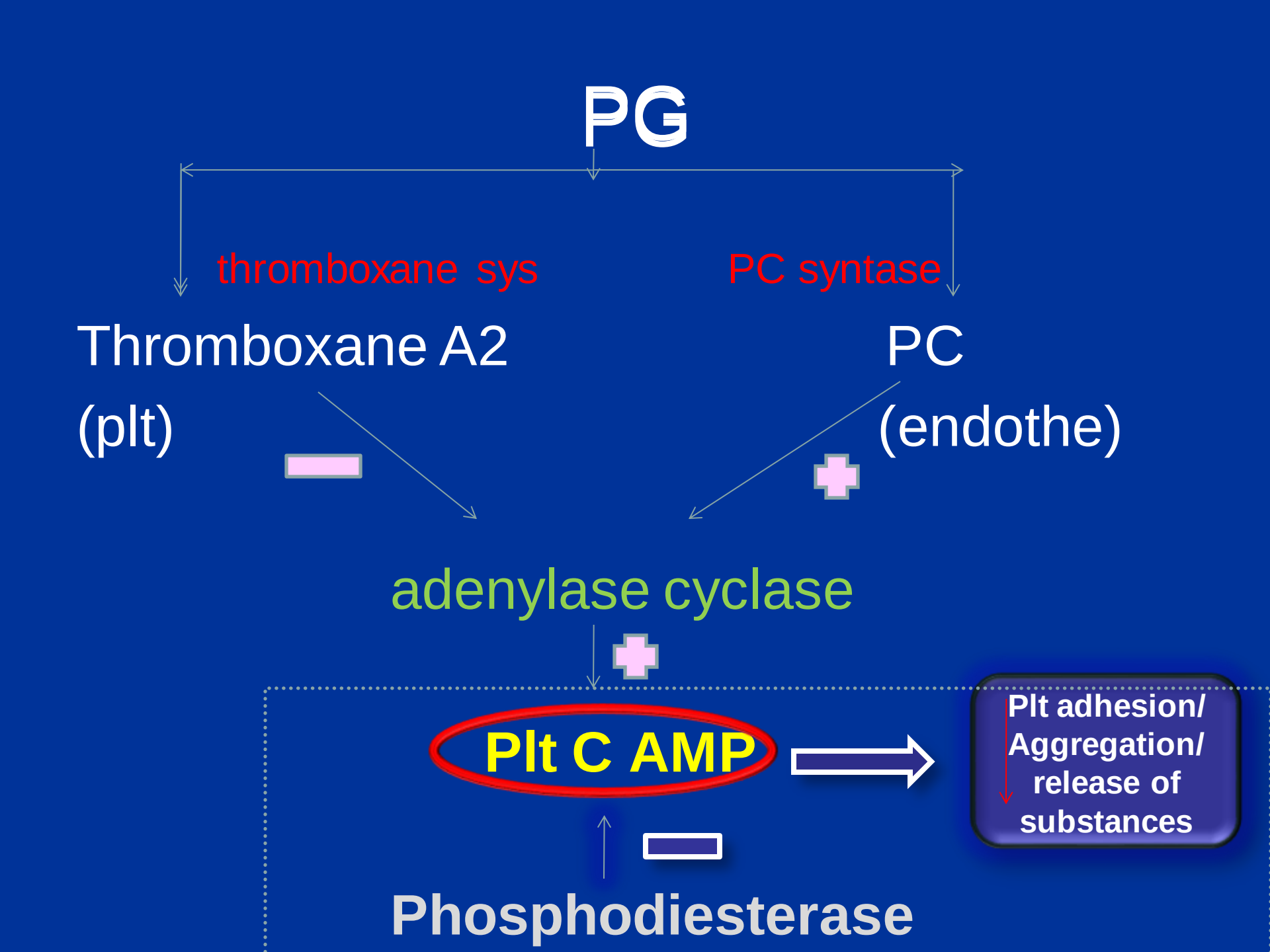
- Idiosyncratic neutropenia

Antiplatelet drugs

- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
  - Dipyridamole
- Glycoprotein IIb/IIIa receptor antagonists

Dipyridamole

- Phosphodiesterase inhibitor


PG
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(plt)
PC
(endothe)
adenylase cyclase
Plt C AMP
Plt adhesion/
Aggregation/
release of
substances
Phosphodiesterase

Dipyridamole cont;

Clinical use

- Ischemic stroke
- TIA

Side effects

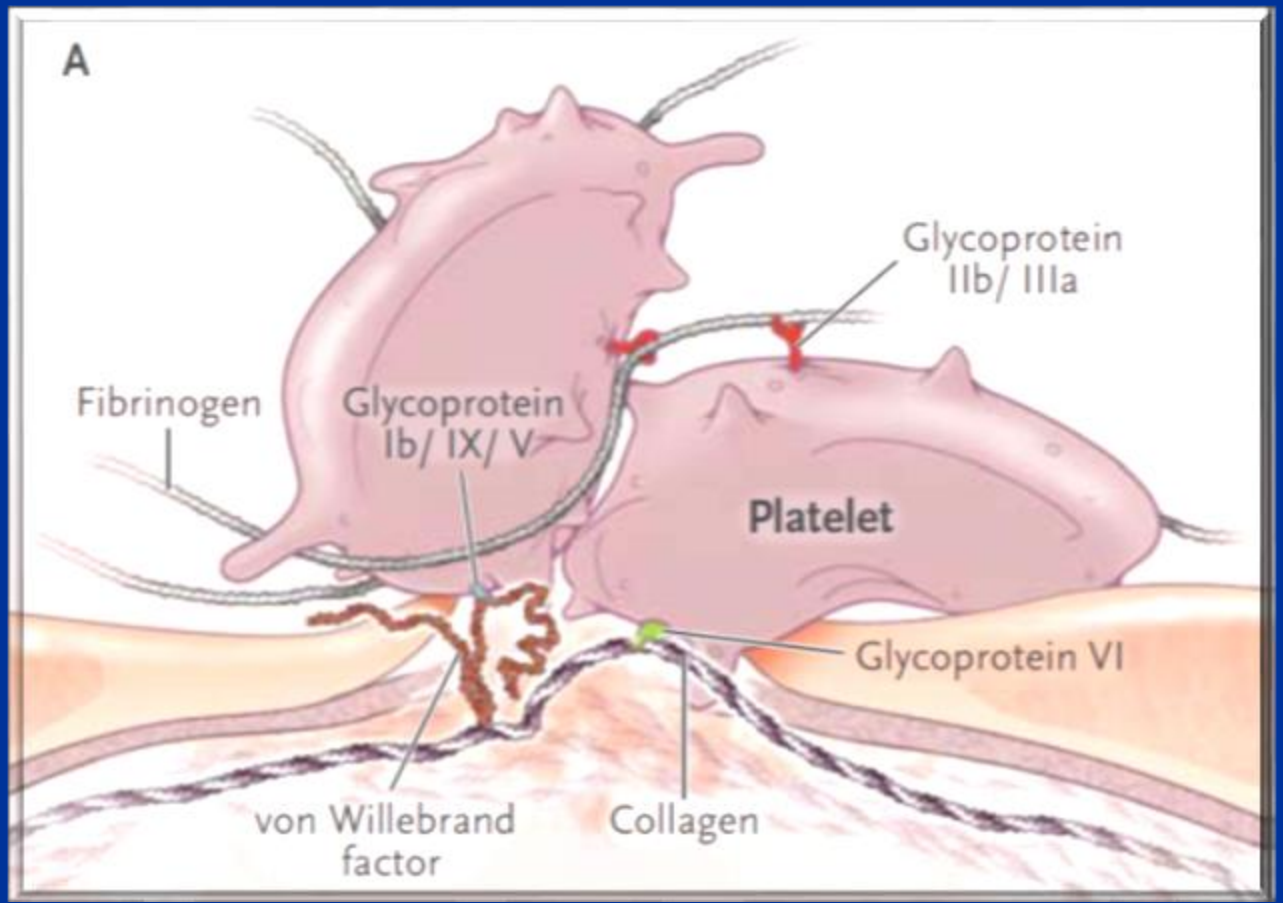
headache

Antiplatelet drugs

- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
- Glycoprotein IIb/IIIa receptor antagonists
  - Abciximab, Eptifibatide

Glycoprotein IIb/IIIa receptor antagonists

– Abciximab, Eptifibatide



- More complete inbibition of platlet function

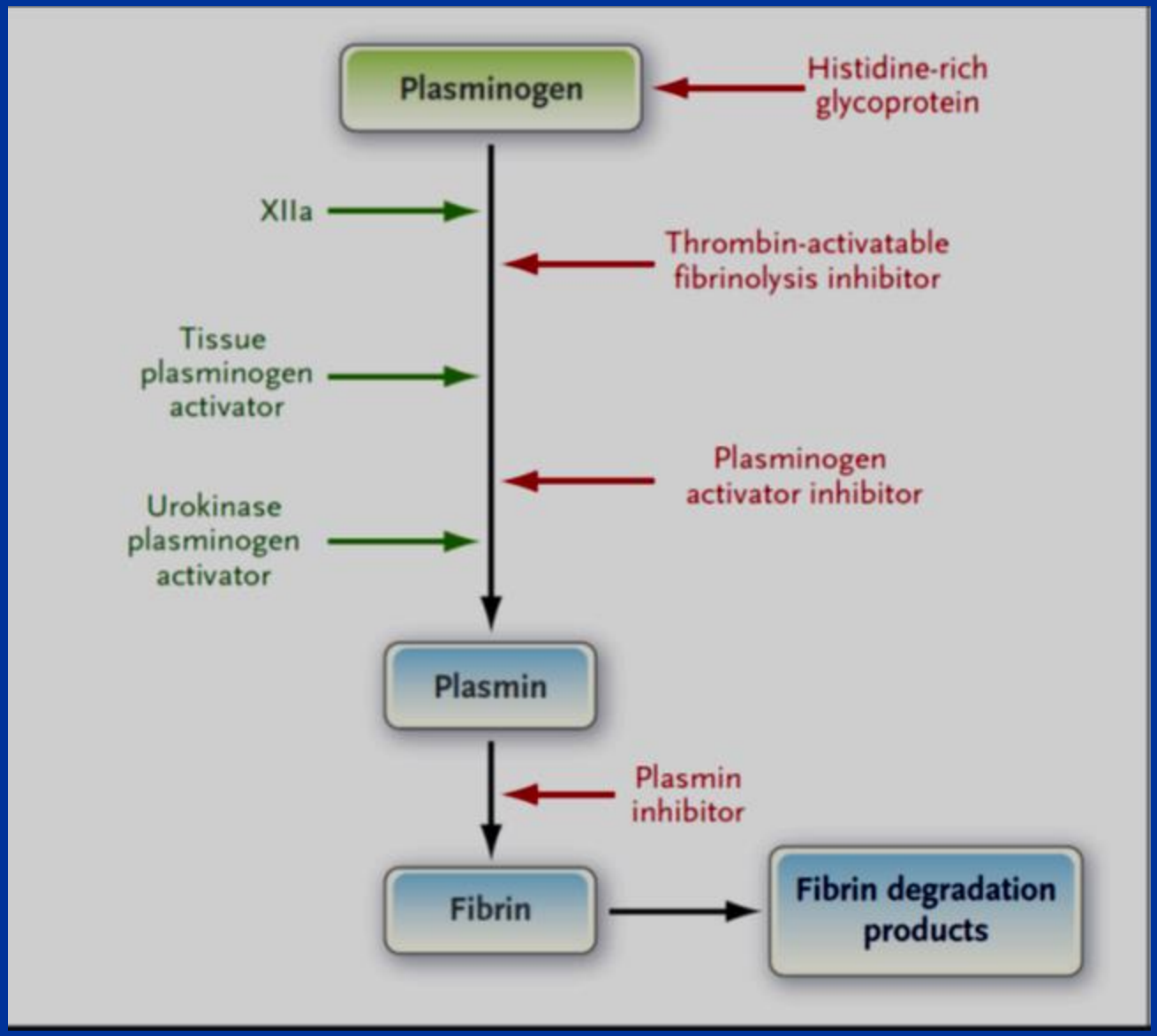
- inceased risk of bleeding

Drugs influencing coagulation

- Anticoagulants
- Antiplatelet drugs
- Thrombolytic drugs

Fibrinolysis

Fibrinolysis



Fibrinolysis

- Exogenously administered drugs
  - Streptokinase
  - Urokinase
  - Tissue plasminogen activator (tPA)

Streptokinase (SK)

- Binds to plasminogen & activates it
- Source: β haemolytic streptococci
- Immunogenic ; not repeated within one years of administration
- T 1/2 - 20 min
- IV


Streptokinase
1,500,000 I.U.
Streptokinase

SK cont ;

Clinical uses

- STEMI
- Massive pulmonary embolism
- Ischaemic stroke

- Better if give within first 3 h

Side effects

- Bleeding
- Multiple microemboli
- Cardic arrhythmias
- Allergy

Urokinase

- Human fetal kdney tisssue
- Activate plaminogen
- T1/2 – 15 min

tPA

- Produced by recombinant DNA technology
- Not immunogenic
- More clot-specific than SK – fibrin selective
- Less coagulation disturbance in plasma

- Short half life – iv infusion

Drug preparations: clotting deficiencies

- Vitamin K (Phytonadione (K1), Mephyton
  - Oral : 5 mg tablets
- Plasma fractions - for hemophilia
  - Antihemophilic factor (VIII, AHF)
  - Parenteral
- Factor IX complex (konyne HT, proplex T)

Drug preparations : to stop bleeding

- Systemic use : Tranexamic acid

- Inhibit plasminogen activation

Use –

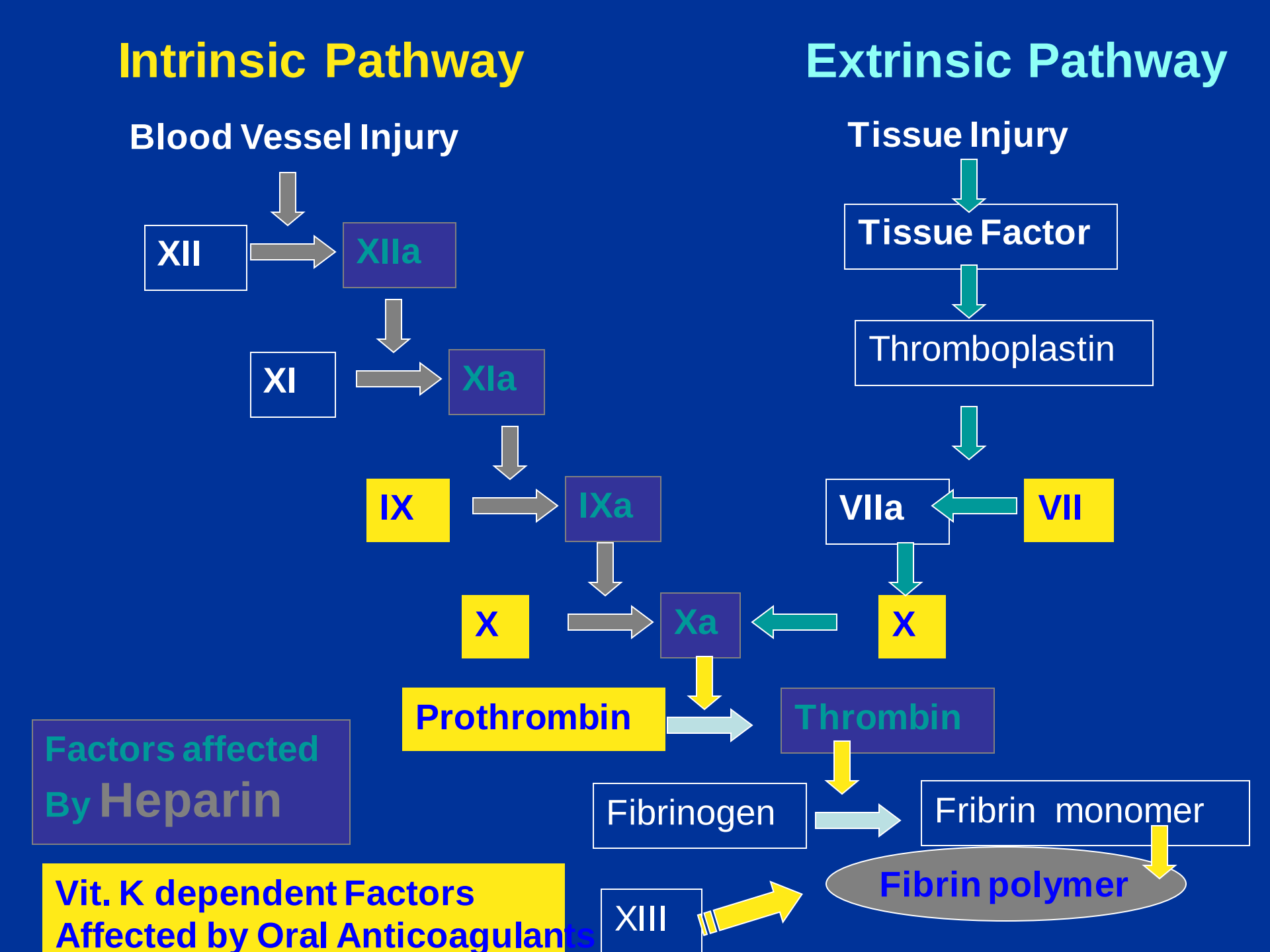
bleeding from thrombolytic drugs

- Hemorrhage form surgery
- Menorrhagia

Summary

Drugs influencing coagulation

- Anticoagulants
- Antiplatelet drugs
- Thrombolytic drugs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Factors affected
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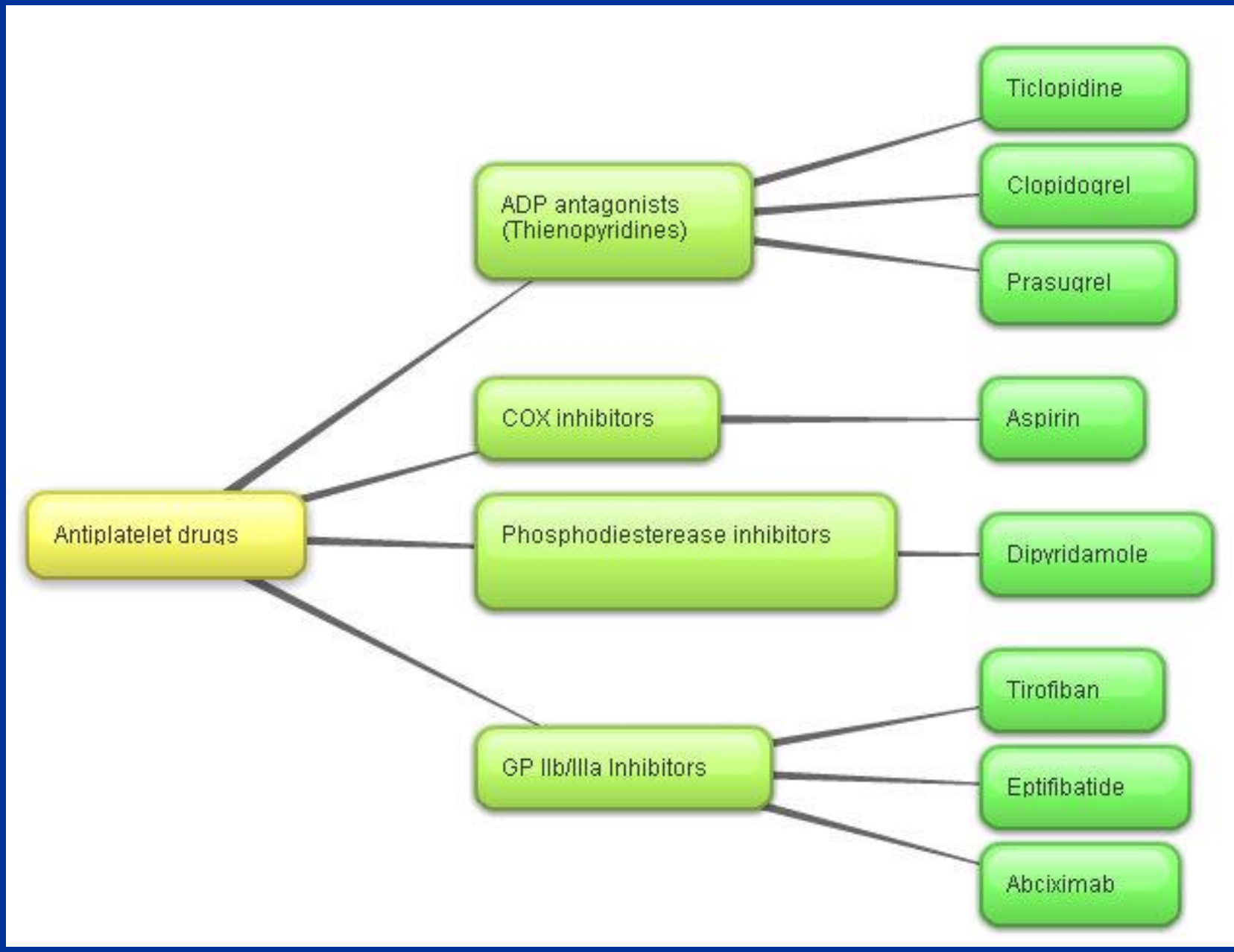
Fribrin monomer
Fibrin polymer
XIII
Vit. K dependent Factors
Affected by Oral Anticoagulants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GP IIb/IIIa Inhibitors
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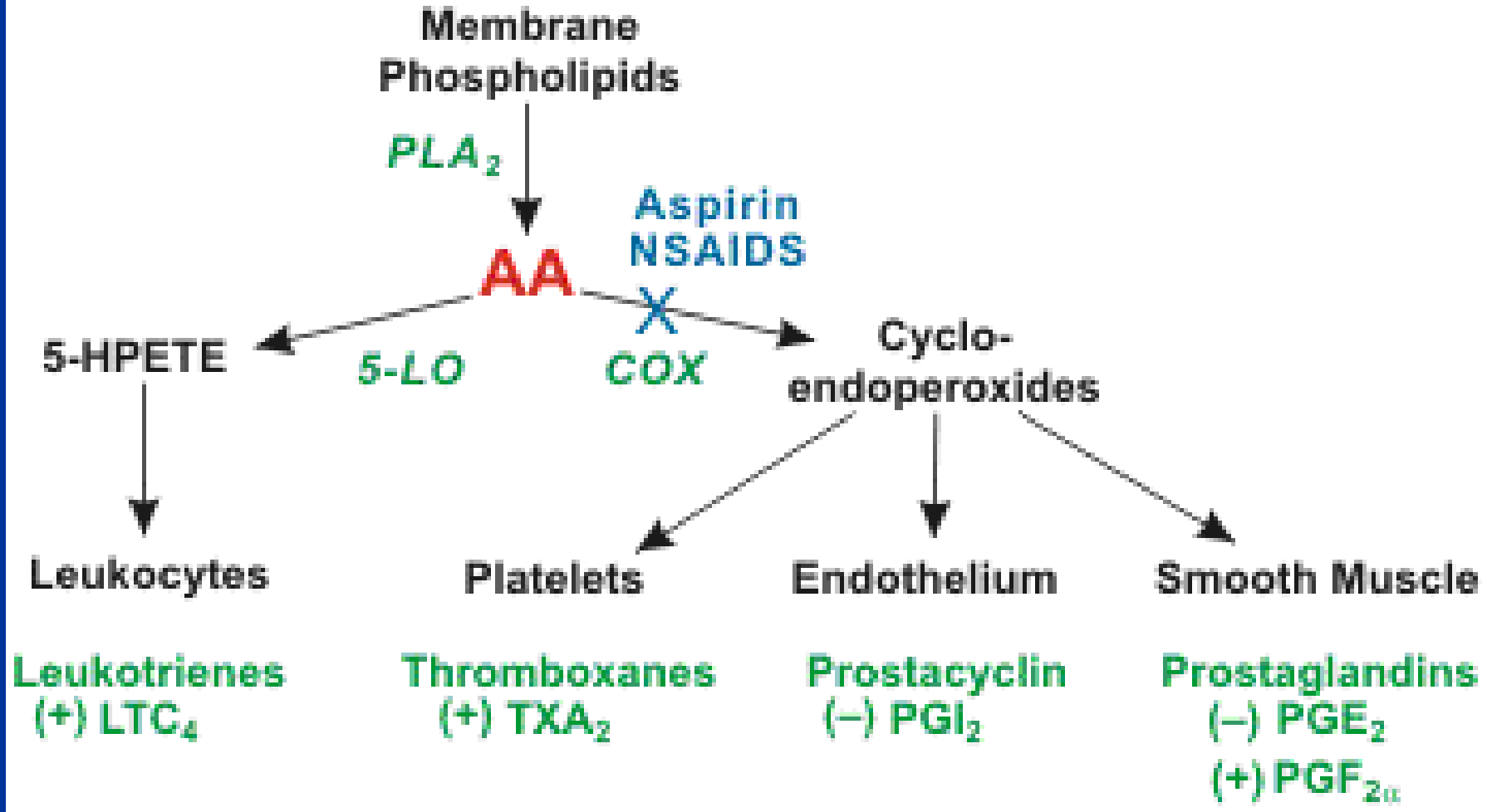
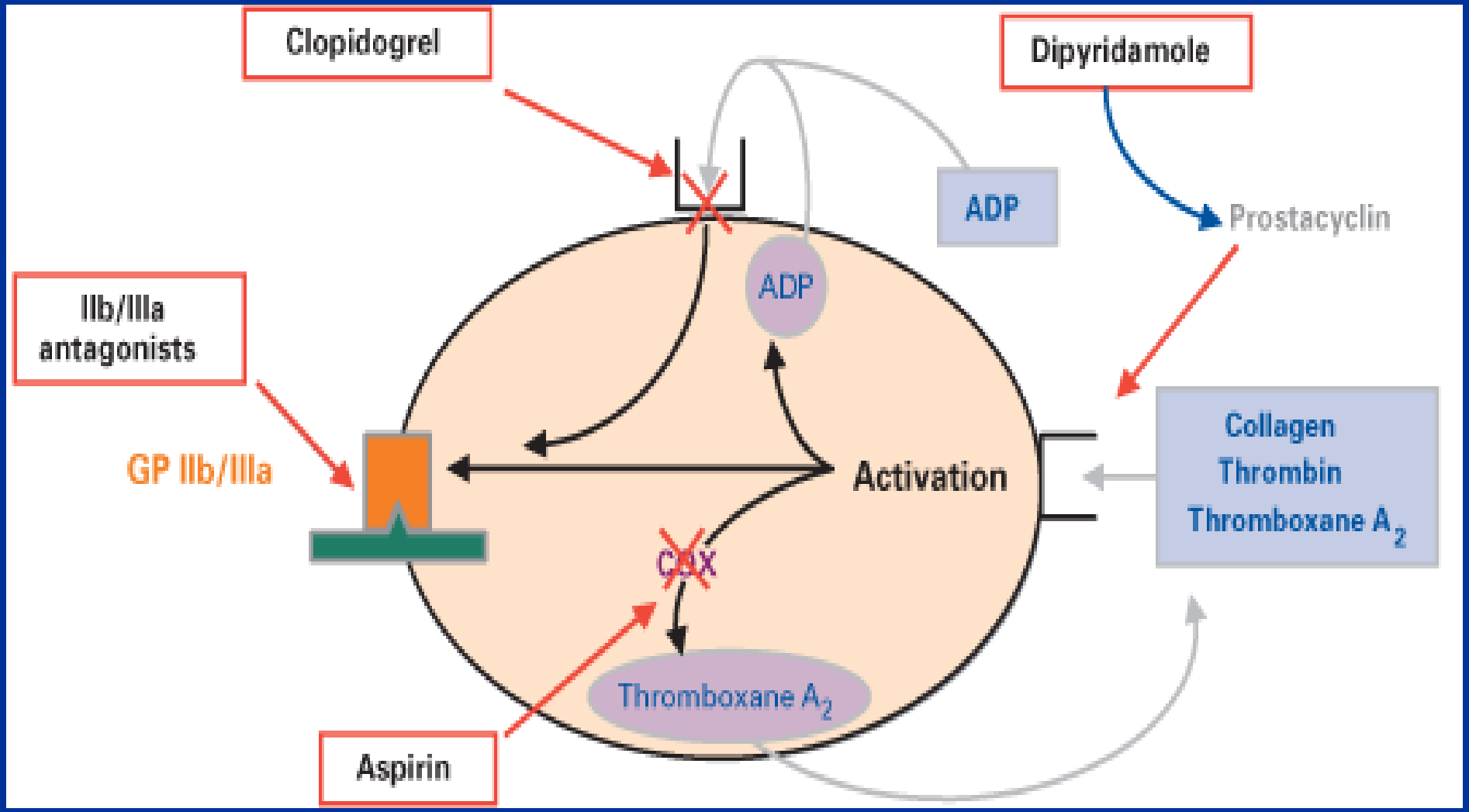
Eptifibatide
Abciximab



Abbreviations: AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.


Clopidogrel
Dipyridamole
ADP
Prostacyclin
IIb/IIIa antagonists
ADP
GP IIb/IIIa
Activation
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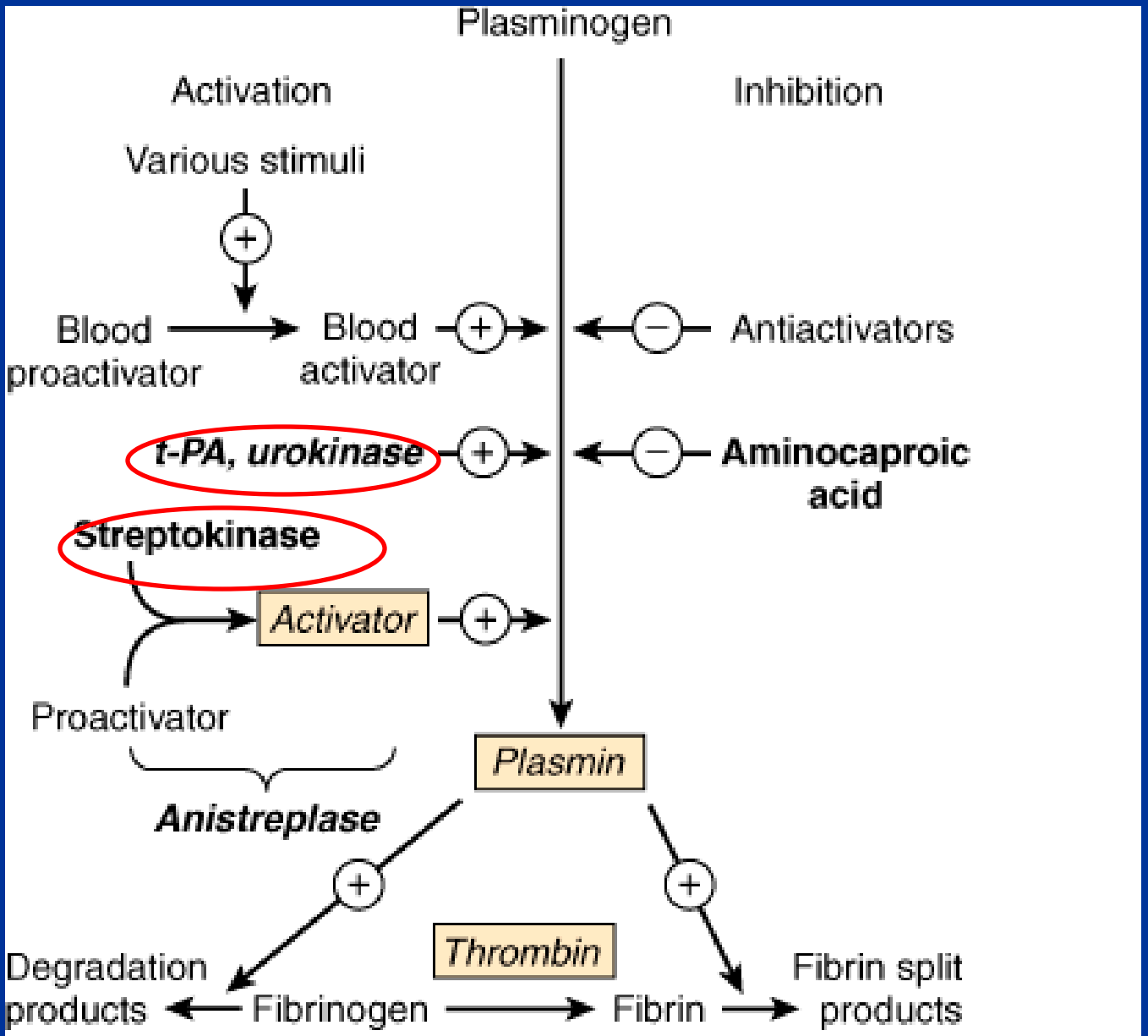
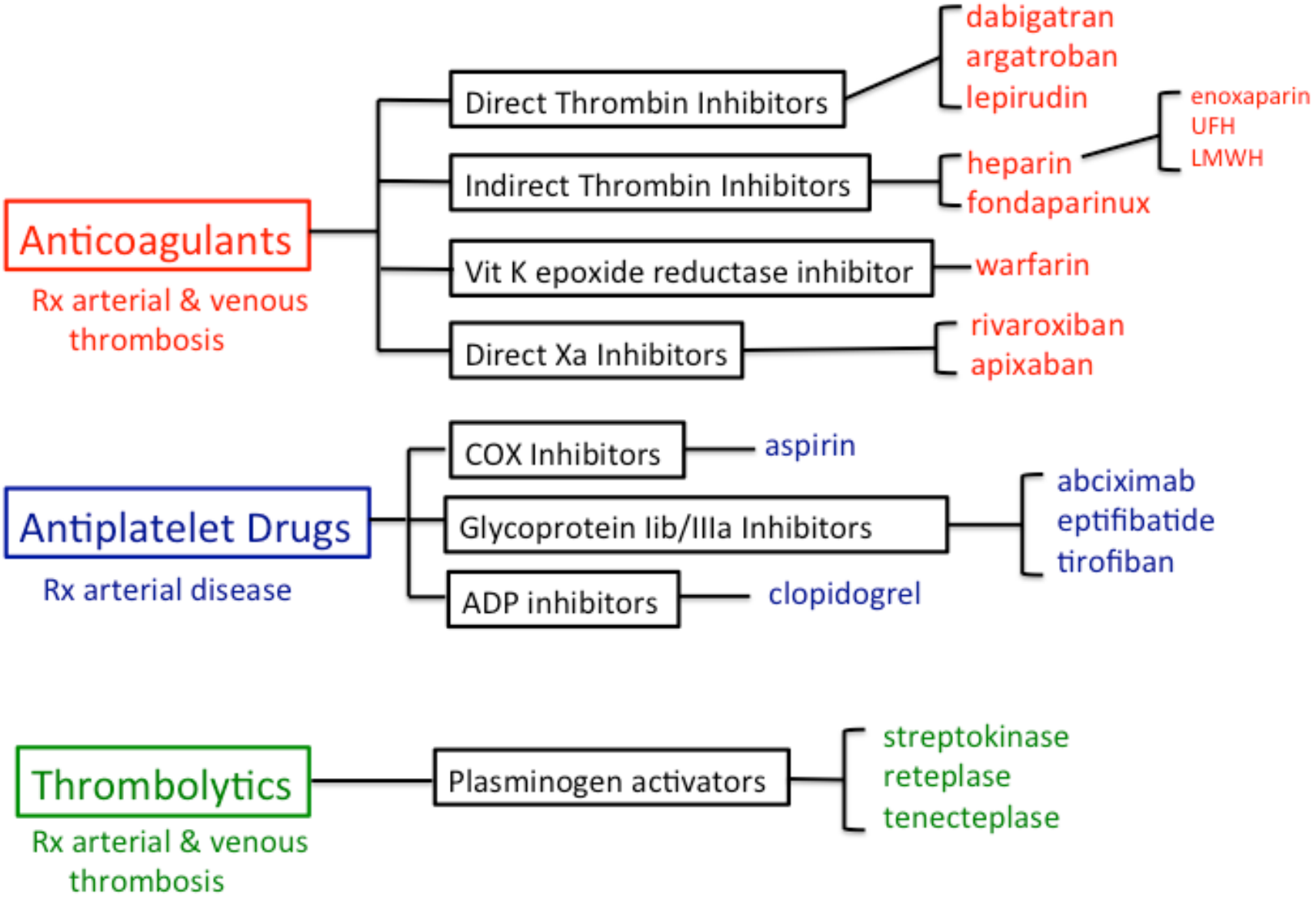
Thrombin
Thromboxane A2
COX
Thromboxane A2
Aspirin



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Drugs Used to Treat Clotting Disorders



Why do we need new anticoagulation drugs?

- Heparin-induced thrombocytopenia
- Heparin prophylaxis is imperfect
- Heparin - iv
- Heparin-associated osteoporosis
- Warfarin takes several days for its effect
- Warfarin is not as effective in some situations e.g antiphospholipid syndrome
- Warfarin interacts with many other drugs
- Warfarin is dangerous if not monitored