Drug use in Cardiovascular system

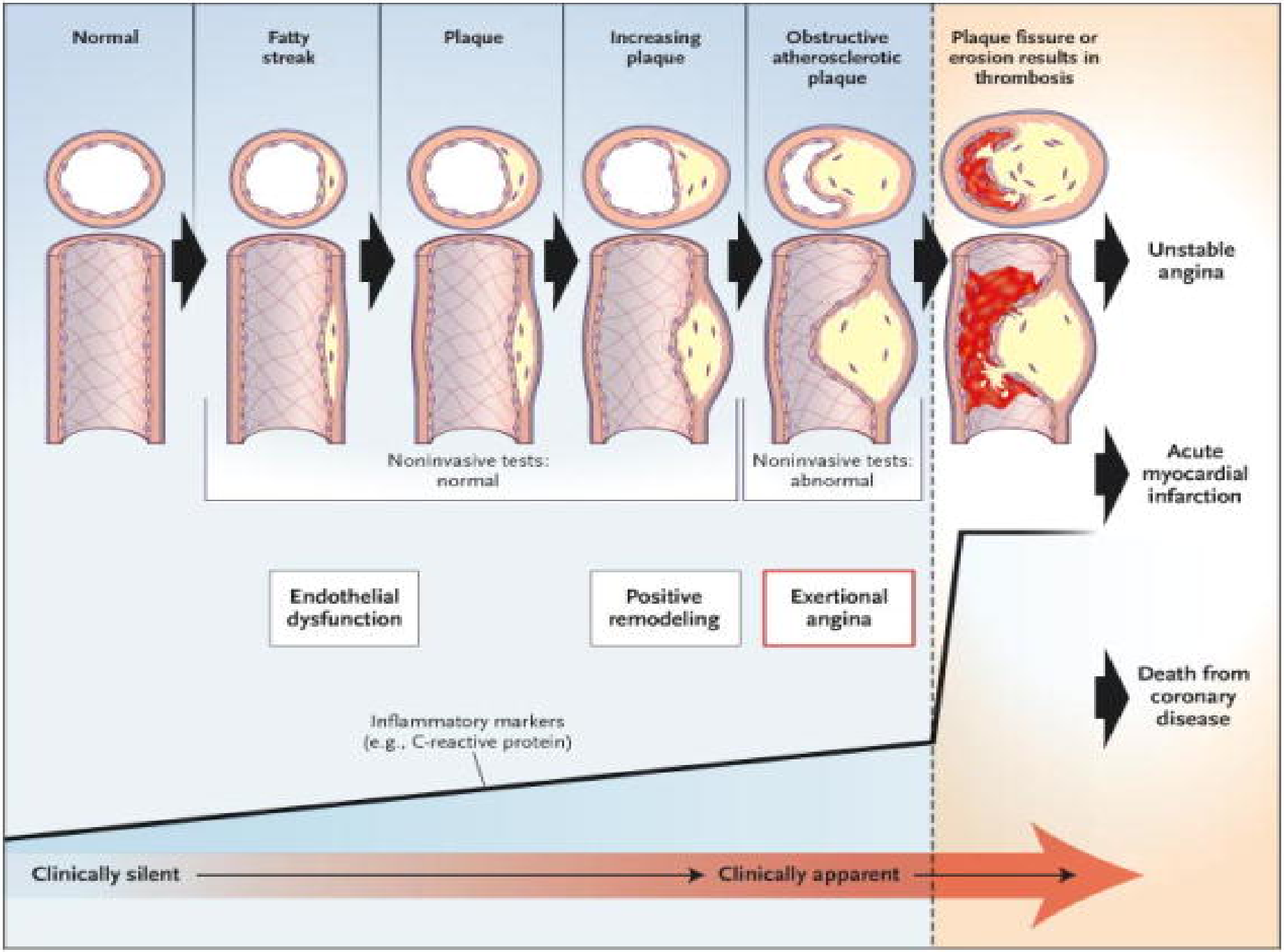
C. Dungkosintr
Cardiac unit
Department of Medicine

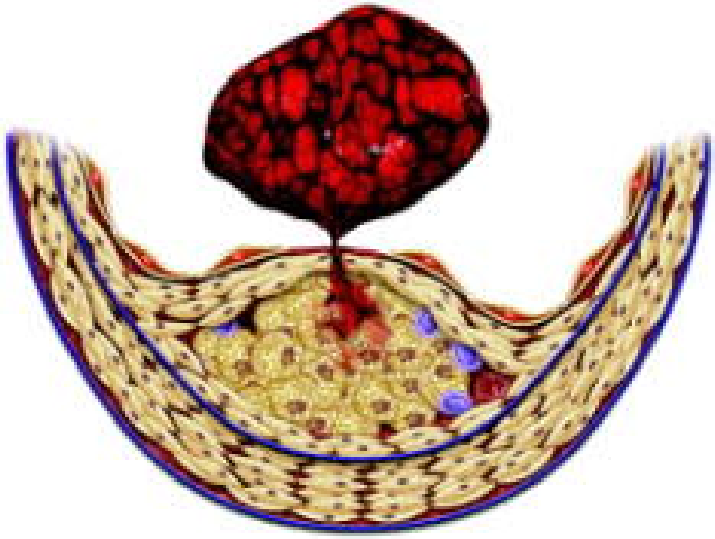
Cardiac drug

- Antihypertensive drugs
- Antiangina drugs
- Antiarrhythmic drugs
- Lipid lowering drugs
- Inotropic drugs
- Cardiac glycosides
- Fibrinolytic drugs
- Antithrombotic drugs
- Antiplatelet agents
- others

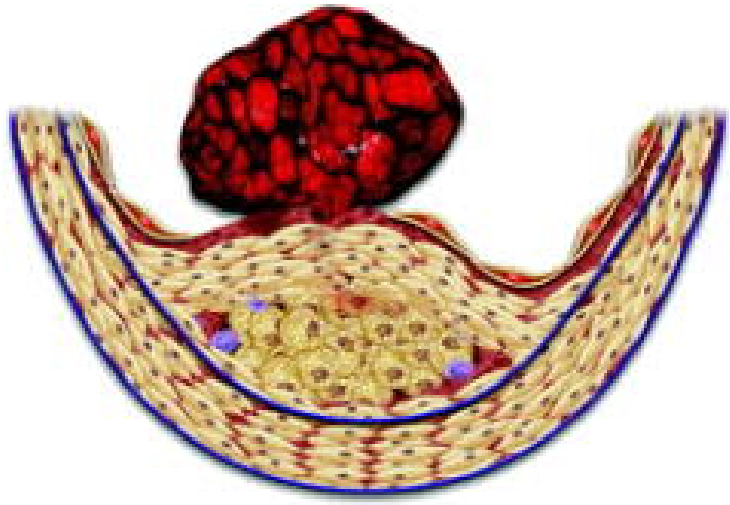
Cardiac drug

- Antihypertensive drugs
- Antianginal drugs
- Antiarrhythmic drugs
- Lipid lowering drugs
- Inotropic drugs
- Cardiac glycosides
- Fibrinolytic drugs
- Antithrombotic drugs
- Antiplatelet agents
- others

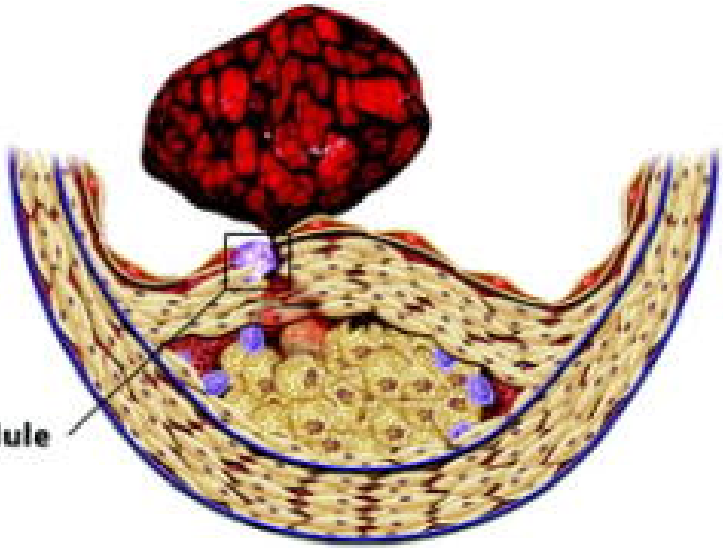

Normal
Fatty streak
Plaque
Increasing plaque
Obstructive atherosclerotic plaque
Plaque fissure or erosion results in thrombosis
Unstable angina
Noninvasive tests: normal
Noninvasive tests: abnormal
Acute myocardial infarction
Endothelial dysfunction
Positive remodeling
Exertional angina
Death from coronary disease
Inflammatory markers (e.g., C-reactive protein)
Clinically silent
Clinically apparent



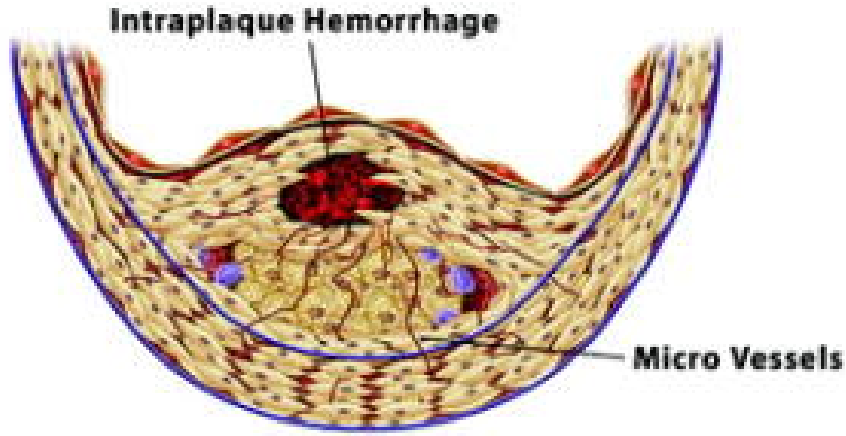
Rupture of Fibrous Cap



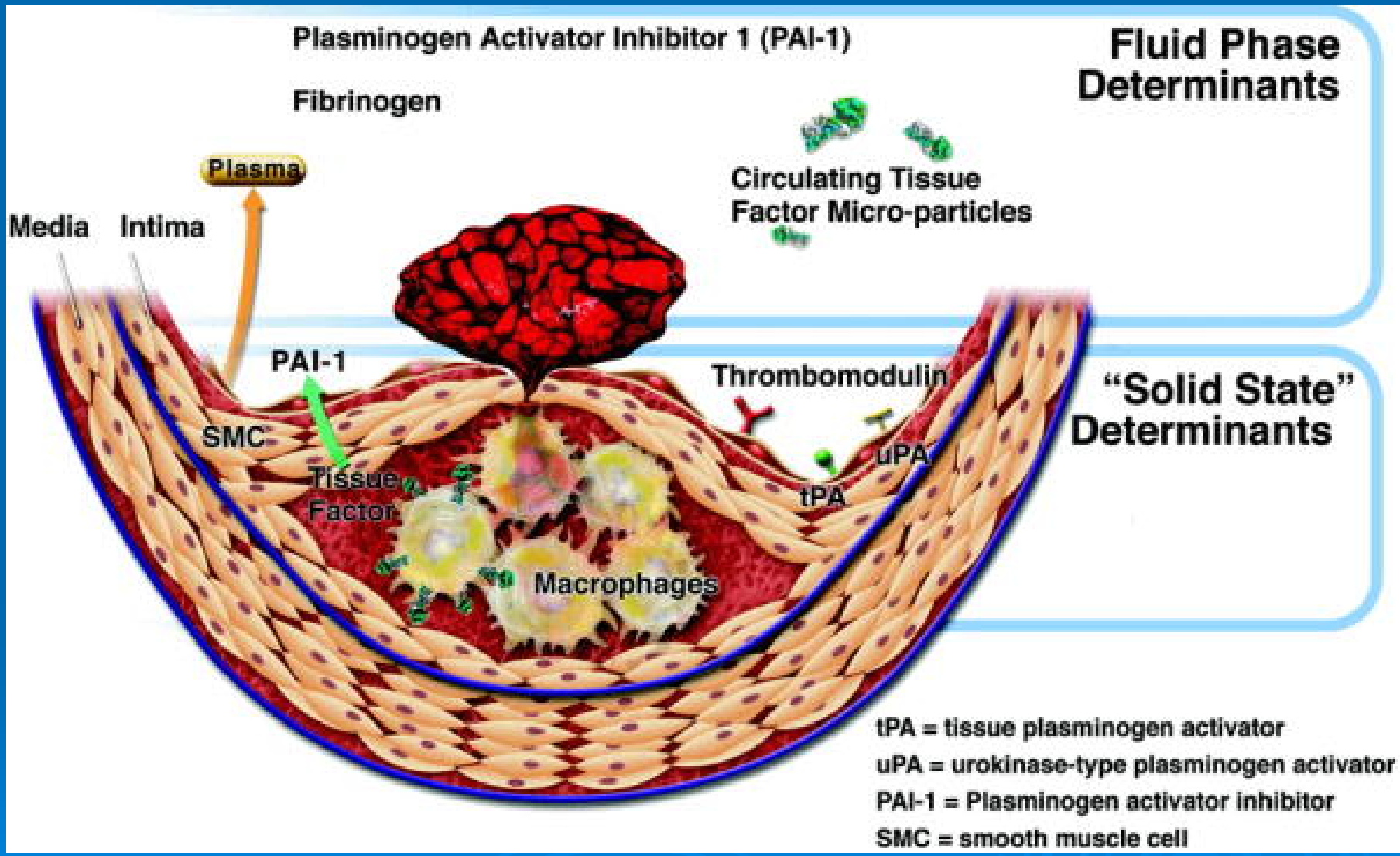
Superficial Erosion

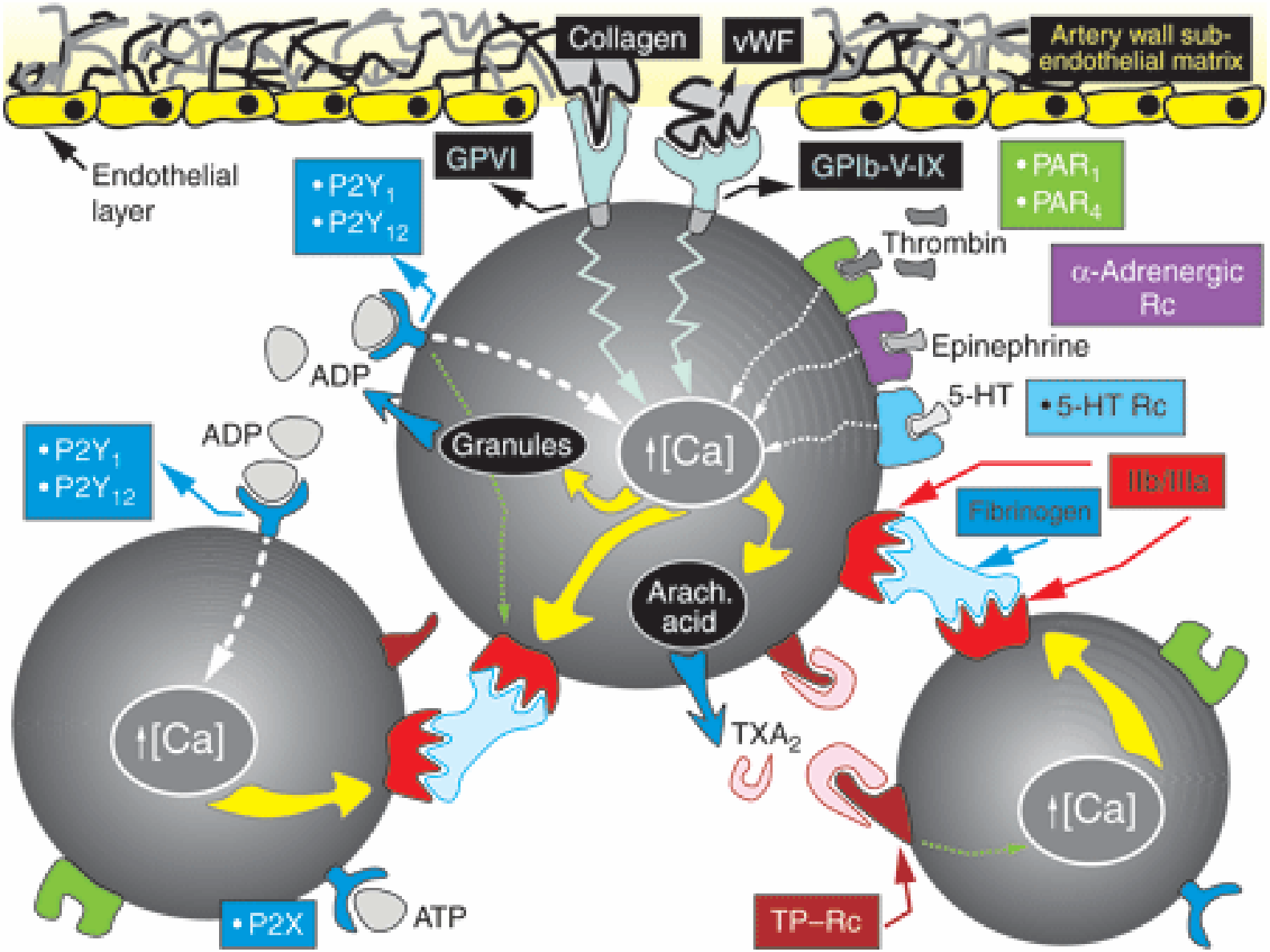


Erosion of Calcium Nodule

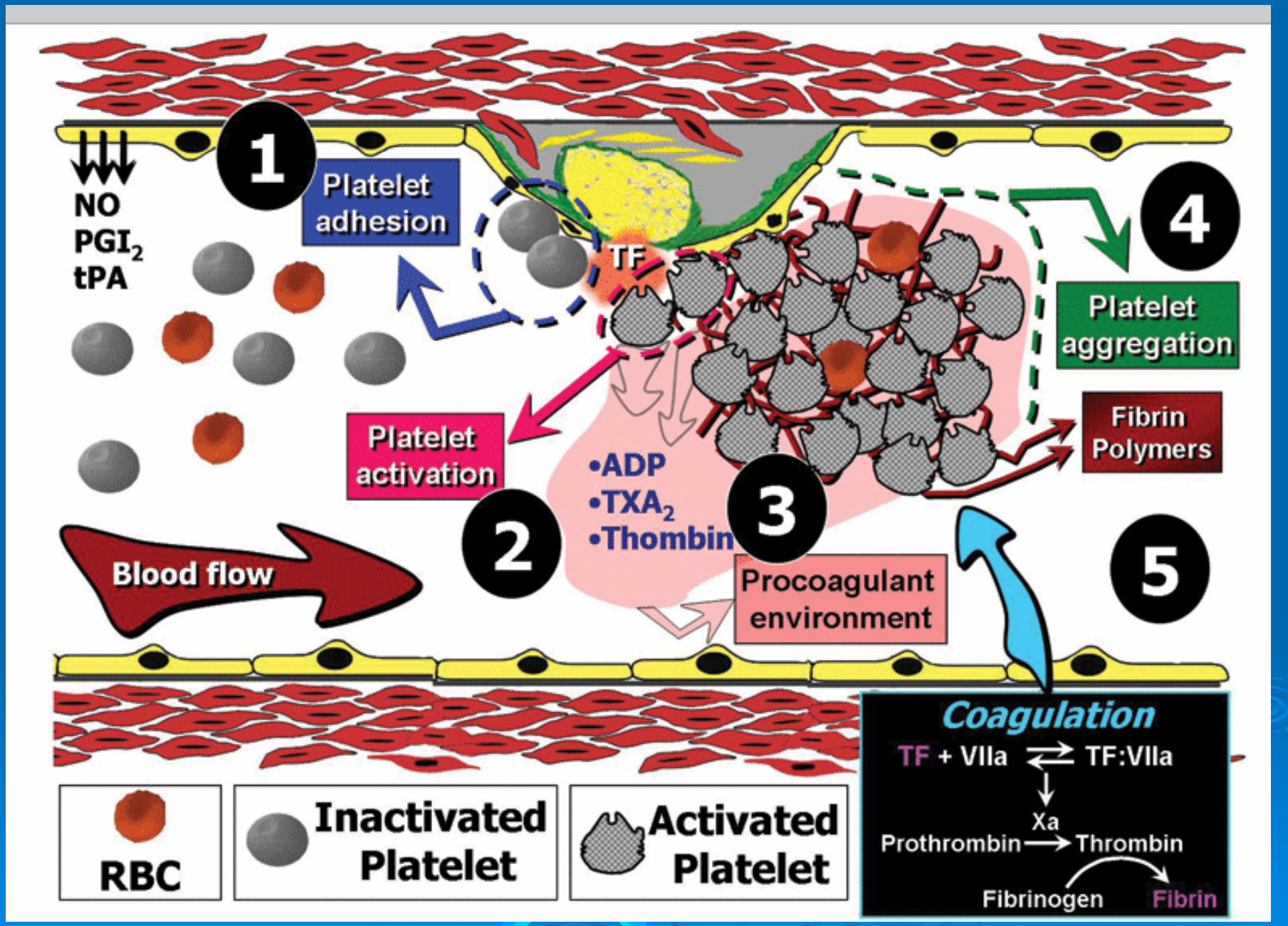


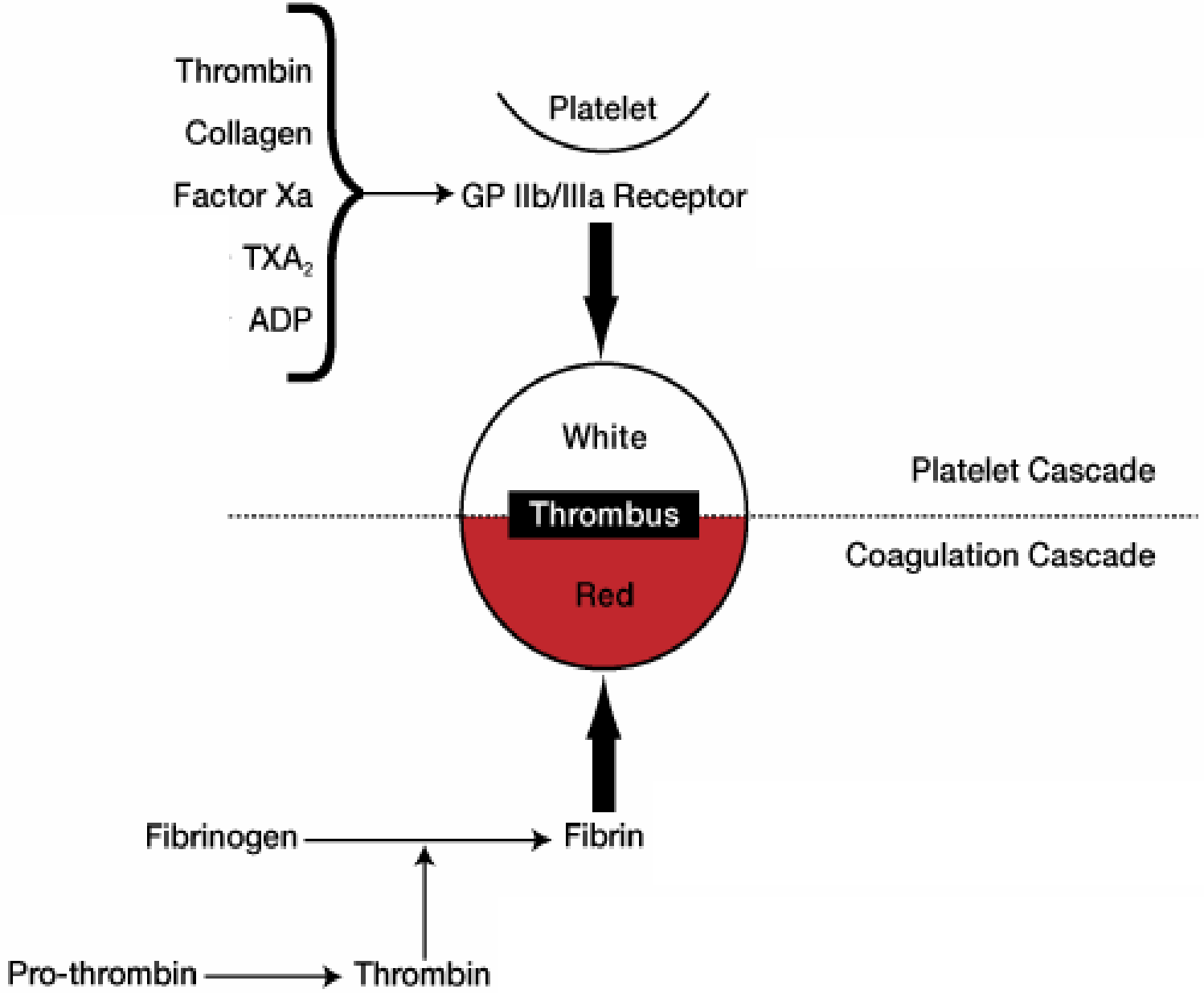
Intraplaque Hemorrhage

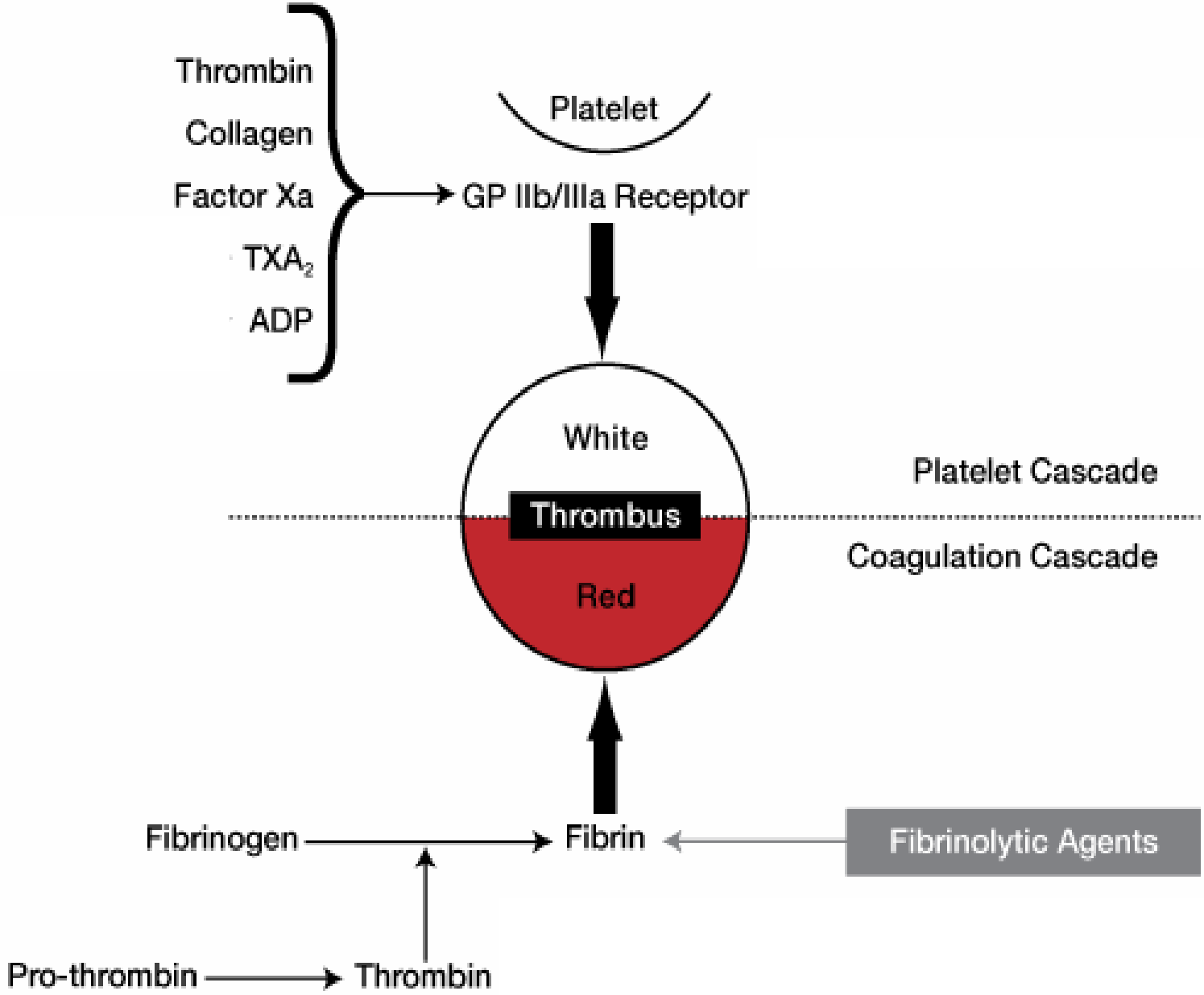

Plasminogen Activator Inhibitor 1 (PAI-1)
Fibrinogen
Fluid Phase Determinants
Circulating Tissue Factor Micro-particles
Plasma
Media
Intima
PAI-1
Thrombomodulin
"Solid State" Determinants
SMC
Tissue Factor
uPA
tPA
Macrophages
tPA = tissue plasminogen activator
uPA = urokinase-type plasminogen activator
PAI-1 = Plasminogen activator inhibitor
SMC = smooth muscle cell



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com


NO
PGI2
tPA
1
Platelet adhesion
TF
4
Platelet aggregation
Platelet activation
Fibrin Polymers
•ADP
•TXA2
•Thombin
2
3
Blood flow
Procoagulant environment
5
Coagulation
TF + VIIa
TF:VIIa
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin
RBC
Inactivated Platelet
Activated Platelet


Thrombin
Collagen
Factor Xa
TXA_2
ADP
Platelet
GP IIb/IIIa Receptor
White
Thrombus
Red
Platelet Cascade
Coagulation Cascade
Fibrinogen
Fibrin
Pro-thrombin
Thrombin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Collagen
Factor Xa
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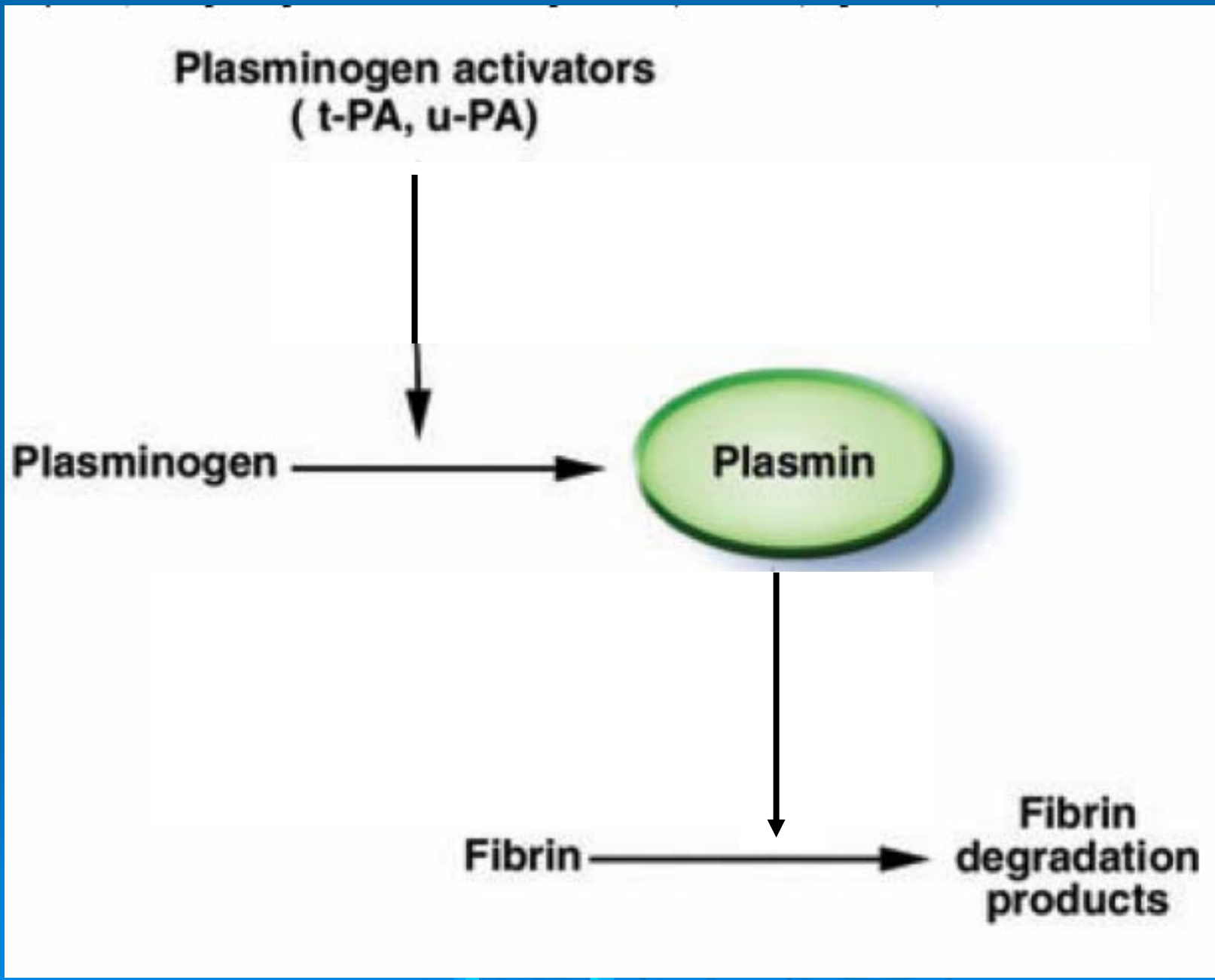
ADP
Platelet
GP IIb/IIIa Receptor
White
Thrombus
Red
Platelet Cascade
Coagulation Cascade
Fibrinogen
Fibrin
Fibrinolytic Agents
Pro-thrombin
Thrombin


Plasminogen activators
(t-PA, u-PA)
Plasminogen
Plasmin
Fibrin
Fibrin
degradation
products

Fibrinolytic agent

- Indications
  - acute ST elevation MI
  - massive pulmonary embolism
  - acute arterial thrombosis

Fibrinolytic agent

Contraindications: Absolute

- Any prior intracranial hemorrhage
- Structural cerebrovascular abnormality: AVM
- Known intracranial malignant lesion
- Ischemic stroke within 3 months (except acute stroke ≤ 3 hours)
- Aortic dissection
- Active bleeding or bleeding diathesis (except menses)
- Significant closed head or facial trauma(≤ 3 months)

Fibrinolytic agent

Contraindications: Relative

- History of chronic severely controlled hypertension
- SBP > 180 mmHg or DBP > 110 mmHg on presentation
- Prior ischemic stroke (≥ 3 months)
- Dementia
- Intracranial pathology
- Traumatic or prolonged(>10 min) CPR
- Major surgery (<3 weeks)
- Internal bleeding (<2-4 weeks)
- Noncompressible vascular punctures
- For streptokinase/anistreplase:prior exposure or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants

Fibrinolytic agent

- Streptokinase (Streptase)
- Alteplase (Actilyse)
- Tenecteplase (Metalyse)

Fibrinolytic agent

- Streptokinase (Streptase)

  1.5 Miu in 1 hr

  250,000 iu by infusion over 30 min follow by 100,000 iu/hr

- Alteplase (Actilyse)

  90 min regimen: 15 mg bolus then infuse 0.75 mg/kg (max 50 mg) over 30 min follow by 0.5 mg/kg (max 35 mg) over 60 min

  3 hr regimen: 10 mg bolus then infuse 50 mg over the first hr follow by 40 mg over 3 hr

  100 mg in 2 hr(10 mg in 2 min then infuse 90 mg over 2 hr)

- Tenecteplase (Metalyse)

  30-50 mg depend on body weight

Fibrinolytic agent

- Side effects

  - bleeding:

  the most serious: Intracerebral hemorrhage (0.5-1%)

  the most common bleeding site: vascular access

  other: GI, GU, retroperitoneal site

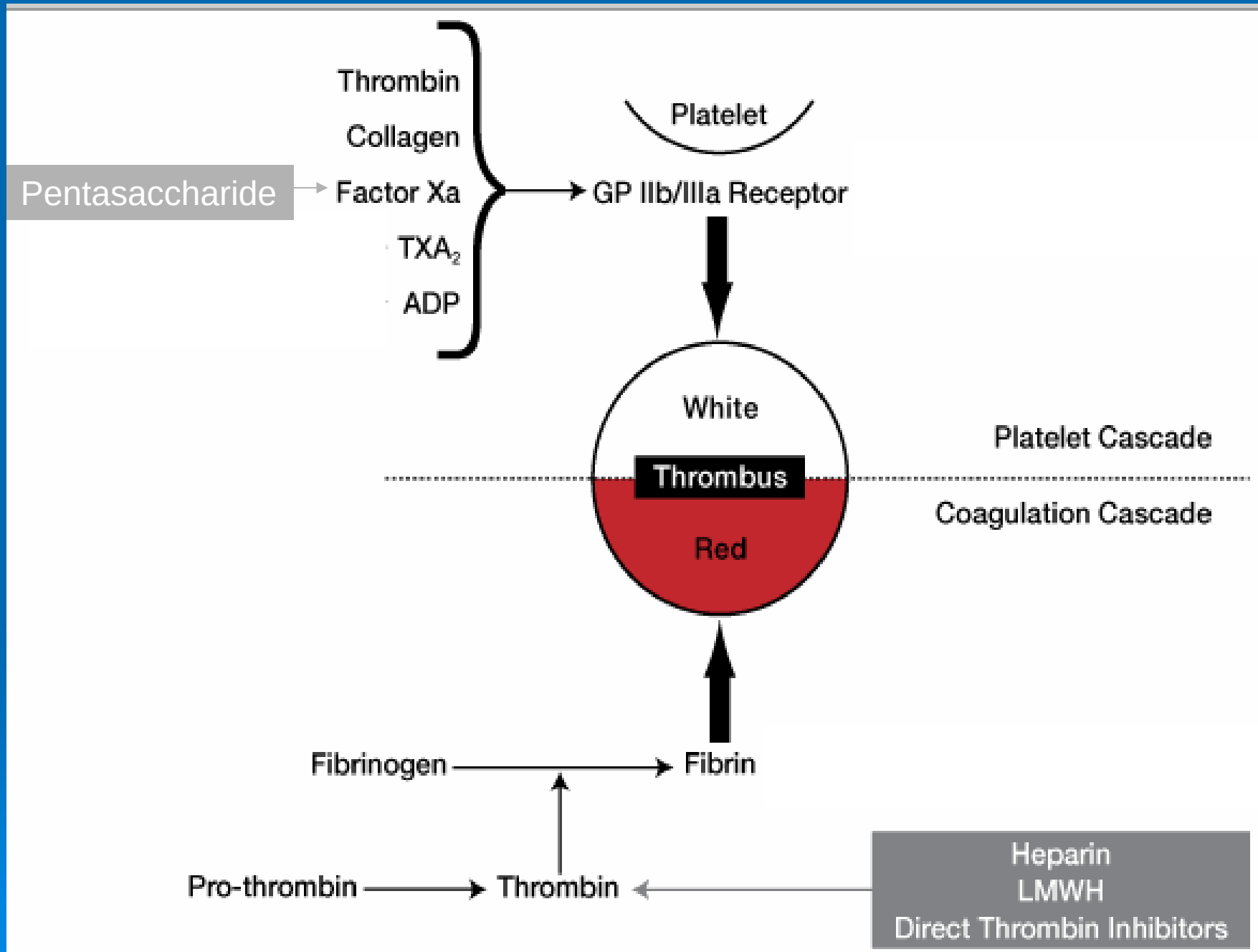
  - allergic reactions

  hypotension, flushing, chill, fever, vasculitis, interstitial nephritis, life threatening anaphylaxis

Fibrinolytic agent

	Streptokinase	Alteplase	tenecteplase
Dose	1.5 M iu	max 100 mg	30-50 mg
Duration	1 hr	90 min	5-10 sec
Bolus	X	√	√
Antigenic	√	x	x
Allergic reactions	√	x	x
Systemic fibrinogen depletion	+++	+	+
90-min patency rate	50%	>70%	>70%
Cost	cheap	expensive	expensive

Antithrombotic agent

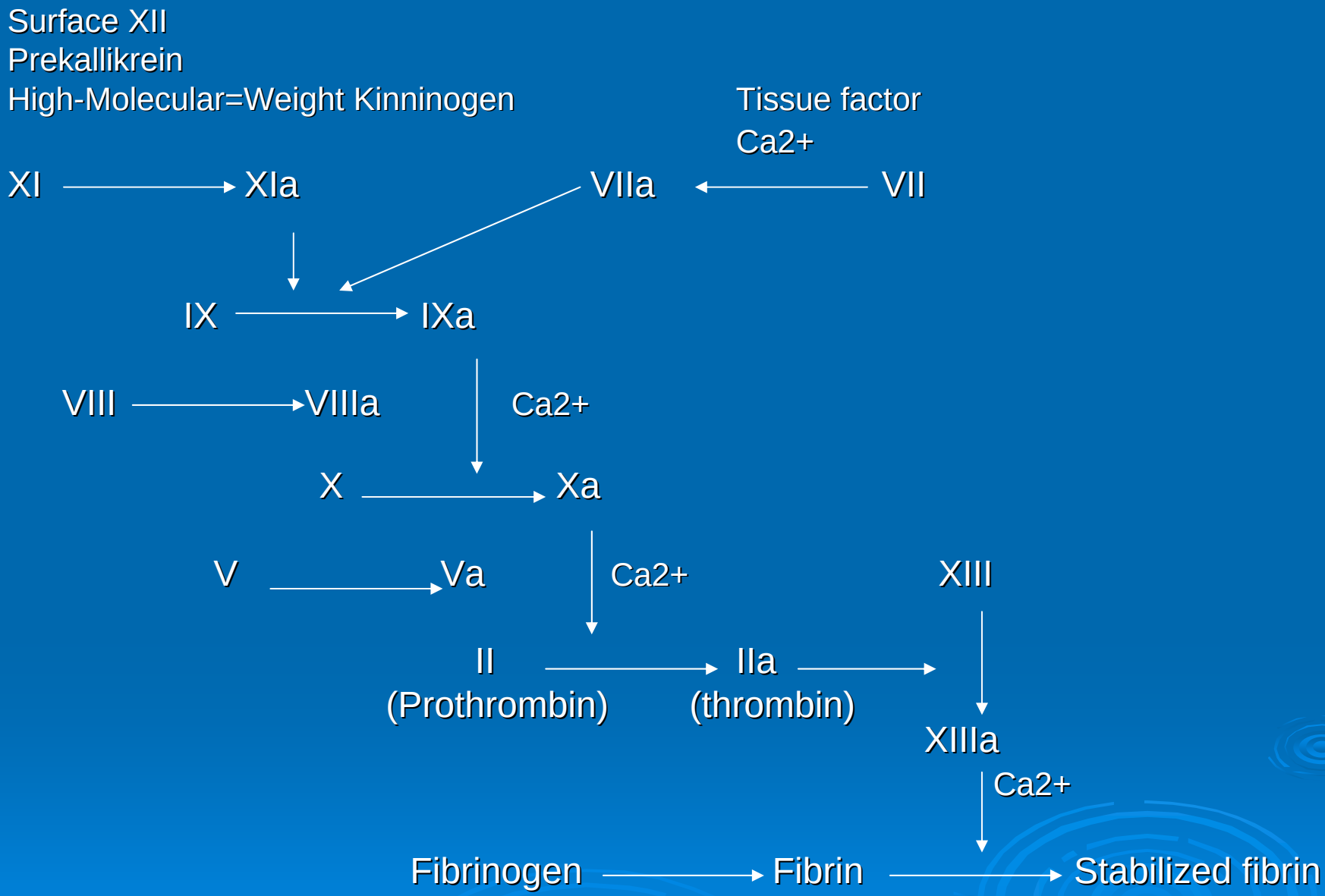

Thrombin
Collagen
Pentasaccharide
Factor Xa
TXA2
ADP
Platelet
GP IIb/IIIa Receptor
White
Thrombus
Red
Platelet Cascade
Coagulation Cascade
Fibrinogen
Fibrin
Pro-thrombin
Thrombin
Heparin
LMWH
Direct Thrombin Inhibitors

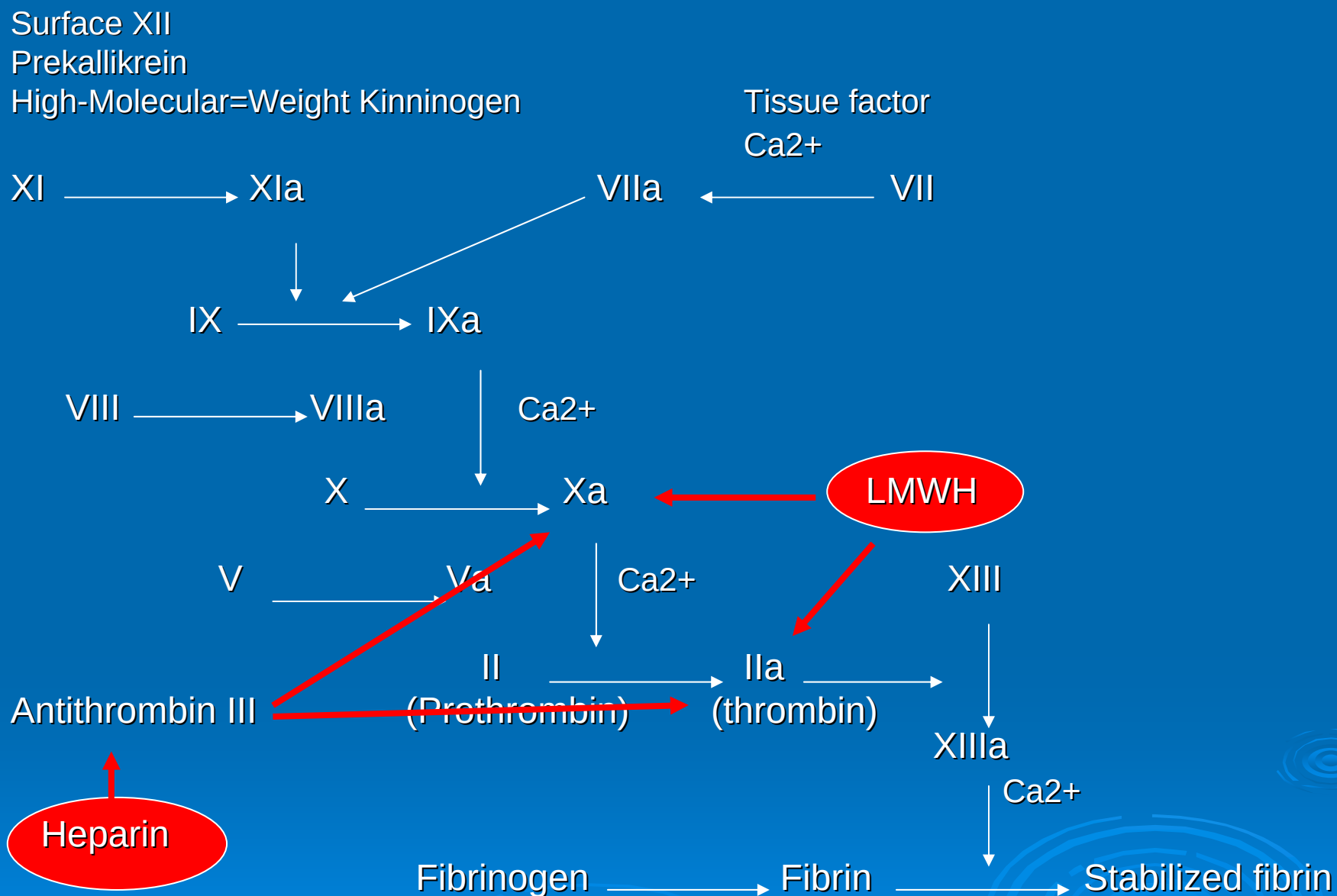
Heparin

Heparin

- 2 types
  - Unfractionated heparin (UH)
  - low molecular weight heparin (LMWH)

- Indications
  - acute coronary syndromes
  - acute venous thromboembolism


Surface XII
Prekallikrein
High-Molecular=Weight Kinninogen
Tissue factor
Ca2+
XI
XIa
VIIa
VII
IX
IXa
VIII
VIIIa
Ca2+
X
Xa
V
Va
Ca2+
XIII
II
(Prothrombin)
IIa
(thrombin)
XIIIa
Ca2+
Fibrinogen
Fibrin
Stabilized fibrin


Surface XII
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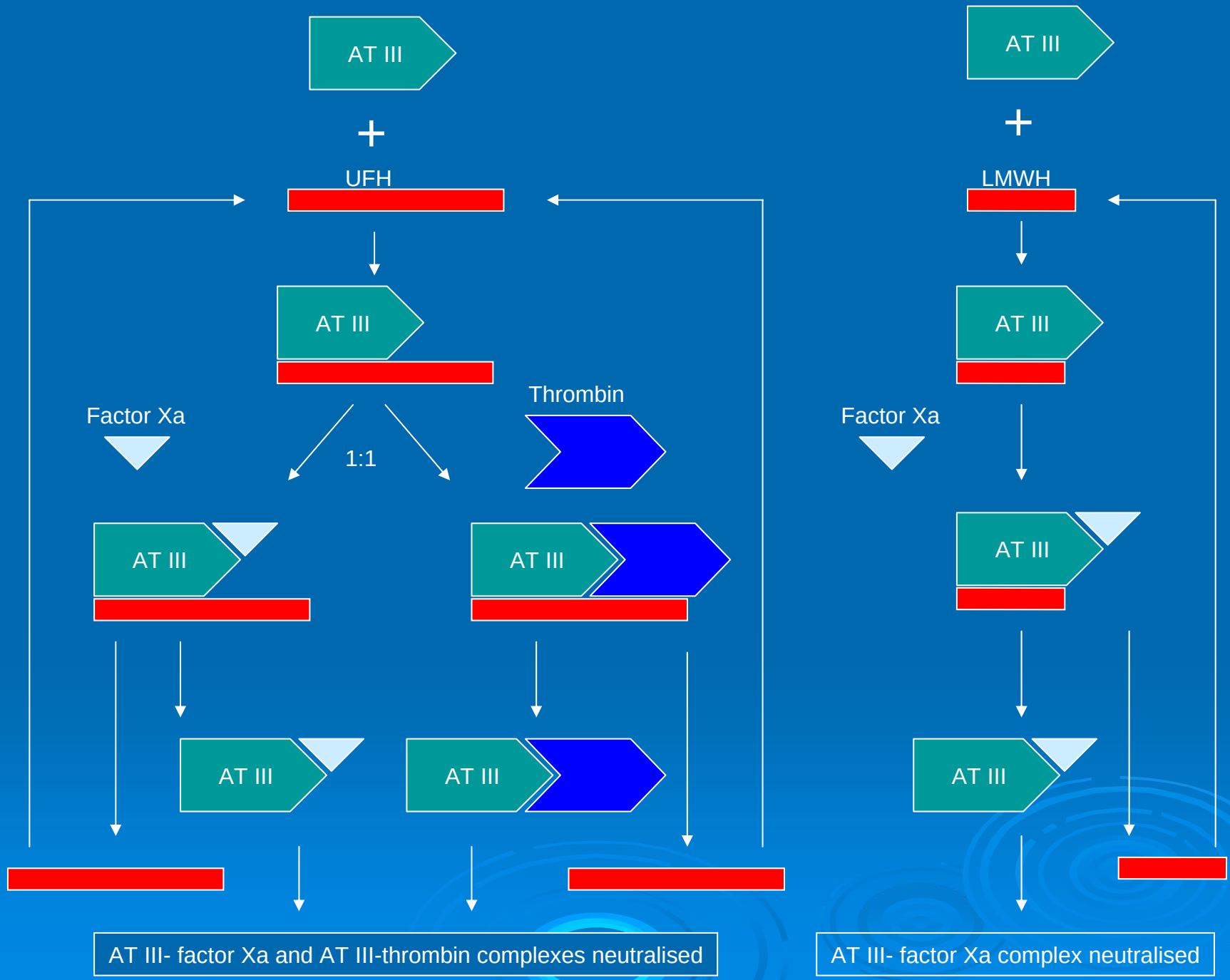
VIII
VIIIa
Ca2+
X
Xa
LMWH
V
Va
Ca2+
XIII
II
(Prothrombin)
IIa
(thrombin)
Antithrombin III
XIIIa
Ca2+
Heparin
Fibrinogen
Fibrin
Stabilized fibrin


AT III
+
UFH
AT III
Factor Xa
1:1
Thrombin
AT III
AT III
AT III
AT III
AT III
+
LMWH
AT III
Factor Xa
AT III
AT III
AT III- factor Xa and AT III-thrombin complexes neutralised
AT III- factor Xa complex neutralised

Heparin

- Side effects

Toxic side effects

- HIT Type I (mild) and Type II (severe)
- Syndrome of thrombohemorrhagic complications
- Hypotension
- Spontaneous arterial emboli

General side effects

- Delayed wound healing
- Minor bleeding
- Priapism
- Osteoporosis (chronic therapy)
- Hypoaldosteronism

J Interv Cardiol 2003;16:357

Heparin

- Side effects

Hypersensitivity

Urticaria, Conjunctivitis, rhinitis, asthma, cyanosis, tachypnea, fever, angioneurotic shock

Rarely-hemorrhagic skin necrosis,vasospastic reactions

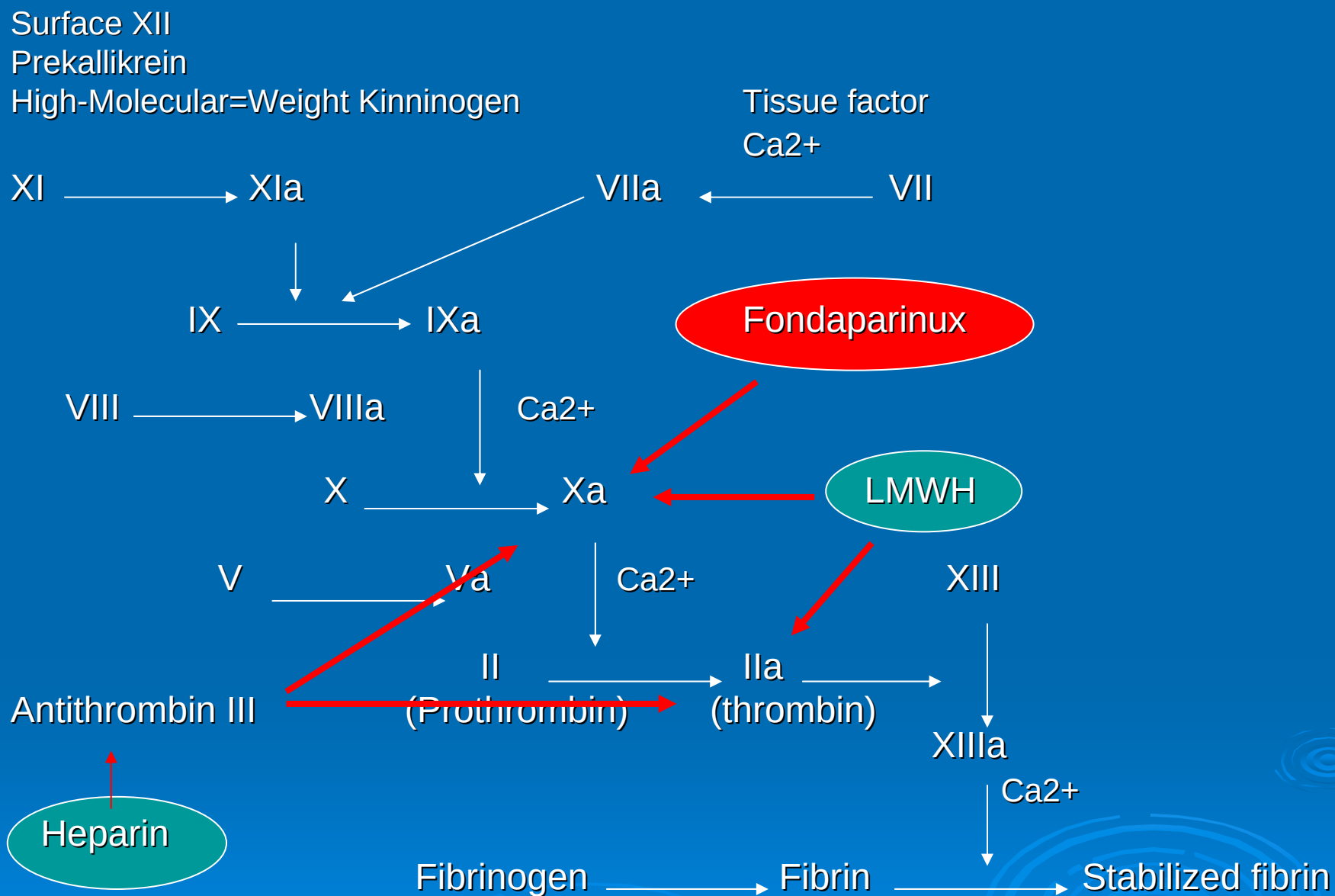
Safe use in pregnancy

Chronic administration: osteopenia for mother (B)

J Interv Cardiol 2003;16:357

	UH	LMWH
Molecular weight	3,000-30,0000 Da	4,000-6,000 Da
Mechanism of action		
F Xa: F II	1 : 1	2-4 : 1
Pharmacokinetics		
- binding to		
plasma proteins	variable	minimal
endothelial and macrophage	variable	no binding
- anticoagulant effects	unpredictable	predictable
- half life	short	longer
- protamine	reversible	partially reversible
Labolatory monitoring	ACT	not required, F Xa level
Cost	inexpensive	more expensive
Thrombocytopenia		
-Type I (mild)	10-20%	less
- type II (serious)	0.3-3.0%	

Fondaparinux


Surface XII
Prekallikrein
High-Molecular=Weight Kinninogen
Tissue factor
Ca2+
XI
XIa
VIIa
VII
IX
IXa
Fondaparinux
VIII
VIIIa
Ca2+
X
Xa
LMWH
V
Va
Ca2+
XIII
II
IIa
Antithrombin III
(Prothrombin)
(thrombin)
XIIIa
Ca2+
Heparin
Fibrinogen
Fibrin
Stabilized fibrin

Fondaparinux

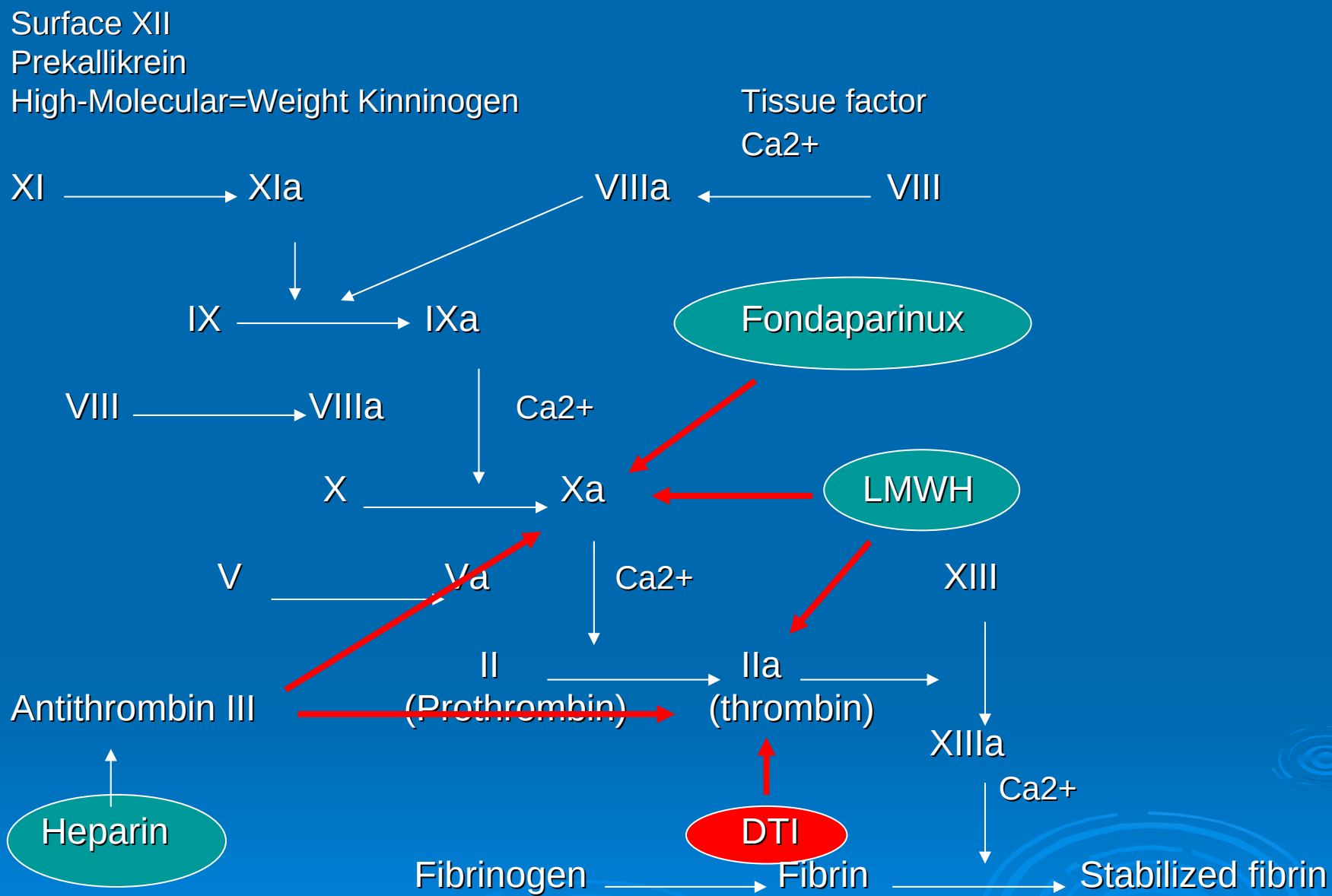
- Synthetic pentasaccharide
- F Xa inhibitor
- Ultra-low-molecular-weight heparin
- 2.5 mg sc daily
- No antidote
- Not require monitor
- No risk of HIT

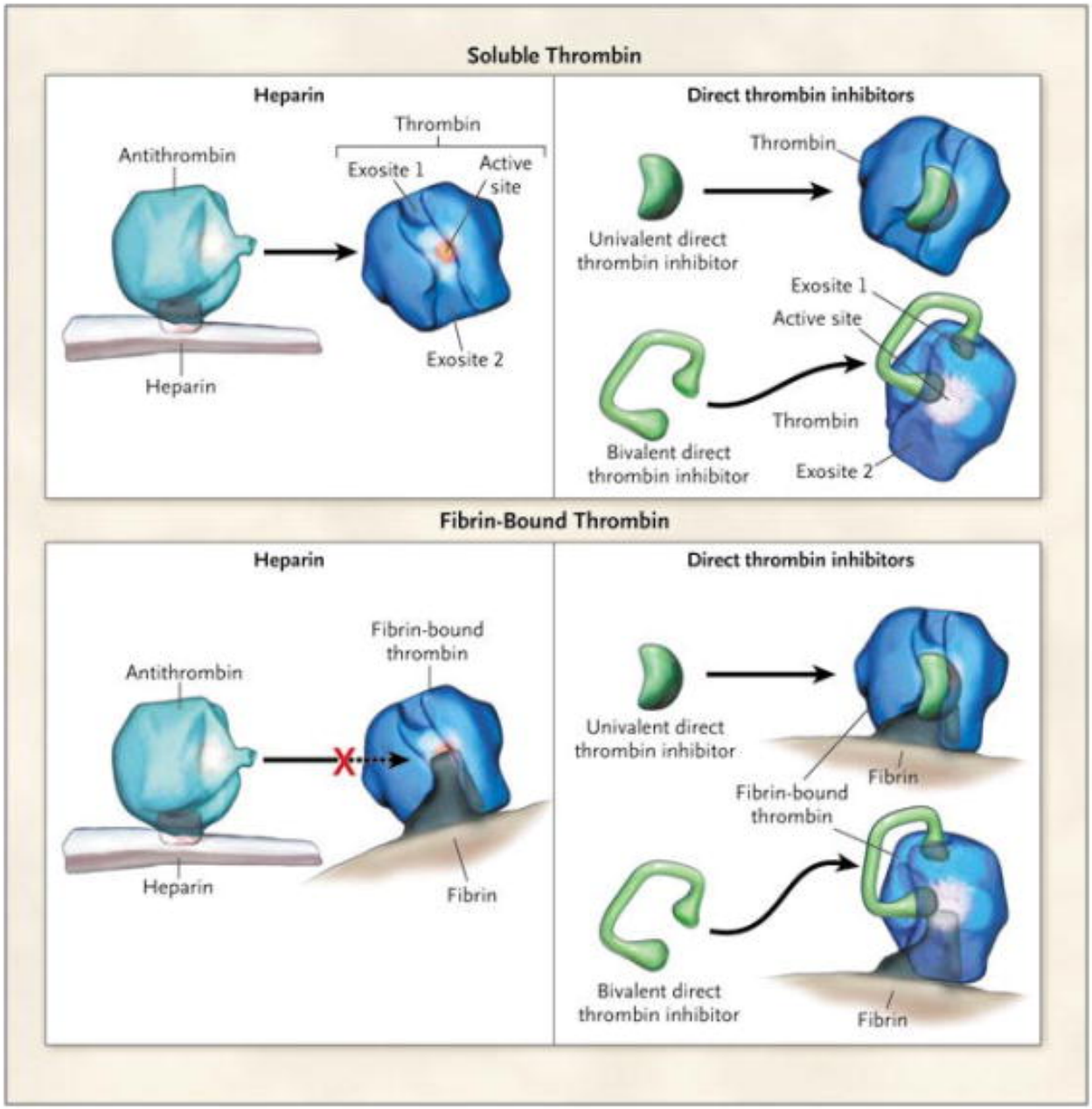
Fondaparinux

- Indications
  - acute coronary syndromes
  - acute venous thromboembolism

- Contraindications
  - CCr < 30 ml/min

Direct thrombin inhibitors


Surface XII
Prekallikrein
High-Molecular=Weight Kinninogen
Tissue factor
Ca2+
XI
XIa
VIIIa
VIII
IX
IXa
Fondaparinux
VIII
VIIIa
Ca2+
X
Xa
LMWH
V
Va
Ca2+
XIII
II
(Prothrombin)
IIa
(thrombin)
Antithrombin III
XIIIa
Ca2+
Heparin
DTI
Fibrinogen
Fibrin
Stabilized fibrin


Soluble Thrombin
Heparin
Thrombin
Antithrombin
Exosite 1
Active site
Exosite 2
Heparin
Direct thrombin inhibitors
Thrombin
Univalent direct thrombin inhibitor
Exosite 1
Active site
Thrombin
Bivalent direct thrombin inhibitor
Exosite 2
Fibrin-Bound Thrombin
Heparin
Fibrin-bound thrombin
Antithrombin
Heparin
Fibrin
Direct thrombin inhibitors
Univalent direct thrombin inhibitor
Fibrin
Fibrin-bound thrombin
Bivalent direct thrombin inhibitor
Fibrin

Direct thrombin inhibitors

- F IIa inhibitors
- Types

  - Hirudin
  - Bivalirudin (hirulog, hirudin analog)
  - Lepirudin (recombinant hirudin)
  - Argatroban

BMJ 2003;327:43-46

Direct thrombin inhibitors

- compare to UFH
  - less bind to plasma proteins
  - more predictable dose responseactivity
  - against fibrin-bound thrombi
  - direct action without a cofactor
  - absence of known inhibitors
  - less platelet binding.
- Indications
  - Lepirudin, Argatroban: used in patients with immune mediated heparin induced thrombocytopenia (HIT)
  - Bivalirudin: PCI

BMJ 2003;327:43-46

Antithrombotic agents

	Heparin	LMWHs	Direct Thrombin inhibitors	Factor Xa Inhibitors
Mechnism of action	1/3 of drug + antithrombin III & inactivation factor IIa, Xa, IXa and XIIa 2/3 of drug + heparin cofactor II & inactivation factor IIa	Anti - factor IIa & anti-factor Xa	Direct thrombin inhibition	Specific binding to antithrombin III Inhibition to factor Xa

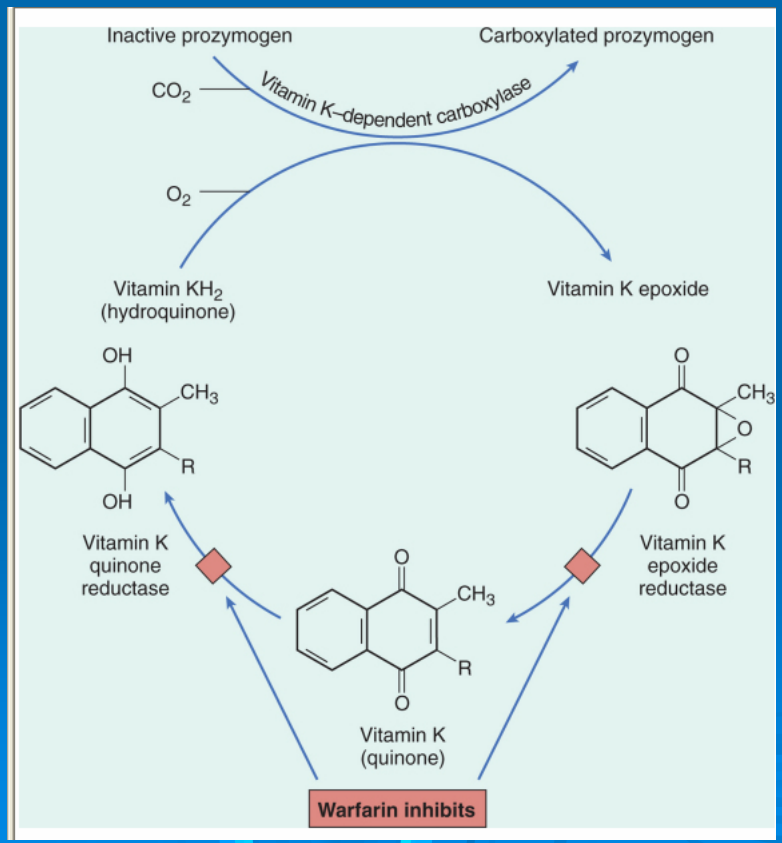
Antithrombotic agents

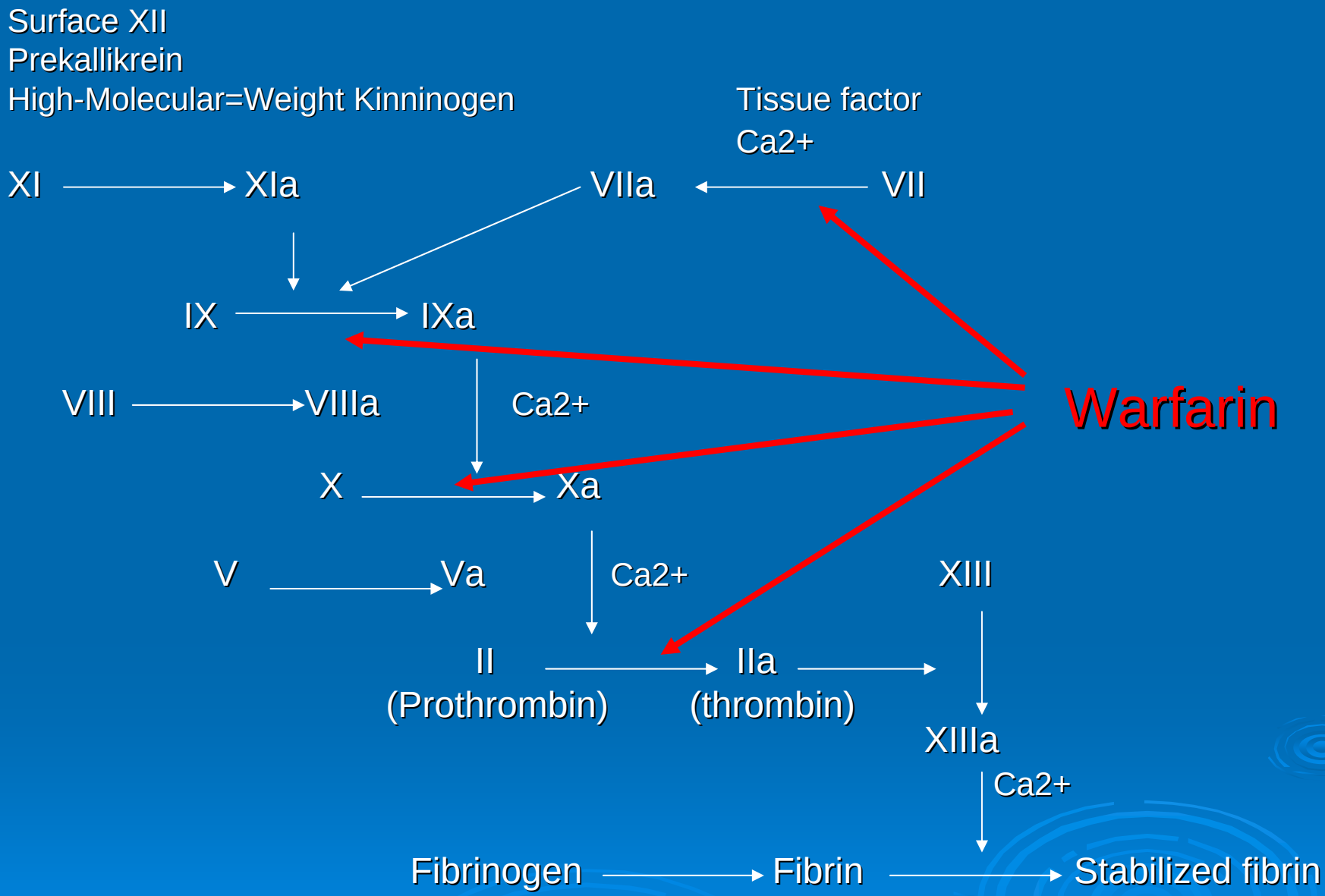
	Heparin	LMWHs	Direct Thrombin inhibitors	Factor Xa Inhibitors
Administration	IV	Sc	IV	Sc
Half life	90 min	18-28 hrs	30-90 min	17-21 hrs
Thrombocytopenia	Yes	Yes	No	Yes
Elimination	Liver	Renal	Renal (lepirudin, bivalirudin) Liver (argatroban)	Renal
Monitor	aPTT	Anti-F Xa	aPTT	Anti-F Xa

Warfarin

Warfarin

- Inhibit Vitamin K dependent coagulation factors II, VII, IX X (inhibit the action of vitamin K epoxide reductase)




Surface XII
Prekallikrein
High-Molecular=Weight Kinninogen
Tissue factor
Ca2+
XI
XIa
VIIa
VII
IX
IXa
VIII
VIIIa
Ca2+
Warfarin
X
Xa
V
Va
Ca2+
XIII
II
(Prothrombin)
IIa
(thrombin)
XIIIa
Ca2+
Fibrinogen
Fibrin
Stabilized fibrin

Warfarin

- Long half life 20-60 hrs.(mean 40 hrs.)
- Steady state requires 5-7 days
- Maximum effect 48 hrs after administration
- The effect last for the next 5 days
- Monitor: INR

Warfarin

- **Tablet size**

  3 mg: blue color

  5 mg: pink color

  2 mg: white color, 4 mg: color was different from each company

Warfarin

- Numerous drugs alter the anticoagulant response to warfarin

Increase warfarin levels	Decrease warfarin levels
phenylbutazone	cholestyramine
erythromycin	barbiturates
fluconazole	rifampin
cimetidine	sucralfate
amiodarone	
clofibrate	
isoniazid	
propranolol	

Warfarin

- dietary variations in vitamin K: high vitamin K intake in the diet
- liver disease, malabsorption, and hypermetabolic states enhance the anticoagulant effect of warfarin.

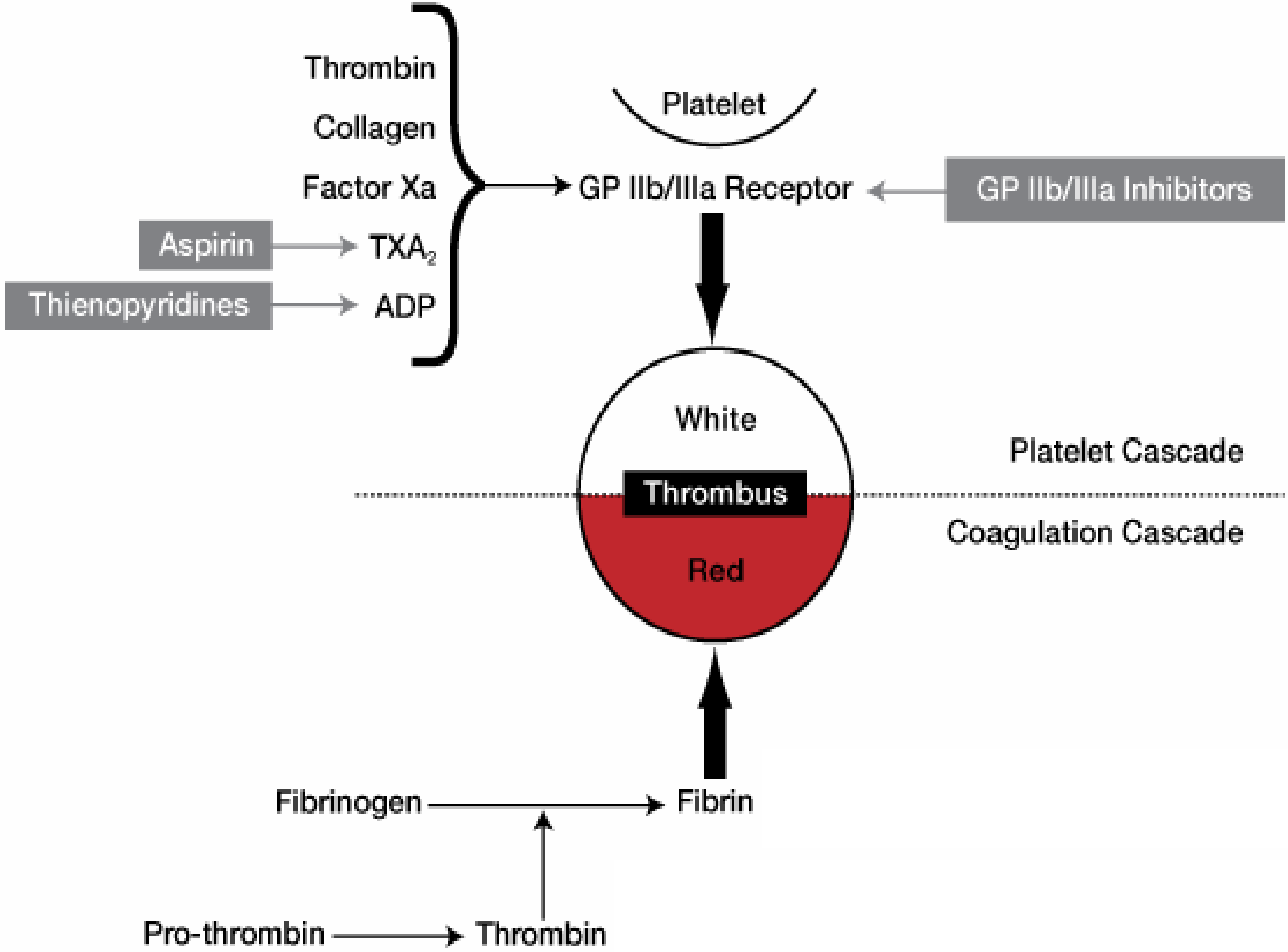
Warfarin

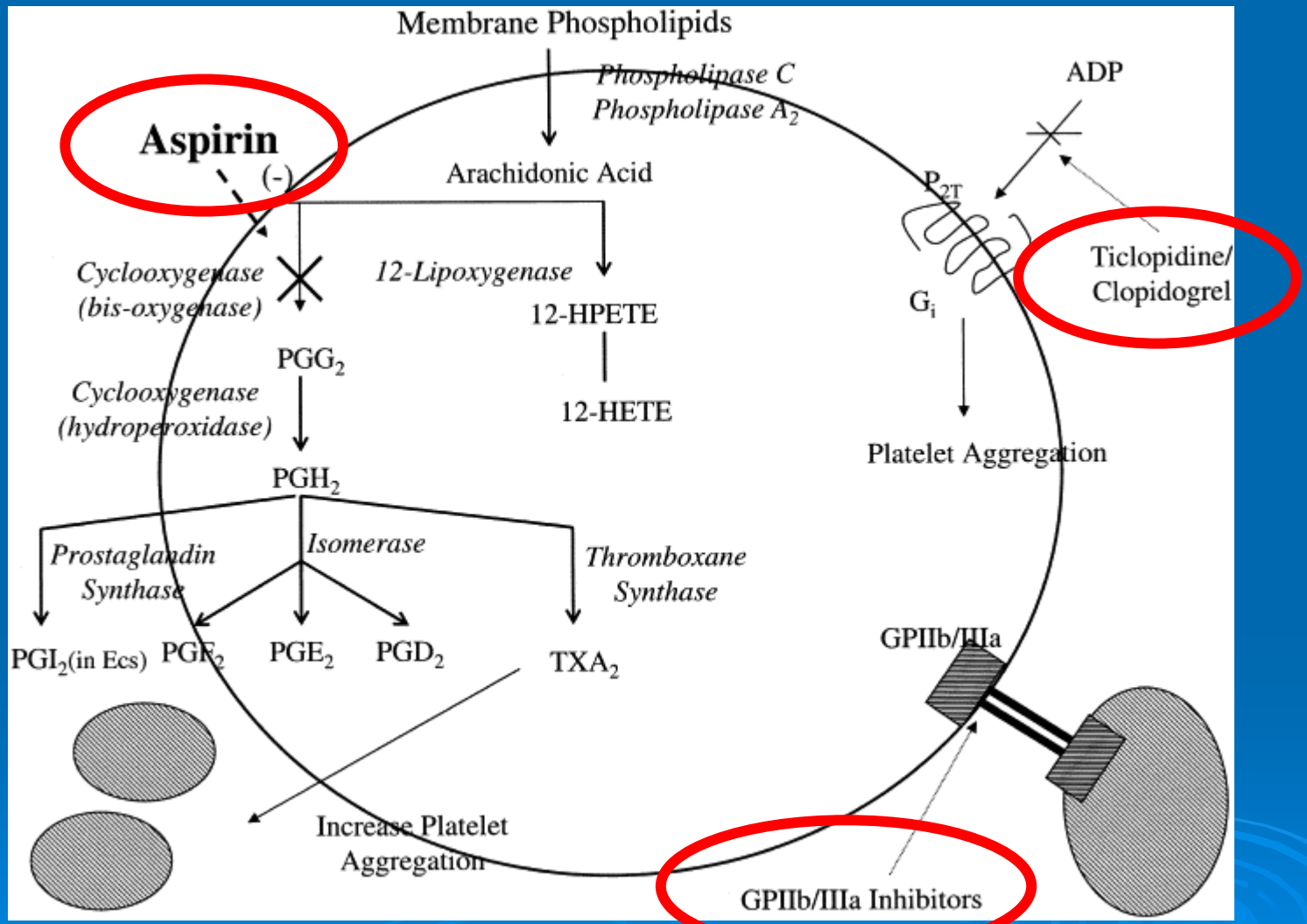
- Side effects
  - bleeding
  - skin necrosis

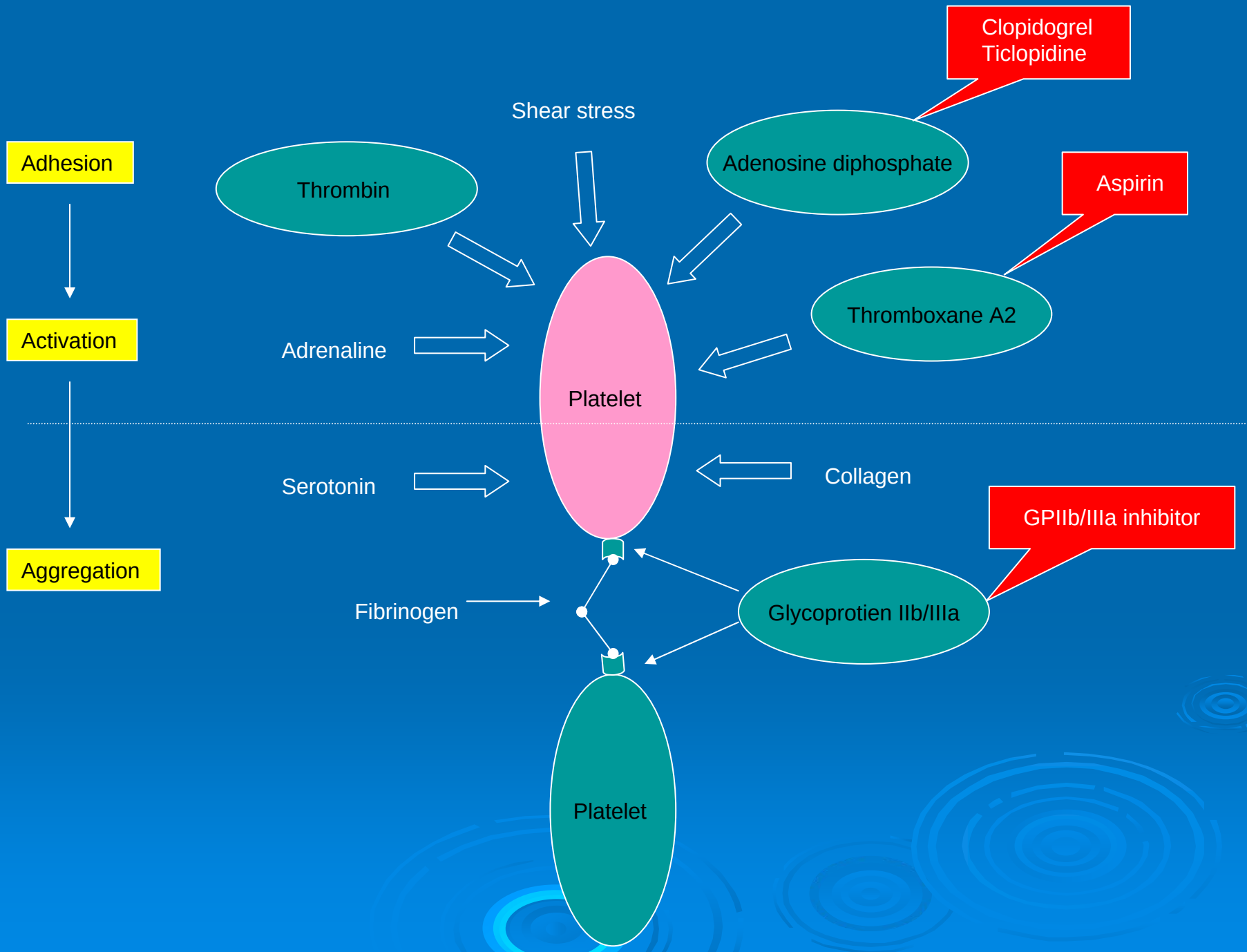
Management high INR or bleeding

bleeding	INR	Vitamin K	FFP	warfarin	Next INR
No	<5	none	none	Hold 1-2 days- Adjust dose?	1-2 days
No	5-9	None or 1-2.5 mg po	none	Hold 1-2 days- Adjust dose	1 day
Yes	<10	1-2.5 mg po	none	Hold-Adjust dose	1 day
No	10-20	2.5-5 mg po	none	Hold-Adjust dose	12-24 hours
Yes	>10	5-10 mg IV	and/or	Hold	6-12 hours
serious	high	10 mg IV	and	hold	Follow FFP

Antiplatelet drugs


Thrombin
Collagen
Factor Xa
Aspirin
TXA_2
Thienopyridines
ADP
Platelet
GP IIb/IIIa Receptor
GP IIb/IIIa Inhibitors
White
Thrombus
Red
Platelet Cascade
Coagulation Cascade
Fibrinogen
Fibrin
Pro-thrombin
Thrombin


Membrane Phospholipids
Phospholipase C
Phospholipase A2
Arachidonic Acid
Aspirin
(-)
Cyclooxygenase
(bis-oxygenase)
12-Lipoxygenase
12-HPETE
PGG2
Cyclooxygenase
(hydroperoxidase)
12-HETE
PGH2
Prostaglandin
Synthase
Isomerase
Thromboxane
Synthase
PGI2(in Ecs)
PGF2
PGE2
PGD2
TXA2
Increase Platelet
Aggregation
ADP
P2T
Gi
Ticlopidine/
Clopidogrel
Platelet Aggregation
GPIIb/IIIa
GPIIb/IIIa Inhibitors


Clopidogrel
Ticlopidine
Shear stress
Adhesion
Thrombin
Adenosine diphosphate
Aspirin
Activation
Adrenaline
Thromboxane A2
Platelet
Serotonin
Collagen
GPIIb/IIIa inhibitor
Aggregation
Fibrinogen
Glycoprotien IIb/IIIa
Platelet

Aspirin

- irreversibly inhibits cyclo-oxygenase
- prevent the synthesis of prothrombotic thromoboxane A2 during platelet activation
- well tolerated
- low incidence of serious adverse effects
- standard dose results in full effect within hours
- mild antiplatelet agent
- no effect in 10% of patients

BMJ 2003;327:43-46

Aspirin

- Indications

  - lone atrial fibrillation (without additional risk)
  - chronic stable angina
  - prior MI
  - unstable angina
  - AMI
  - stroke

Aspirin

- Side effects

Toxic side effects

- Rye syndrome (children)
- GI ulceration
- Pulmonary edema
- Bleeding
- Renal toxicity

General side effects

- Tinnitus and hearing changes
- Hemolytic anemia
- Minor bleeding
- gastritis

J Interv Cardiol 2003;16:357

Aspirin

- Side effects

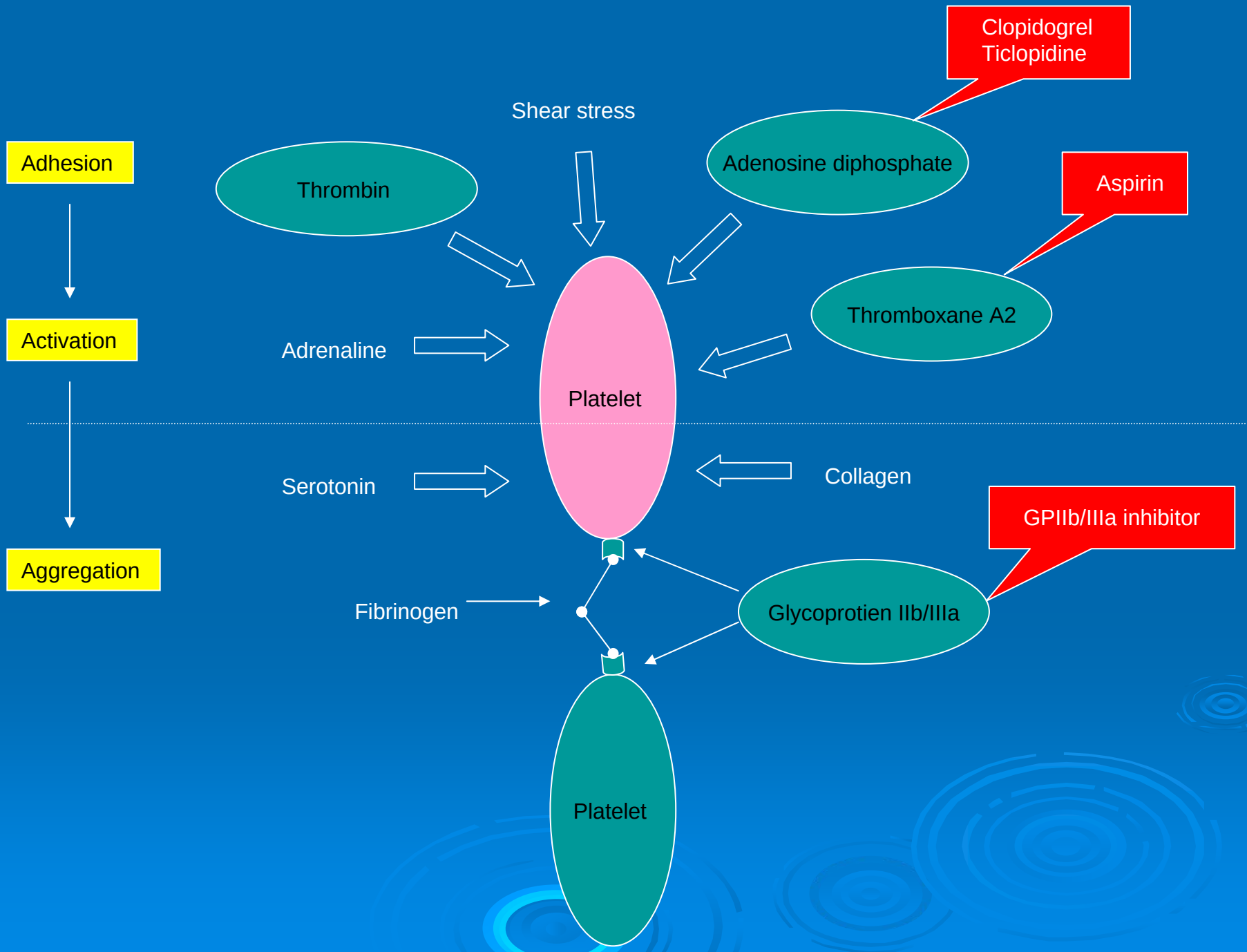
Hypersensitivity

Bronchospasm, Urticaria, Angioedema, Vasomotor rhinitis, Anaphylaxis, Hemorrhagic vasculitis, Erythema multiforme, Stevens-Johnson syndrome

Safe use in pregnancy

yes

J Interv Cardiol 2003;16:357


Clopidogrel
Ticlopidine
Shear stress
Adhesion
Thrombin
Adenosine diphosphate
Aspirin
Activation
Adrenaline
Thromboxane A2
Platelet
Serotonin
Collagen
GPIIb/IIIa inhibitor
Aggregation
Fibrinogen
Glycoprotien IIb/IIIa
Platelet

Thienopyridines

- irreversibly inhibit binding of adenosine diphosphate (ADP) during platelet activation

  - Clopidogrel

  - Ticlopidine

  Clopidogrel :

  - fewer serious side effects, more rapid onset, longer duration of action (compare to Ticlopidine)

- New P2Y12 receptor antagonists

  - Prasugrel

  - Ticagrelor

  - Cangrelor

BMJ 2003;327:43-46

Thienopyridines

- Indications

  - alternative treatement for patients could not take aspirin
  - non STEMI (combined with aspirin)
  - coronary stent implantation(combined with aspirin)

BMJ 2003;327:43-46

Thienopyridines

- Side effects (Clopidogrel)

Toxic side effects

- Hemorrhage
- Skin reactions
- Gastric ulceration
- Thrombotic thrombocytopenia purpura (TTP): rare

General side effects

- Gastritis (similar to aspirin)
- Fatique
- Flu-like syndrome
- Myalgia (similar to aspirin)

J Interv Cardiol 2003;16:357

Thienopyridines

- Side effects (Clopidogrel)

Hypersensitivity

  Allergic reactions (necrosis, ischemic)

Safe use in pregnancy

  Unknown

J Interv Cardiol 2003;16:357

Thienopyridines

- Side effects (Ticlopidine)

Toxic side effects

- Hemorrhage
- Hematologic disorders (leukopenia, agranulocytosis, thrombocytopenia, and pancytopenia): reversible
- Thrombotic thrombocytopenia purpura (TTP)
- Hepatitis

General side effects

- Skin rashes
- Severe chronic diarrhea

J Interv Cardiol 2003;16:357

Thienopyridines

- Side effects (Ticlopidine)

Hypersensitivity

Rashes (immunogenically mediated unknown)

Safe use in pregnancy

Unknown

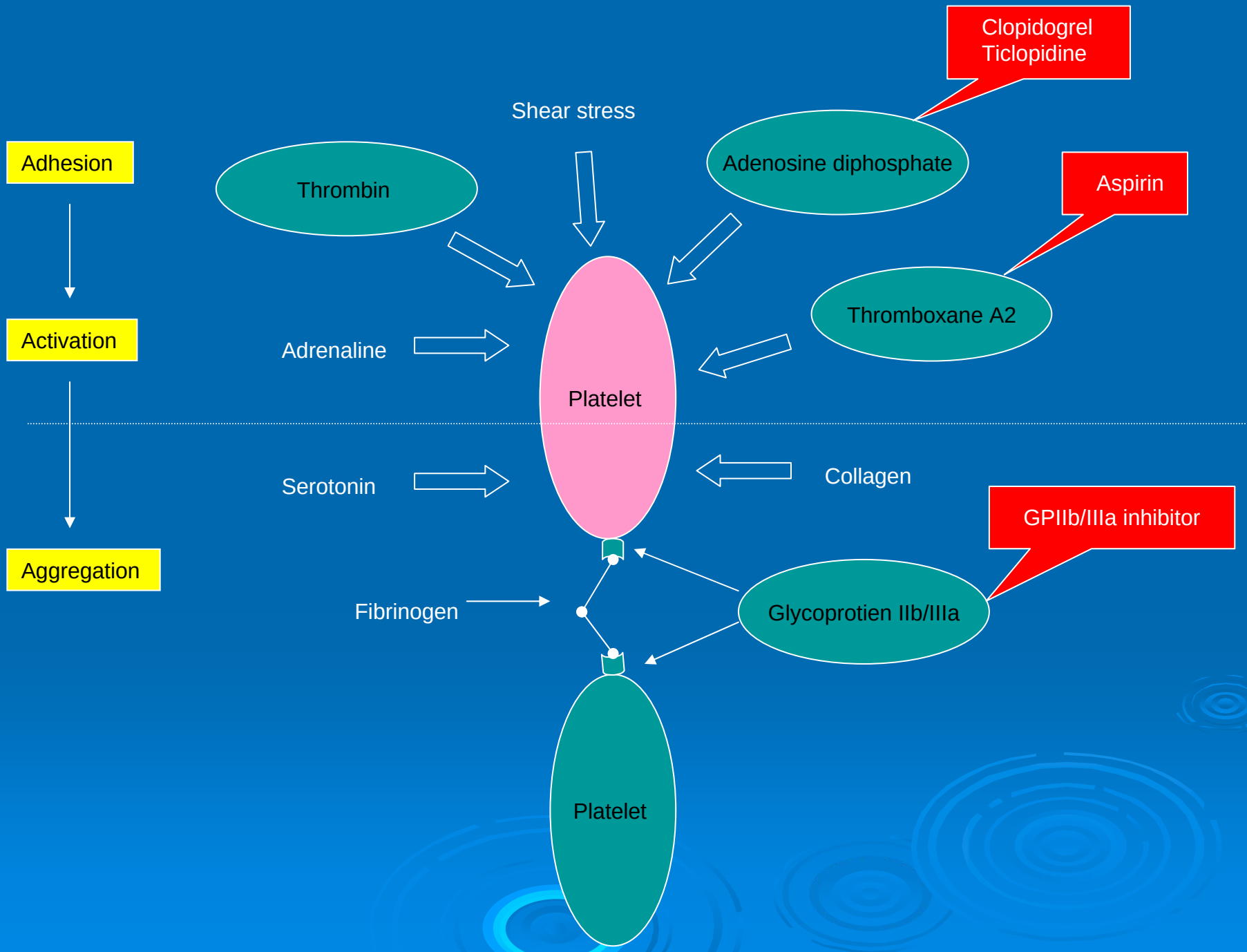
J Interv Cardiol 2003;16:357

Glycoprotein IIb/IIIa receptor inhibitors

- potent inhibitors of platelet aggregation
- 3 types

  - Abciximab (Reopro)
  - Ebtifibatide (Integrillin)
  - Tirofiban (Aggrastat)

BMJ 2003;327:43-46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Glycoprotein IIb/IIIa receptor inhibitors

- Indications

  - Abciximab: high risk angioplasty and stenting

  - Tirofiban, Eptifibatide: non STEMI

- Contraindications

  - not recommended as a fibrinolytic adjunctive agent

Glycoprotein IIb/IIIa receptor inhibitors

- Side effects (Abciximab)

Toxic side effects

- Bleeding (intraabdominal, retroperitoneal)
- Thrombocytopenia
- Hypotension
- Alveolar hemorrhage

General side effects

- Pain
- Sweating

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Glycoprotein IIb/IIIa receptor inhibitors

- Side effects (Abciximab)

Hypersensitivity

- Unknown (none reported with chimeric form)
- Rare with re-exposure

Safe use in pregnancy

- Unknown (C)

J Interv Cardiol 2003;16:357

Glycoprotein IIb/IIIa receptor inhibitors

- Side effects (Tirofiban)

Toxic side effects

Hemorrhage Thrombocytopenia

General side effects

Mild bleeding Edema

Pain CNS

Hypersensitivity

Not reported , no repeat exposure information available

Safe use in pregnancy

(B)

J Interv Cardiol 2003;16:357

Glycoprotein IIb/IIIa receptor inhibitors

- Side effects (Eptifibatide)

Toxic side effects

- Hemorrhage
- Thrombocytopenia
- Hypotension

General side effects

- Minor bleeding
- Other rare

Safe use in pregnancy

- Unknown (B)

J Interv Cardiol 2003;16:357

Glycoprotien IIb/IIIa inhibitors

	Abciximab	Ebtifibatide	Tirofiban
Source	monoclonal mouse Ab	peptide	non-peptide
Time for platelet inhibition to return to normal (hours)	24-48	4-6	4-8
Severe thrombocytopenia	1.0%	= placebo	= placebo
Reversible with platelet Transfusion	yes	no	no
Cost per PCI	$ 1031 (12 h)	$ 263 (18 h)	$ 404 (18 h)

Thank you