Anti-platelet drugs

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Learning objectives

- **Basic concept of Activation of platelets and aggregation**
- **Anti-platelet drugs:**
- A. Inhibition of thromboxane A2 synthesis via inhibiting COX-1: Aspirin
- **B.** Antagonist of ADP receptors: Clopidogrel Ticlopidine
- C. GP IIb / IIIa receptor antagonists: Abciximab Tirofiban and Eptifibatide
- D. Phosphodiestrase 3 (PDE) inhibitors / adenosine uptake inhibitors
- Pharmacotherapeutic profile of the individual classes (mechanism , indications, adverse drugs reactions)

Platelets and vessels

- In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide (NO) and prostacyclinre (PGI2)released by endothelial cells lining the blood vessels.

- An injury to vascular system leads to interaction between Platelets, Endothelial system and Coagulation factors which lead to formation of the CLOT

Activation of platelets after vascular injury

- **Injury exposes reactive subendothelial matrix proteins, platelet adherence & activation, + secretion & synthesis of vasoconstrictors & platelet activating molecules.**

- **Thus, thromboxane A_2 (TXA_2) is synthesized from arachidonic acid within platelets & is platelet activator & potent vasoconstrictor.**

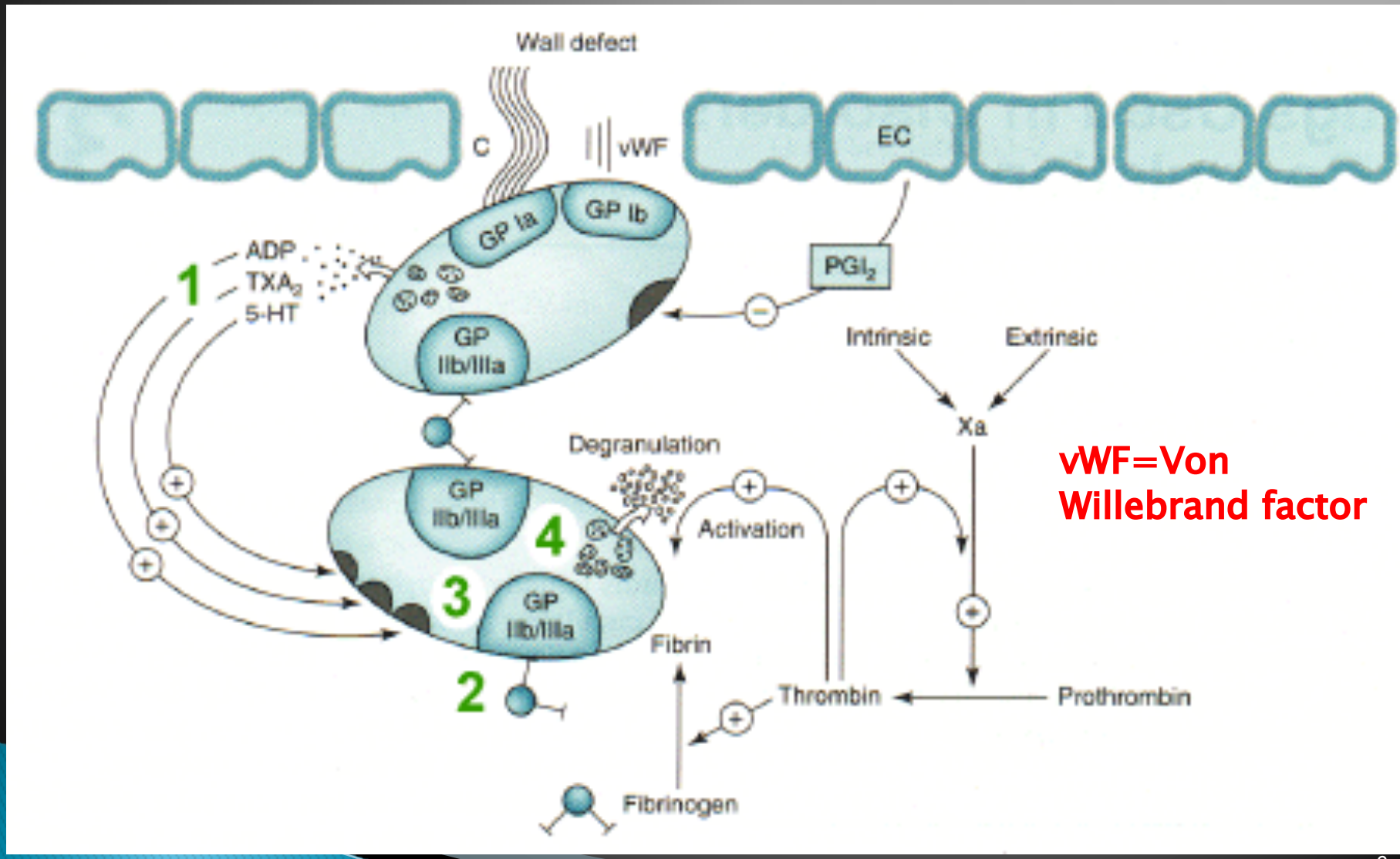
- **Adenosine diphosphate (ADP), secreted from platelet, a powerful inducer of platelet aggregation**

- **Serotonin (5HT), which stimulates aggregation & vasoconstriction.**

- **Activation of platelets, ⟹ aggregation & conformational change in the GP11b/111a, enabling it to bind fibrinogen, which cross-links adjacent platelets, ⟹ aggregation & formation of a platelet plug.**

- **Simultaneously, the coagulation system cascade is activated, ⟹ thrombin generation & a fibrin clot, which stabilizes the platelet plug.**

Damage to endothelium and Platelets aggregation (formation of clot)



vWF=Von Willebrand factor

Clot

- **THROMBUS**: is the CLOT that adheres to vessel wall
- **EMBOLUS**: is the CLOT that floats in the blood

- **THROMBOSIS**: is the formation of unwanted clot with in the blood vessel, producing life threatening condition.
- Acute myocardial infarction
- Acute ischemic stroke
- Deep vein thrombosis
- Pulmonary embolism

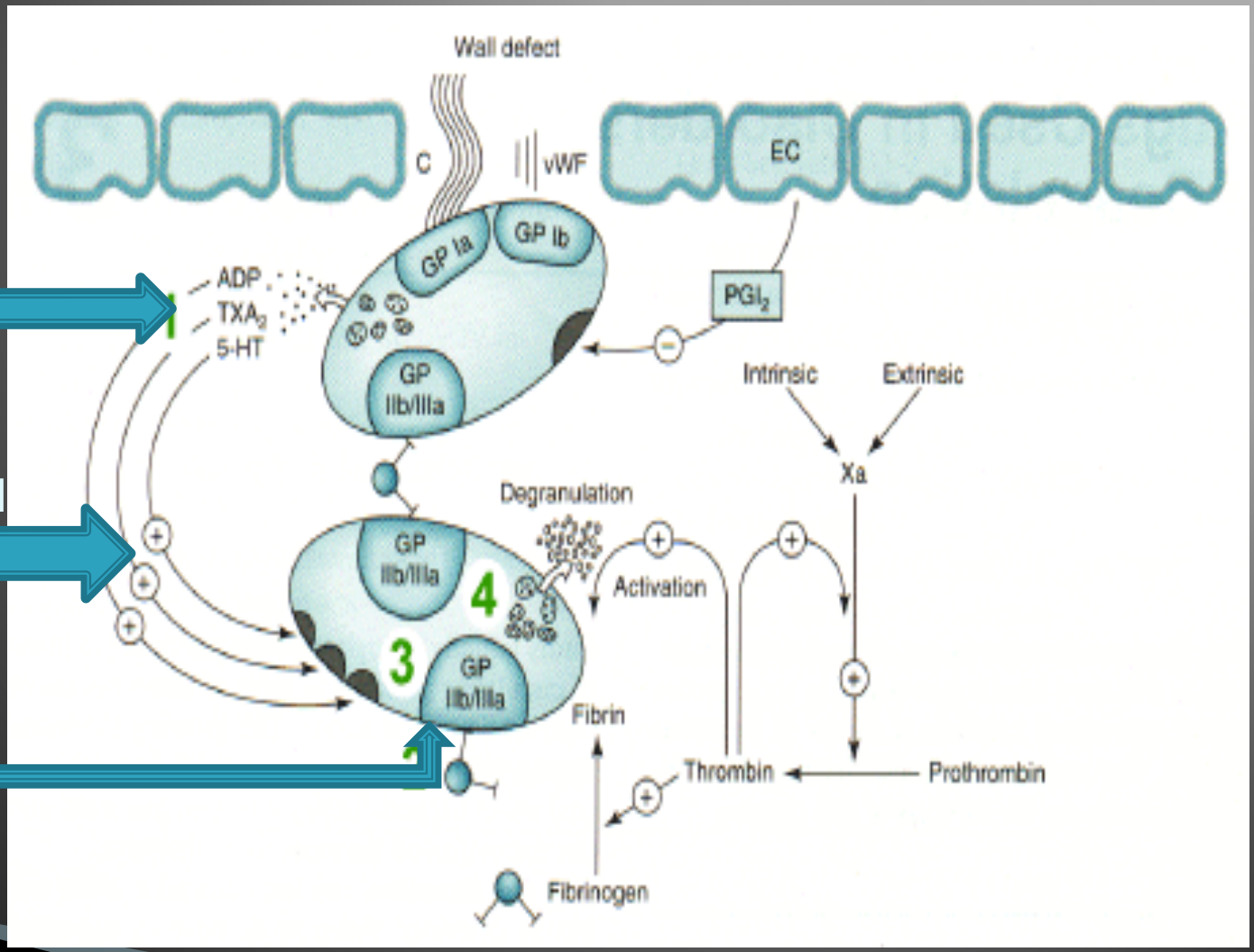
DRUGS

- **Antiplatelets (drugs which prevent and inhibit platelet aggression)**

- **Anticoagulants (drugs which prevent clotting by inhibiting clotting factors)**

- **Thrombolytics (Fibrinolytics)(drugs which reduce or lysis the clot.**

Antiplatelet drugs target



Ticlopidine &clopidogrel

TXA2: Aspirin

Abciximab

Drugs targets for platelet inhibition:

	Mechanism of action	Drug	ROA
(1)	Inhibition of thromboxane A2 synthesis via inhibiting COX-1	Aspirin	Oral
(2)	Inhibition of ADP-induced platelet aggregation (Antagonist of ADP receptors)	Clopidogrel Ticlopidine	Oral
(3)	GP IIb / IIIa receptor antagonists (Inhibitors)	Abciximab Tirofiban Eptifibatide	I / V
(4)	Phosphodiestrase 3 (PDE) inhibitors / adenosine uptake inhibitors	Dipyridamol Cilostazol	

Aspirin

Mechanism of action: (Low dose)

irreversible inhibition (acetylation) of cyclooxygenase enzyme-1 (COX-1)

thus inhibits the synthesis of thromboxane A_2

(thromboxane A 2 ---- causes platelet aggregation)

Aspirin with a low dose (75-160 mg per selectively inhibits COX-1 , decreasing synthesis of platelet TxA2 and inhibit platelet aggregation.

,low dose spares the protective PGI2 synthesis.

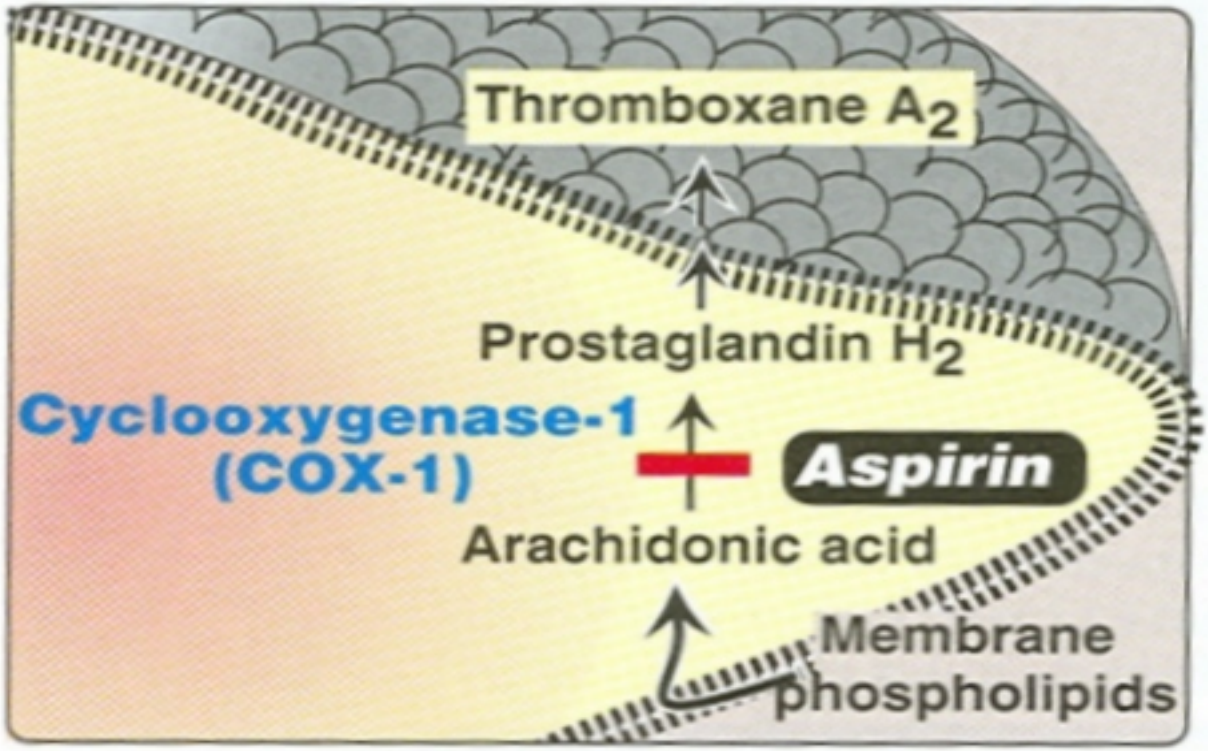
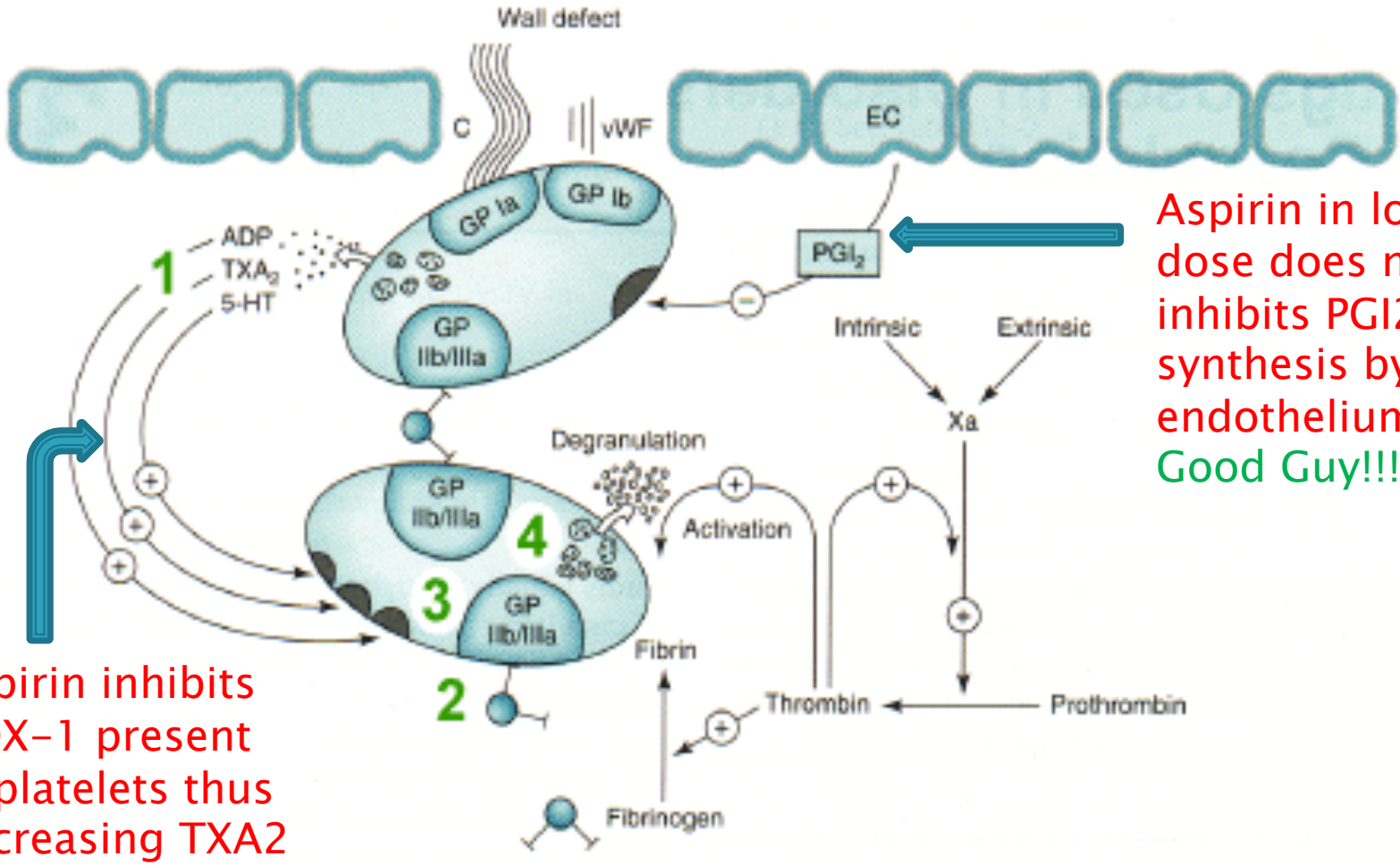


Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

Targets of Aspirin in low doses drugs



Aspirin in low dose does not inhibits PGI2 synthesis by endothelium) Good Guy!!!!

Aspirin inhibits COX-1 present in platelets thus decreasing TXA2 synthesis.

Aspirin

Uses:

Prophylaxis of thromboembolism e.g. unstable angina / myocardial infarction, ischemic stroke, can also be used in combination with other antiplatelet aggregating (Clopidogrel) and anticoagulant drugs (Heparin)

Adverse effects:

Hyperacidity

Contraindication:

Peptic ulcer

Clopidogrel & Ticlopidine

Mechanism of action:

irreversibly block ADP receptors on platelets

This action inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets.

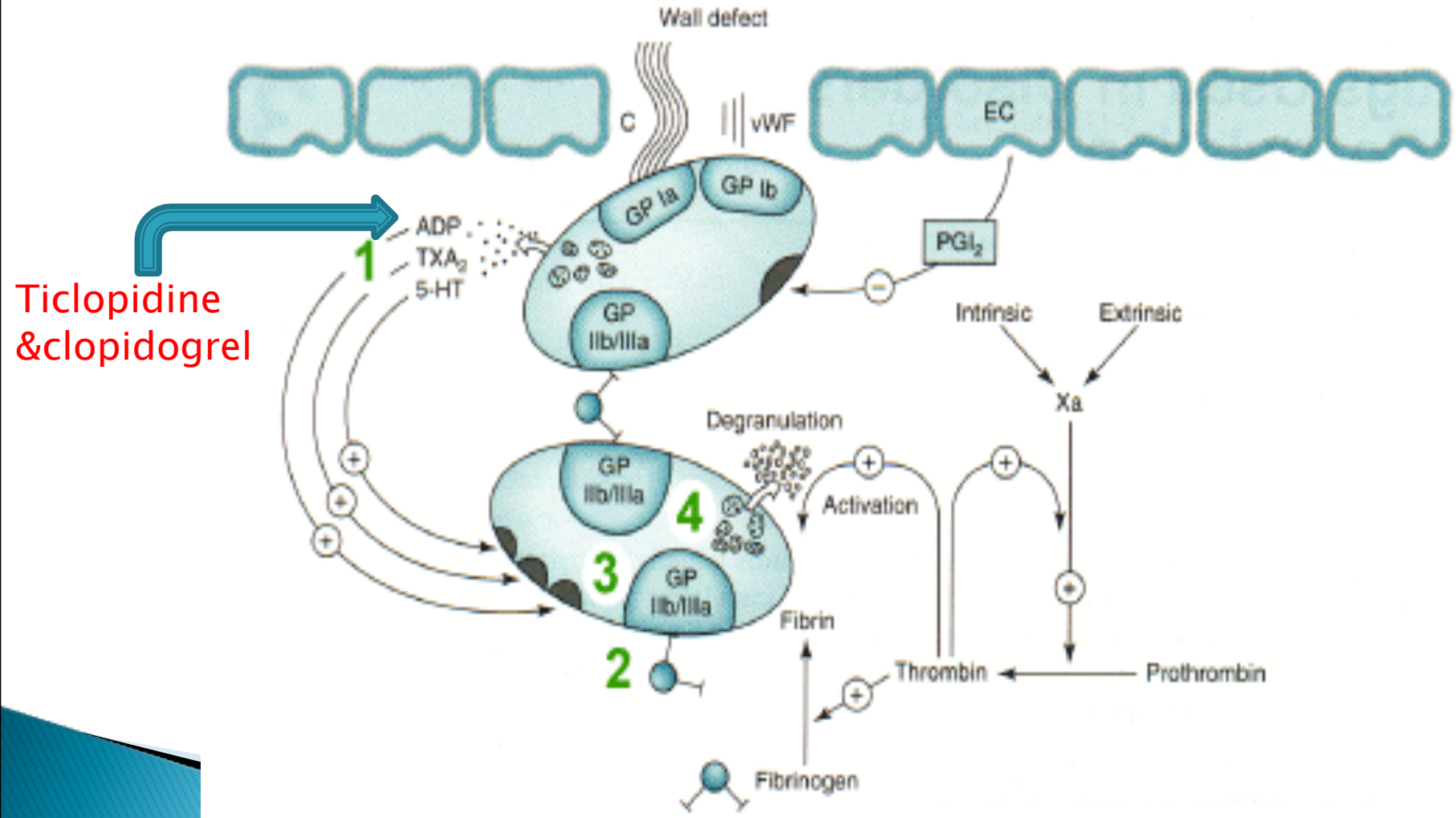
Uses:

To prevent thrombosis

(Prevention of vascular events in pts with):

- **transient ischemic attacks**
- **unstable angina pectoris**
- **placement of a coronary stent**

Target of clopidogrel and ticlopidine



Ticlopidine &clopidogrel

Ticlopidine

Adverse effects:

- nausea , dyspepsia , diarrhea
- hemorrhage
- leucopenia
- TTP (thrombotic thrombocytopenic purpura)

Precaution:

Regular monitoring of WBC count during first three months

(Therapy with ticlopidine requires regular monitoring for neutropenia)

Clopidogrel

Adverse effects:

- same but fewer than ticlopidine

- long duration of action

(once daily dosing, ticlopidine given twice daily)

clopidogrel is more potent than ticlopidine and has a better safety profile, clopidogrel has replaced ticlopidine.

Clopidogrel & Ticlopidine

- Ticlopidine and clopidogrel are prodrugs that require metabolism by the hepatic cytochrome P450 (CYP) enzyme system to active form.

Abciximab , Tirofiban , Eptifibatide (monoclonal antibodies)

Mechanism of action:

- GP IIb / IIIa receptor Blockers (antagonists)

GPIIb/IIIa is found on the surface of platelets and is the most abundant receptor.

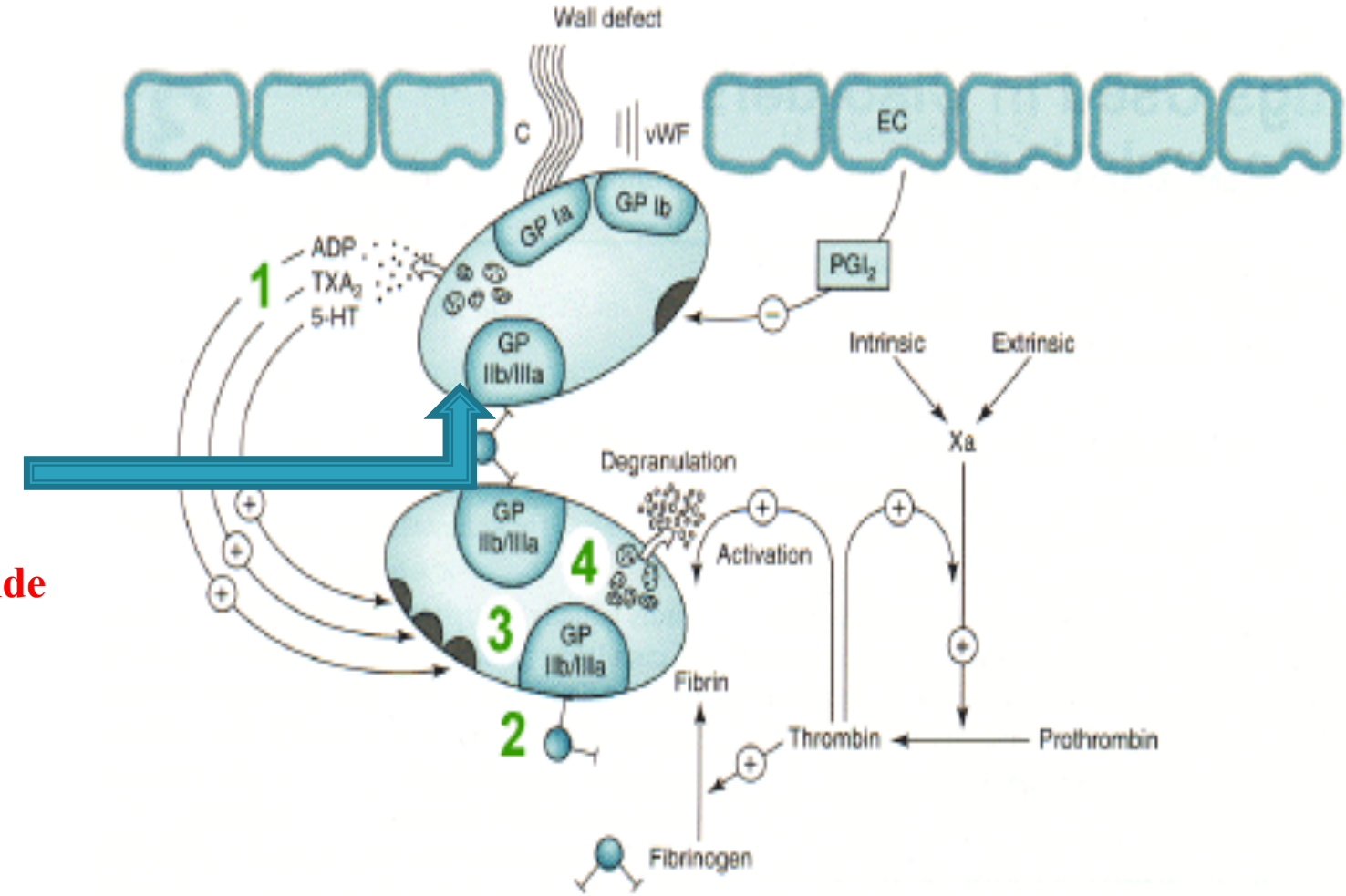
activated, GPIIb/IIIa binds adhesive molecules, such as fibrinogen and vWF to promote clotting.

Abciximab binds to GPIIb/IIIa and stops the clot fromation.

Mechanism of action of Abciximab , tirofiban & eptifibatide

Abciximab

Tirofiban & Eptifibatide



(Abciximab)

- Abciximab is monoclonal antibody directed against glycoprotein GPIIb/IIIa.

- ***Clinical Efficacy:*** In acute MI patients,
- Abciximab is administered iv as an adjuvant to angioplasty surgery for the prevention of ischemic complications of angioplasty.

- Heparin or aspirin is given with abciximab

- **Abciximab** has long half life while **Tirofiban & Eptifibatide have short half life.**

- **Given parenteraly only**

Abciximab , Tirofiban , Eptifibatide

Uses:

To prevent thrombosis

(Prevention of vascular events in pts with):

- Acute coronary syndrome
- Percutaneous coronary intervention

Adv effects: Bleeding

Thrombocytopenia (immune reaction)

Dipyridamol

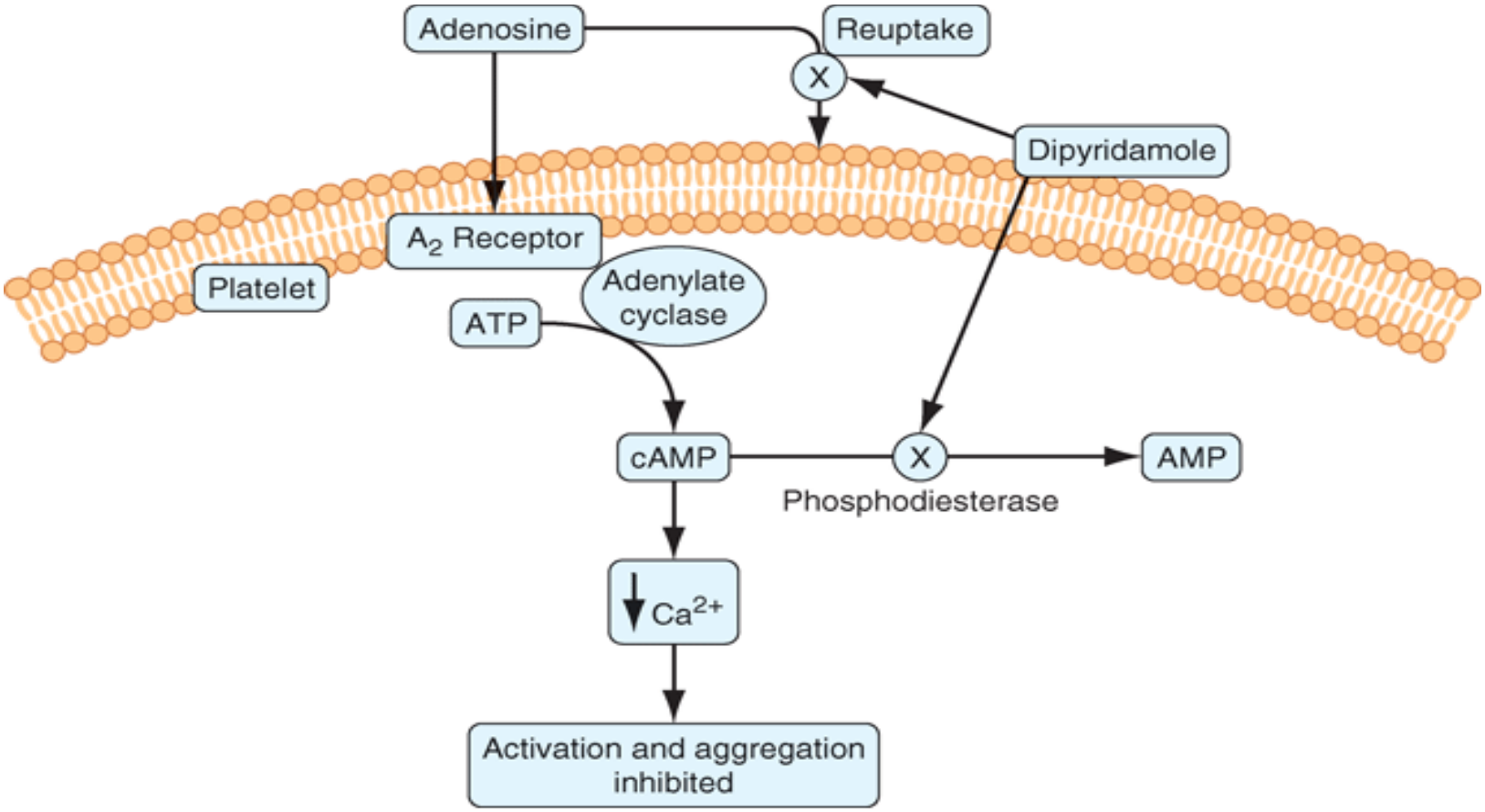
- vasodilator
- inhibits platelet function --- by --- inhibiting ----
  adenosine uptake &
  inhibits cAMP metabolism by inhibiting phosphodiestrase activity.

Uses:

- When give alone it has little or no beneficial effect ----- therefore given in combination with ---- aspirin ----- to prevent cerebrovascular ischemia

Because of vasodilatory properties dipyridamol should be used with cuation in corornary problem , clopidogrel is a better choice.

Dipyridamole (mechanism of action)



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Cilostazole

- phosphodiestrase inhibitor(on PDE3)

---- promotes ----- vasodilation & inhibition of platelet aggregation

Uses:

-To prevent intermittent claudication

Antiplatelet drugs

- **Prevent blood clots from forming in the arteries.**
- **Aspirin is the most commonly prescribed antiplatelet drug.**

- **Clopidogrel works by reducing the "stickiness" of platelets in a similar way to aspirin & is often recommended as an alternative for people who cannot take aspirin.**
- **Aspirin and clopidogrel are given together in high risk patients**

clopidogrel & aspirin may be recommended for people who have had a heart attack, a severe attack of angina, or who have undergone a coronary angioplasty & stenting.

Monitoring:

- Bleeding time

(Antiplatelet drugs increase bleeding time)

Aspirin Resistance:

The reported incidence of resistance varies greatly, from 5 % to 75%.
Resistance: recurrent thrombosis while on antiplatelet therapy.

Although aspirin reduces the production of TX_{A2}, it may fail to inhibit platelet aggregation because platelets continue to respond strongly to other agonists.

TX_{A2}-induced platelet aggregation is only ONE of many factors leading to thrombus formation, which is the most common, but not the only, mechanism leading to ischemic events.

Antiplatelet drugs

Monitoring:

- Bleeding time

(Antiplatelet drugs increase bleeding time)