Anti-platelet drugs

Platelets and vessels

- In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide (NO) and Prostacyclin (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.

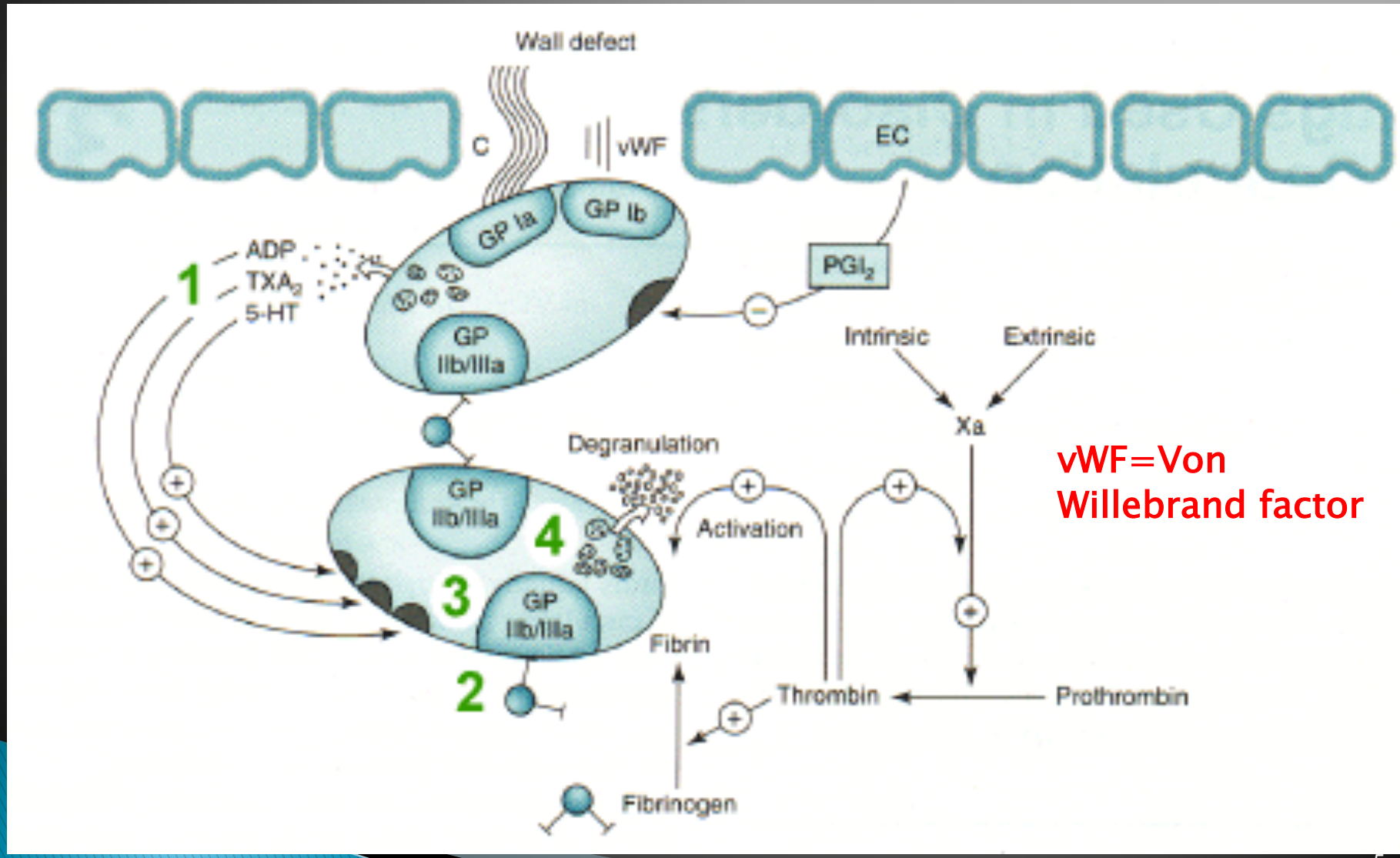
- Adenosine diphosphate (ADP), secreted from platelet, a powerful inducer of platelet aggregation

- 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

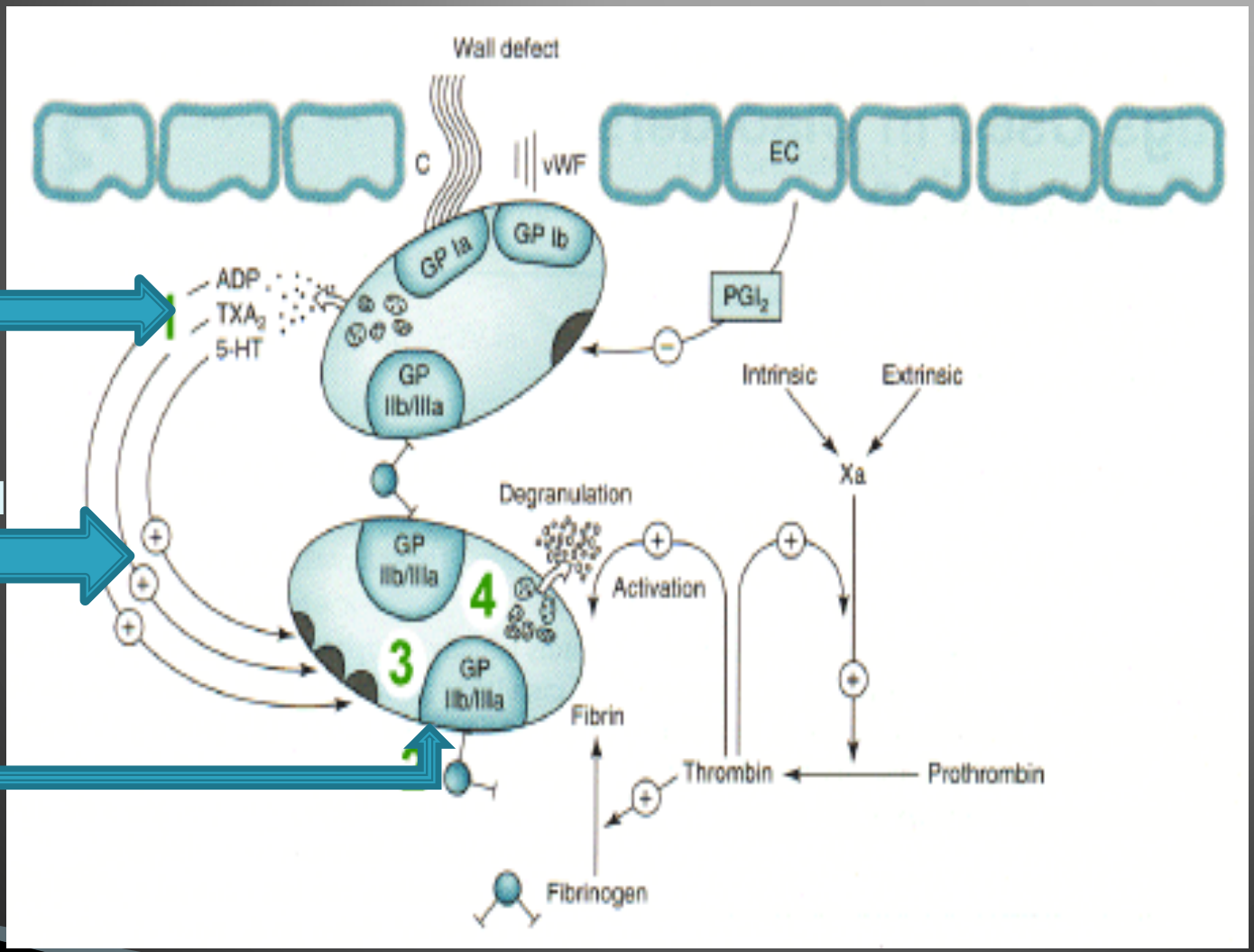
DRUGS

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.

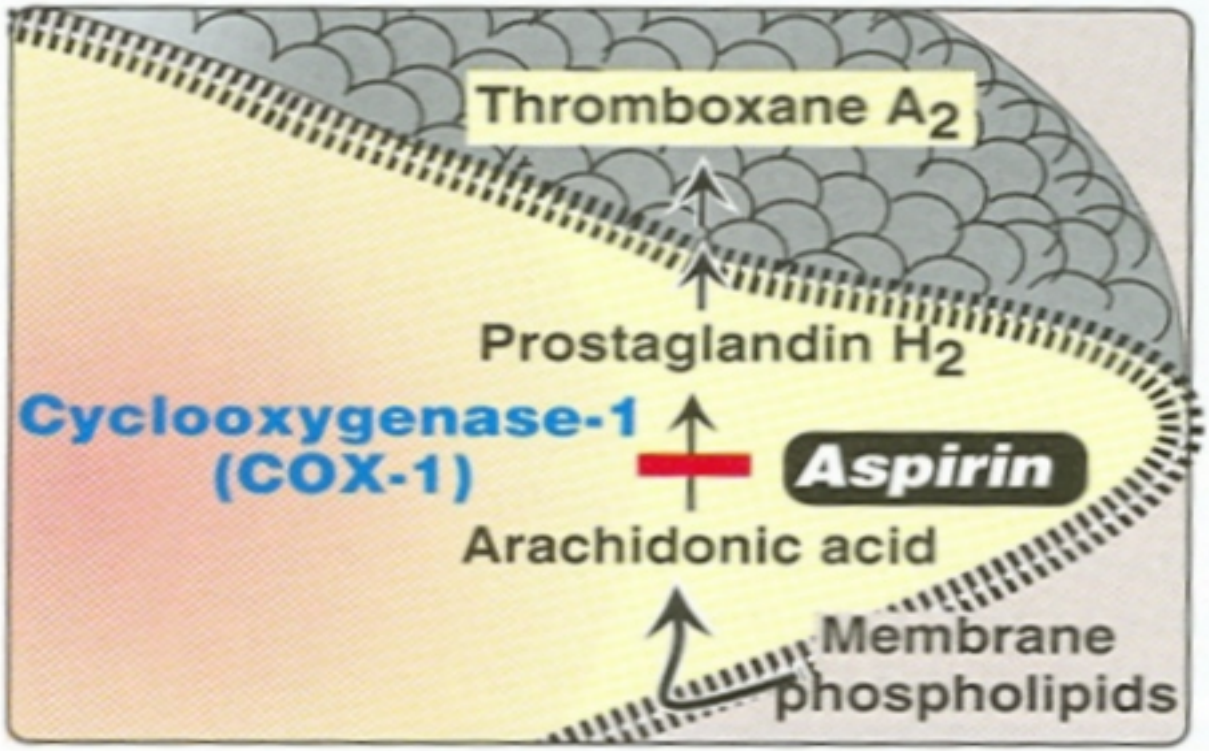
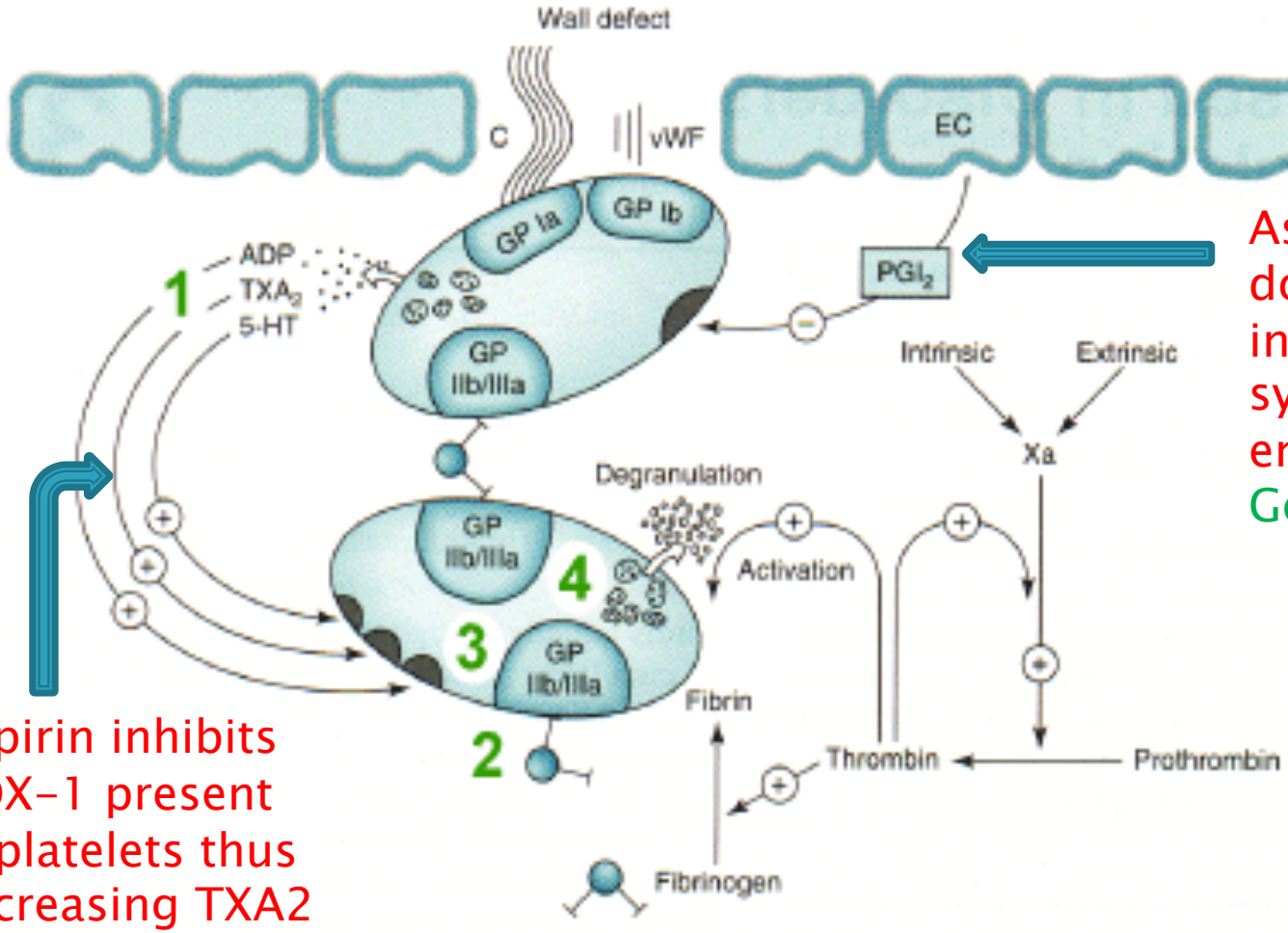


Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

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.

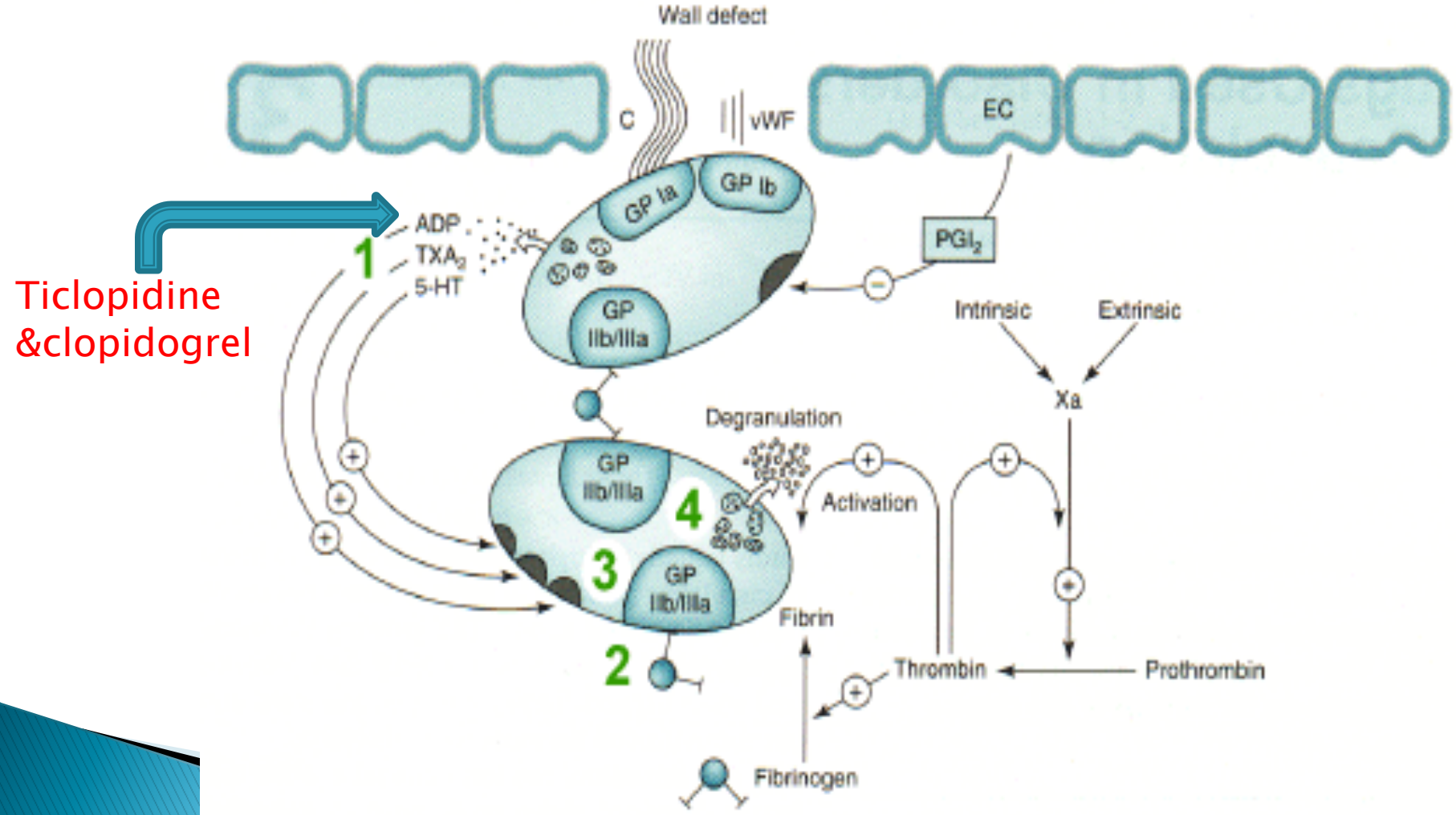
Uses:

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

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.

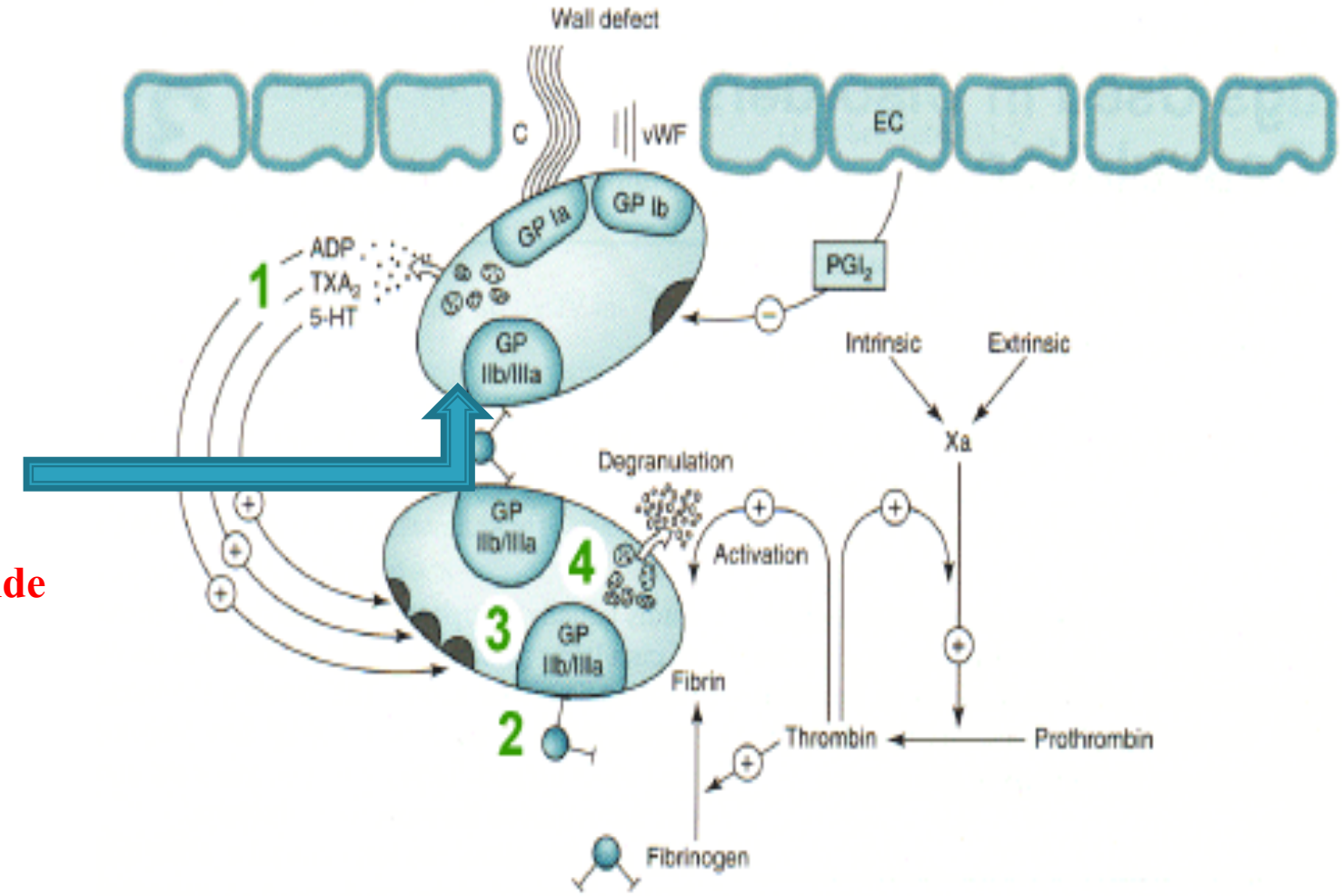
activated, GPIIb/IIIa binds adhesive molecules, such as fibrinogen and vWF to promote clotting.

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 parenterally 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)

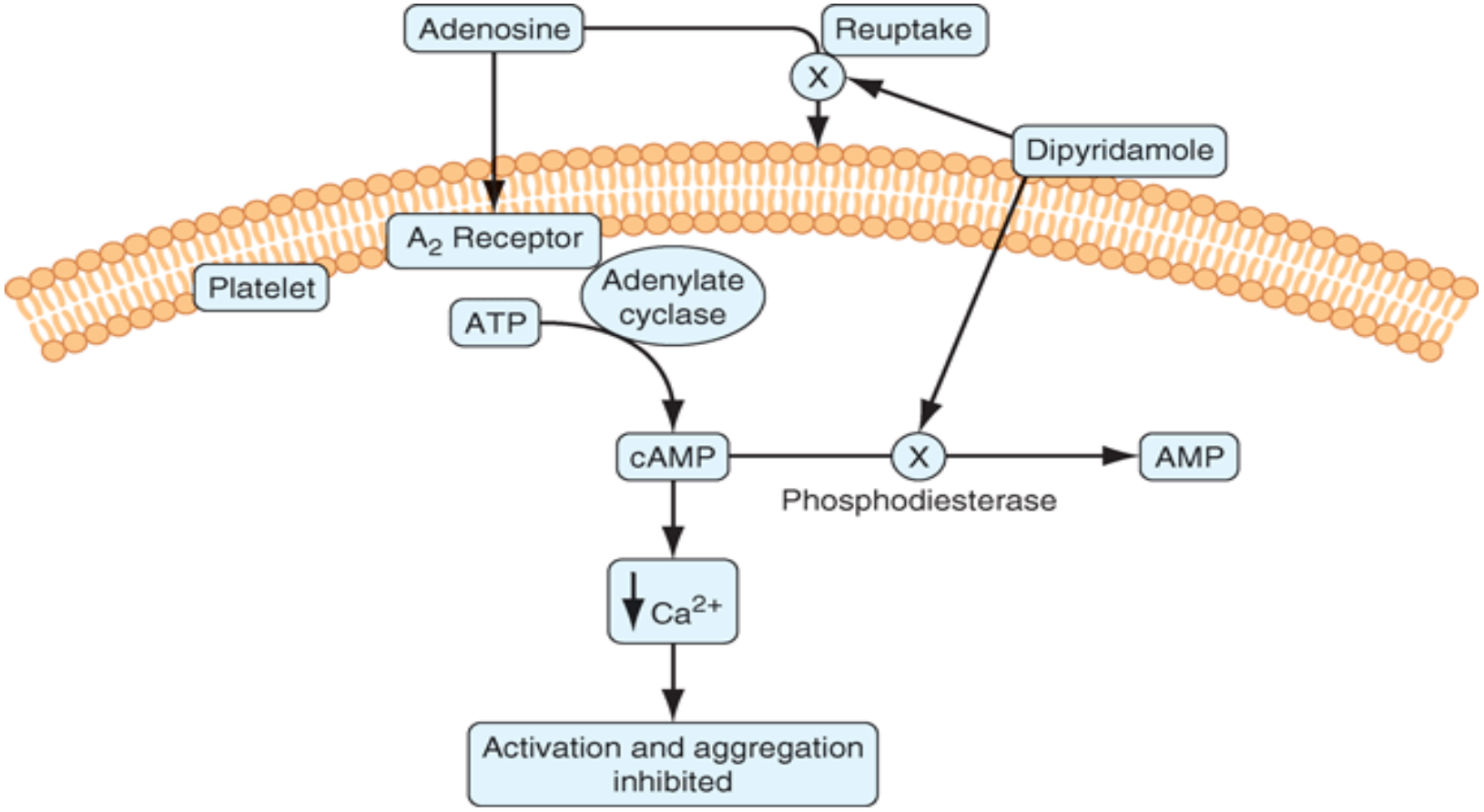
Dipyridamol

- 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 caution in coronary [illegible] 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).

Thank You