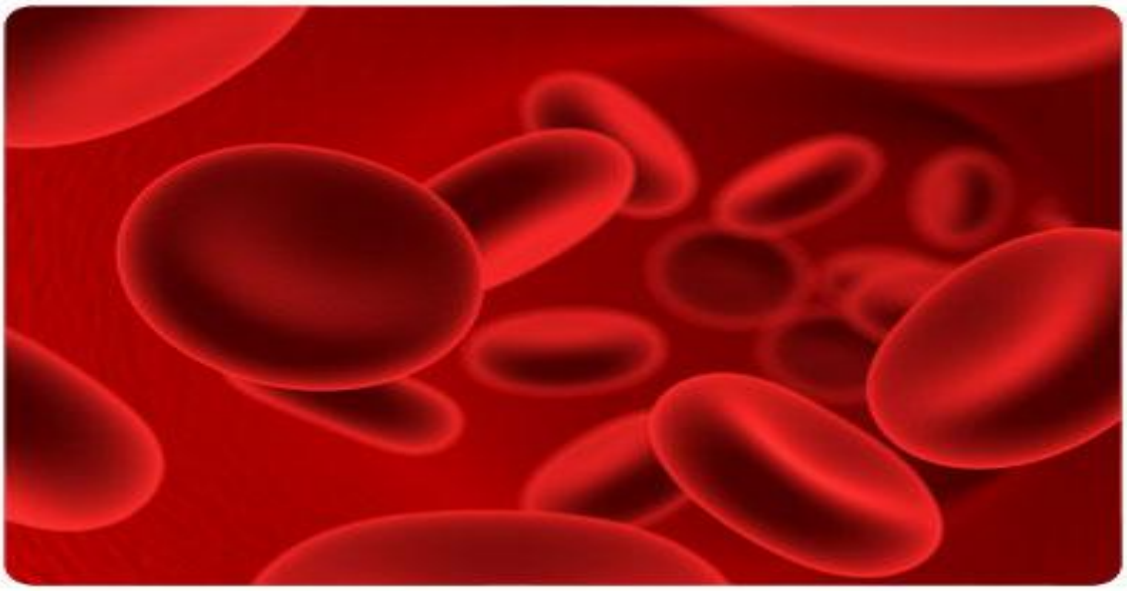
King Saud University
College Of Medicine
Pharmacology Team 430
Hematology Block

Anti-platelet Drugs



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Introduction

An injury to vascular system leads to interaction between:

1. Platelets
2. Endothelial system
3. Coagulation factors

} Which results to, formation of the CLOT

THROMBUS: is the CLOT that adheres to vessel wall

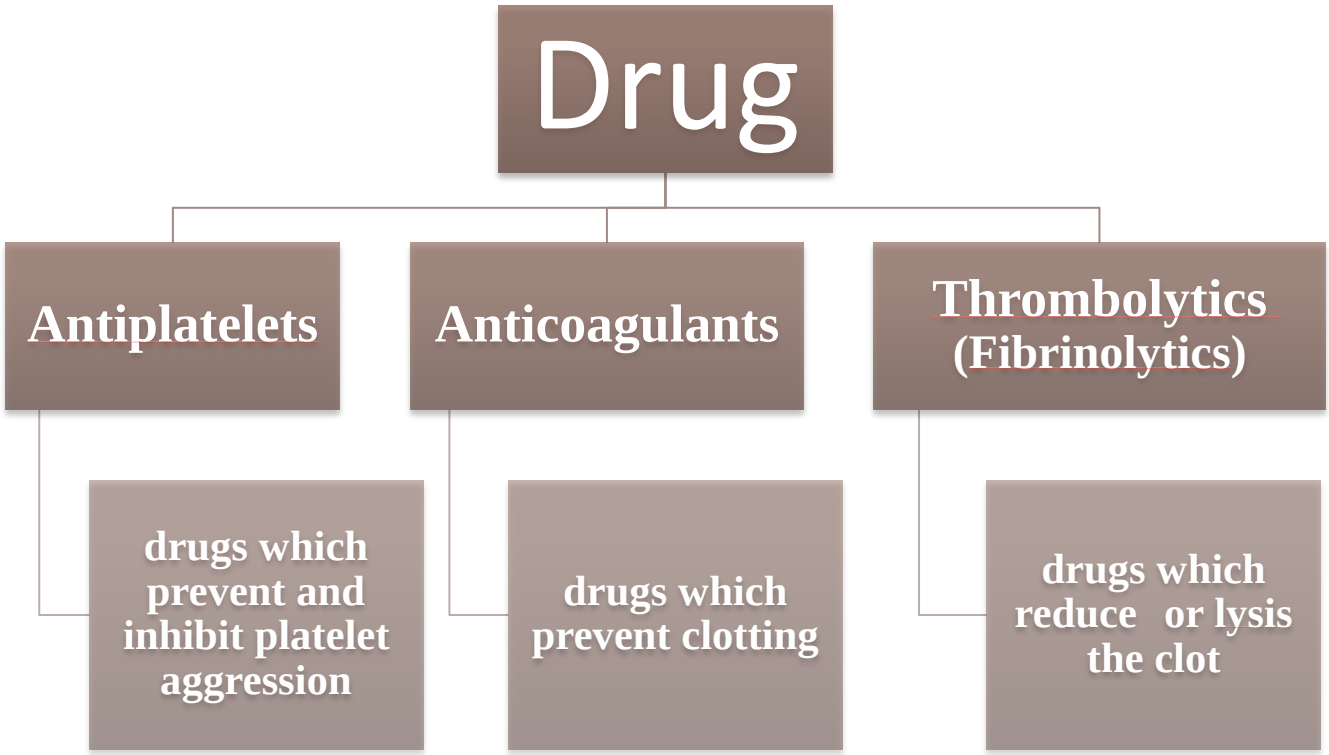
EMBOLUS: is the CLOT that floats in the blood

THROMBOSIS: is the formation of unwanted clot with in the blood vessel, producing

- Acute myocardial infarction
- Acute ischemic stroke
- Deep vein thrombosis
- Pulmonary embolism

- Arterial thrombosis is platelet rich clot, is mostly caused by atherosclerosis, usually makes problem distal to the thrombus

- Venous thrombosis is fibrin rich clot and is mostly caused by stasis of blood, usually cause problem proximal to clot and when this clot get detached and is trapped in some vital area.



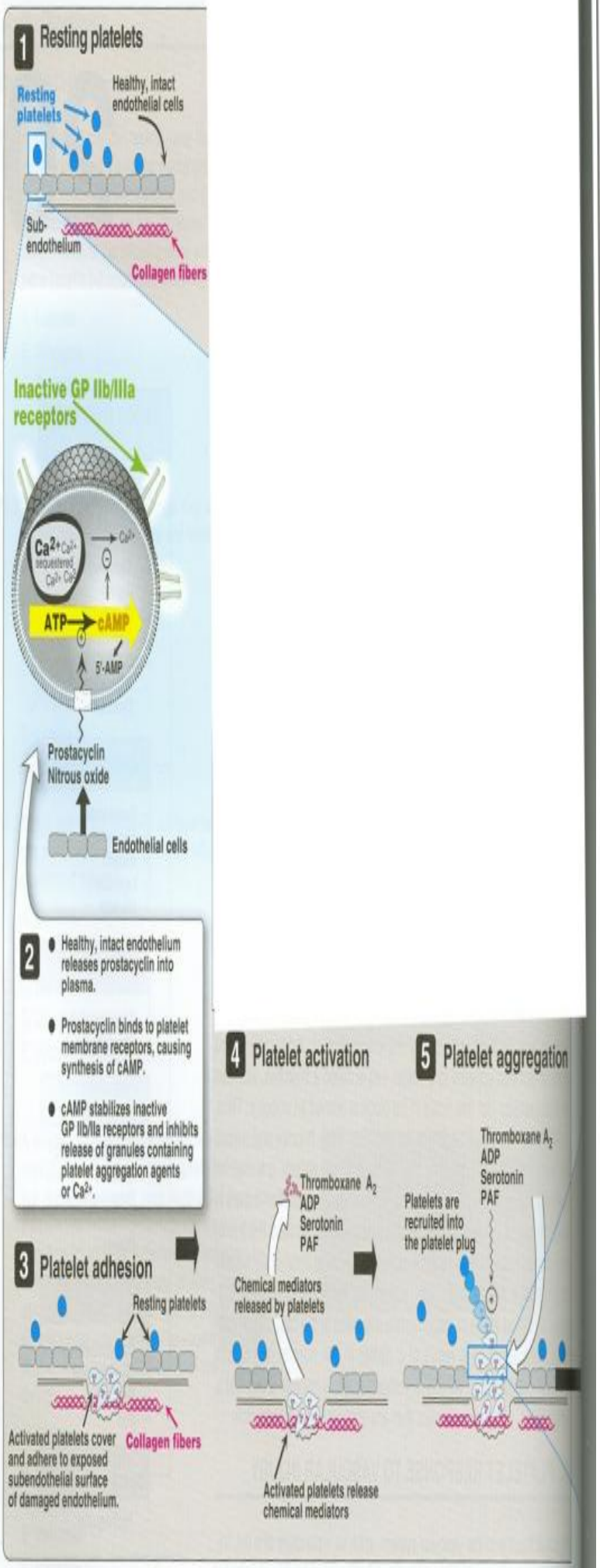


Figure 20.2
Formation of a hemostatic plug. (Continued on facing page.)

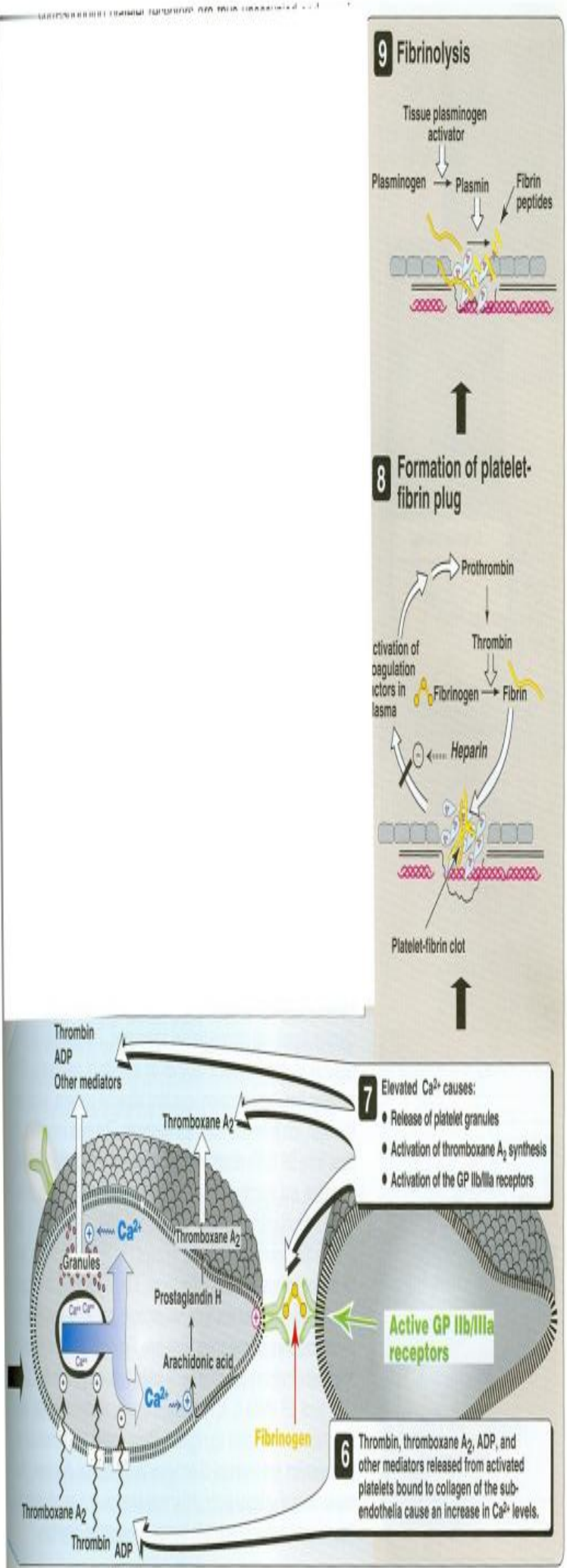


Figure 20.2 (continued)
Formation of a hemostatic plug. PAF = platelet-activation factor.

- In normal blood circulation blood doesn't clot because of **Prostacycline** and **nitric oxide** which are synthesized by intact endothelium, They bind to platelet receptors cause increase in the cAMP, which reduces calcium concentration hence inhibits the release of platelet activating factors from platelet granules (**prevents platelet aggregation**). (No. 2)

- Injury exposes reactive sub-endothelial matrix proteins, platelet adherence & activation + secretion & synthesis of vasoconstrictors & platelet activating molecules. Those:

  - **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. (No. 3,4, &5)

- 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. (No. 6&7)
- Simultaneously, the coagulation system cascade is activated ⟶ thrombin generation & a fibrin clot, which stabilizes the platelet plug. (No. 8)

➢ Platelet Aggregation:

- Activated platelets undergo three consecutive processes:
  a) **Shape change**
  b) **Secretion of platelet granular contents (ADP, fibrinogen & serotonin)**
  c) **And finally platelet aggregation**
- The final common pathway in platelet aggregation is cross-linking of the activated GP IIb/IIIa receptor with circulating adhesive arginine-glycine-asparagine (R-G-D) sequence macromolecules, predominantly fibrinogen and von Willebrand factor.

- There is ~50,000-80,000 GP IIb/IIIa receptors on the surface of each platelet.
- GP IIb/IIIa receptors undergo ***inside-out*** (low-high affinity) signaling in order to bind to vWf/fibrinogen **(inside-out means that these receptors (GP IIb/IIIa) can reveal information about the status of the cell (intra-cellular) to the outside, allowing rapid and flexible responses to changes in the environment)**
- Main stimuli for full platelet aggregation include:
  Collagen, ADP, thromboxane A_2 (TXA_2), & thrombin
- All, except collagen act through G-protein coupled receptors activating two transductions

  - Phospholipase C
  - Phospholipase A_2

- Stored ADP and synthesized TXA_2 act as **positive feedback mediators**

Drugs affecting platelet function:

	Mechanism of action	Drug	ROA
(1)	Inhibition of prostaglandin metabolism	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	Oral

Drugs may be prescribed to prevent:

- **unwanted blood clots (thrombi) from developing in blood vessels.**
- **existing blood clots from enlarging**

& to reduce the risk of an embolism, in which a piece of an existing clot in a vein breaks off & travels to a vital organ.

Therapeutic Uses of Antiplatelets:

1. **Prophylaxis of venous thrombosis.**
2. **Transient cerebral ischemic attacks.**
2. **Following coronary artery bypass grafting.**
3. **Prevention of myocardial infarction.**
4. **Following coronary artery angioplasty.**
5. **Prosthetic heart valves.**
6. **Chronic disseminated intravascular coagulation.**

I. Aspirin:

MOA: irreversible inhibition (acetylation) of cyclooxygenase enzyme thus inhibits the synthesis of thromboxane A_2 (thromboxane A 2 ---- causes platelet aggregation)

Note: Its action persist to lifetime of the platelet.

Small dose inhibits TX_{A2} synthesis in platelets But not prostacyclin (PGI_2) synthesis in endothelium (larger dose).

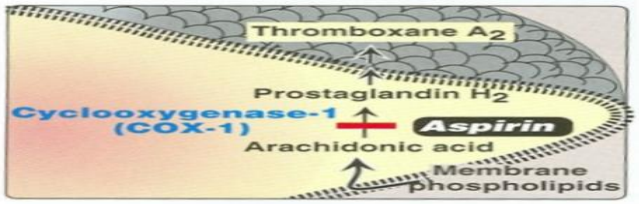


Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

Uses:

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

Adverse effects: Hyperacidity, it comes from salicylic acid –weak acidic substance. **Increased incidence of GIT bleeding**

Contraindication: Peptic ulcer

A, Efficacy of aspirin in patients with unstable angina

- ❑ Studies have demonstrated *reductions in morbid ischemic events* in patients with unstable angina following the ingestion of aspirin using varying doses of aspirin and varying periods between the onset of symptoms and treatment with aspirin

B. Efficacy of aspirin in patients following acute MI

- ▶ Analysis of 10 trials of antiplatelet agents (mainly aspirin) for secondary prophylaxis of vascular events following acute MI, the Antiplatelet Trialists Collaboration reported *striking reductions in nonfatal MI and nonfatal stroke in patients treated chronically with antiplatelet therapy (n=18,441) as well* as a highly significant reduction in cardiovascular mortality.
- ❑ Similar reductions were seen for patients receiving antiplatelet therapy following stroke. *There were no differences in effect between varying doses of aspirin*.

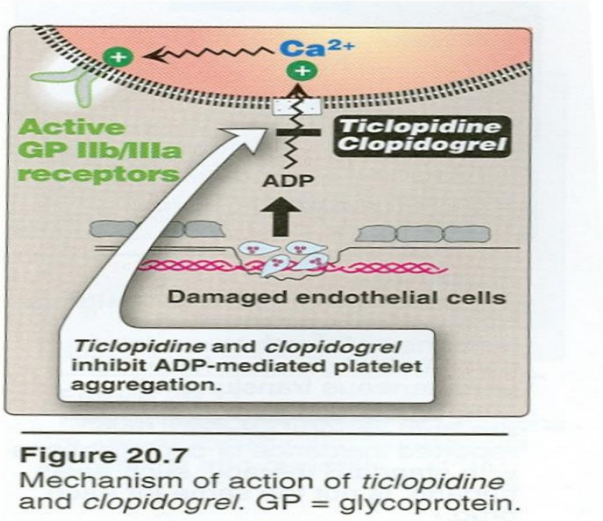


Figure 20.7
Mechanism of action of *ticlopidine* and *clopidogrel*. GP = glycoprotein.

II. Clopidogrel & Ticlopidine:

MOA:

- Irreversibly block ADP receptors on platelets. **thus inhibits platelets aggregation.**
- **- No effect on prostaglandin metabolism**

USES: To prevent thrombosis

Prevention of vascular events in patients with:

- **Transient ischemic attacks-TIAs.**
- **completed strokes.**
- **Unstable angina pectoris.**
- **Placement of a coronary stent.**

Pharmacokinetics

- **Given orally.**
- **Extensively bound to plasma proteins.**
- **Metabolized in the liver to give active metabolites.**
- **Slow onset of action (3 - 5 days).**
- **Ticlopidine is taken 250 mg twice daily.**

Ticlopidine

Adverse effects:

- Nausea, dyspepsia, diarrhea.
- Hemorrhage.
- Leucopenia.
- TTP (thrombotic thrombocytopenic purpura).
  - **CYT P_{450} inhibitor**
  - **Allergic reactions.**

Drug interaction: **Increased plasma levels of drugs as Phenytoin, Carbamazepines.**

Precaution: Regular monitoring of WBC count during first three months.

Clopidogrel potent & longer duration of action than Ticlopidine .

Adverse effects:

- same but fewer than ticlopidine
- long duration of action (once daily dosing, ticlopidine given twice daily)

III. Abciximab , Tirofiban , Eptifibatide

Note: They are taken I.V only, fast onset of action, Short duration.

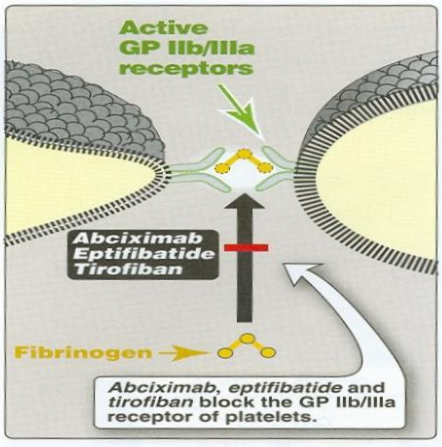


Figure 20.8
Mechanism of action of glycoprotein (GP) IIb/IIIa–receptor blockers.

MOA:

GP IIb / IIIa receptor Blockers (antagonists)

- GP IIb / IIIa receptor complex on platelet surface (membrane) function as a receptor for:
  - fibrinogen
  - vitronectin
  - fibronectin
  - von Willebrand factor
- **Activation of this receptor complex is the "final common pathway" for platelet aggregation**

USES: To prevent thrombosis

Prevention of vascular events in patients with:

- **Acute coronary syndrome.**
- **Percutaneous coronary intervention.**

1- Glycoprotein IIb/IIIa murine-derived 7E3 Fab monoclonal antibody (Abciximab):

- **1-Abciximab** is composed of 7E3 Fab fragments a murine-derived (m) monoclonal antibody directed against glycoprotein GPIIb/IIIa.
- ***Mechanism:*** The m7E3 Fab binds selectively to the glycoprotein GPIIb/IIIa receptors inhibiting platelets binding to fibrinogen and von Willebrand factor, and consequently inhibiting platelet aggregation.

- ***Clinical Efficacy:*** In acute MI patients, when the m7E3 Fab antibody was administered 3, 6, or 15 hours after beginning treatment with rt-PA (Recombinant Tissue Plasminogen Activator), the incidence of recurrent ischemia was lower than expected.
- ***Administration and therapeutic use:*** Abciximab is administered intravenously as an adjuvant to angioplasty surgery for the prevention of ischemic complications of angioplasty.
- Heparin or aspirin is given with abciximab. **for prevention of cardiac ischemic complications & in stenting.**
- Blockade of glycoprotein IIb/IIIa receptors following a bolus injection of c7E3 Fab (0.25 mg/kg): Although the plasma half-life of this monoclonal antibody is only several minutes, a potent biologic effect can be measured 2 hours after the injection.
- In patients undergoing elective angioplasty, at this point, more than 80% of receptors are bound by the antibody (and therefore unable to participate in aggregation). At 6 hours, between 60% and 70% of receptors are bound, and at 24 hours, 50% are bound.
- In patients undergoing thrombolysis for acute MI, the return toward baseline occurs more rapidly. A continuous infusion leads to sustained blockade of the receptor.

2. Tirofiban

3. Eptifibatide

- **Their t1/2 is short (2 hr)**

used in acute coronary syndromes to decrease incidence of thrombotic complications

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IV. Dipyridamol & Cilostazole

Dipyridamol

MOA:

- **Vasodilator**
- inhibits platelet function by inhibiting adenosine uptake & cyclic GMP phosphodiestrase activity. **thus ↑ cAMP in the blood platelets → vasodilatation + inhibition of platelet aggregation.**

Uses:

- Taken orally When give alone it has little or no beneficial effect.
- Therefore given in combination with **aspirin** to **prevent cerebrovascular ischemia & angina pectoris**
- And with **warfarin** for **prophylaxis of thromboemboli in patients with prosthetic heart valves**.

Disadvantages : **Headache**

Advantage : **No excess risk of bleeding**

Cilostazole

MOA:

- phosphodiestrase inhibitor(on PDE3) promotes vasodilation & inhibition of platelet aggregation.

Uses: To prevent intermittent claudication, **which is a clinical diagnosis given for muscle pain (ache, cramp, numbness or sense of fatigue), classically in the calf muscle, which occurs during exercise, such as walking, and is relieved by a short period of rest. It may be caused by poor circulation of the blood to the affected area.**

Antiplatelet drugs:

Generally they 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.

- Combination treatment with 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.

- When used together with aspirin, clopidogrel further reduces the likelihood of another heart attack or a stroke during such periods of high risk.

Monitoring:

- Bleeding time

(Antiplatelet drugs increase bleeding time)

Aspirin 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.

The reported incidence of resistance varies greatly, from 5 % to 75%.

Summary:

- **Prostacyclin and nitric oxide are synthesized by intact endothelium. They bind to platelet receptors causing an increase in the cAMP, which reduces calcium concentration hence inhibits the release of platelet activating factors from platelet granules (prevents platelet aggregation).**
- **Injury exposes reactive sub-endothelial matrix proteins, platelet adherence & activation + secretion & synthesis of vasoconstrictors & platelet activating molecule (TXA2, ADP, 5HT).**
- **Activated platelets undergo three consecutive processes (shape changes, secretion of platelet granular contents, platelet aggregation).**
- **The final common pathway in platelet aggregation is cross-linking of the activated GP IIb/IIIa receptor, which undergo inside-out (low-high affinity) signaling in order to bind to vWf/fibrinogen.**
- **Main stimuli for full platelet aggregation include :Collagen, ADP, thromboxane A2 (TXA2), & thrombin.**
- **Stored ADP and synthesized TXA2 act as positive feedback mediators.**
- **Aspirin act through the irreversible inhibition (acetylation) of cyclooxygenase enzyme thus inhibits the synthesis of thromboxane A 2. Used as prophylactic to thromboembolism. It can be combined with other drugs.**
- **S/E include hyperacidity, thereby may be contraindicated in patients with peptic ulcer.**
- **Clopidogrel & Ticlopidine act by irreversibly blocking ADP receptors on platelets.**
- **Ticlopidine S/E include: (Leucopenia, thrombotic thrombocytopenic purpura). Clopidogrel has milder S/E with longer duration of action.**
- **Abciximab , Tirofiban , Eptifibatide act by blocking GP IIb/IIIa receptor. they are taken I.V only, fast onset of action, Short duration.**
- **uses include: Prevention of vascular events in patients with Acute coronary syndrome, Percutaneous coronary intervention.**
- **Dipyridamol act by inhibiting adenosine uptake & cyclic GMP phosphodiestrase activity (vasodilator).**
- **alone ineffective, but given in combination with aspirin to prevent cerebrovascular ischemia and with warfarin for prophylaxis of thromboemboli in patients with prosthetic heart valves.**
- **Cilostazole is phosphodiestrase inhibitor(on PDE3) which promotes vasodilation & inhibition of platelet aggregation, used to prevent intermittent claudication.**
- **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.**
- **Antiplatelet drugs increase bleeding time therefore it must be monitored.**
- **Although aspirin reduces the production of TXA2, it may fail to inhibit platelet aggregation because platelets continue to respond strongly to other agonists.**