Antiplatelet Drugs

Drug	MOA	Uses and Pharmacokinetics	ADRs
Aspirin:	Inhibits the synthesis of TX_{A2} by irreversible acetylation of CYCLOOXYGENASE enzyme. Its action persist to lifetime of the platelet. Thus prevent platelets aggregation. * Small dose inhibits TX_{A2} synthesis in platelets But not prostacyclin (PGI_2) synthesis in endothelium (larger dose).	• Prophylaxis of thromboembolism e.g. (unstable angina / myocardial infarction, ischemic stroke) • can also be used in combination with other antiplatelet aggregating and anticoagulant drugs	Hyperacidity + Increased incidence of GIT bleeding --- **Contraindication:** Peptic ulcer
ADP pathway inhibitors : **Clopidogrel & Ticlopidine:**	Inhibits the binding of ADP to its platelet receptor by irreversibly modifying the platelet ADP receptor; thus inhibits platelets aggregation. * No effect on prostaglandin metabolism.	**PK:** • 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. --- **USES:** To prevent thrombosis. Prevention of vascular events in pts with (Alternative prophylactic therapy to aspirin): • transient ischemic attacks • completed strokes • unstable angina pectoris • placement of a coronary stent	Ticlopidine Adverse effects: • nausea , dyspepsia , diarrhea • hemorrhage (prolong bleeding time) • severe neutropenia and leucopenia • TTP (thrombotic thrombocytopenic purpura) • CYT P_{450} inhibitor • Allergic reactions. Precaution: * Regular monitoring of WBC count during first three months * Monitoring of blood count every month is essential. Drug interaction: Increased plasma levels of drugs as Phenytoin, Carbamazepines. --- 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)
2- Cilostazole MOA: phosphodiestrase inhibitor(on PDE3) promotes vasodilation & inhibition of platelet aggregation Uses: To prevent intermittent claudication			
Phosphodiestrase inhibitor : **1 - Dipyridamole**	inhibits platelet function by inhibiting adenosine uptake & cyclic GMP phosphodiestrase activity thus ↑ cAMP in the blood platelets → vasodilatation + inhibition of platelet aggregation.	aking 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 pts with prosthetic heart valves.	Disadvantages : Headache Advantage : No excess risk of bleeding
Glycoprotein IIb/ IIIa receptor inhibitors **1- Abciximab**: is composed of 7E3 Fab fragments a murine-derived (m) monoclonal antibody directed against glycoprotein GPIIb/IIIa	It binds selectively to the glycoprotein GPIIb/IIIa receptors inhibiting platelets binding to fibrinogen and von Willebrand factor, and consequently inhibiting platelet aggregation.	• administered intravenously as an adjuvant to angioplasty surgery for the prevention of ischemic complications of angioplasty. • Given I.V. infusion for acute coronary syndromes. • Heparin or aspirin is given with abciximab. for prevention of cardiac ischemic complications & in stenting.	**2. Tirofiban + 3. Eptifibatide** • Their t1/2 is short (2 hr) • used in acute coronary syndromes to decrease incidence of thrombotic complications.

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.

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.

Monitoring:

- Bleeding time (Antiplatelet drugs increase bleeding time)

Aspirin Resistance:

Resistance: recurrent thrombosis while on antiplatelet therapy.

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

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.

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.