Antiplatelet drugs

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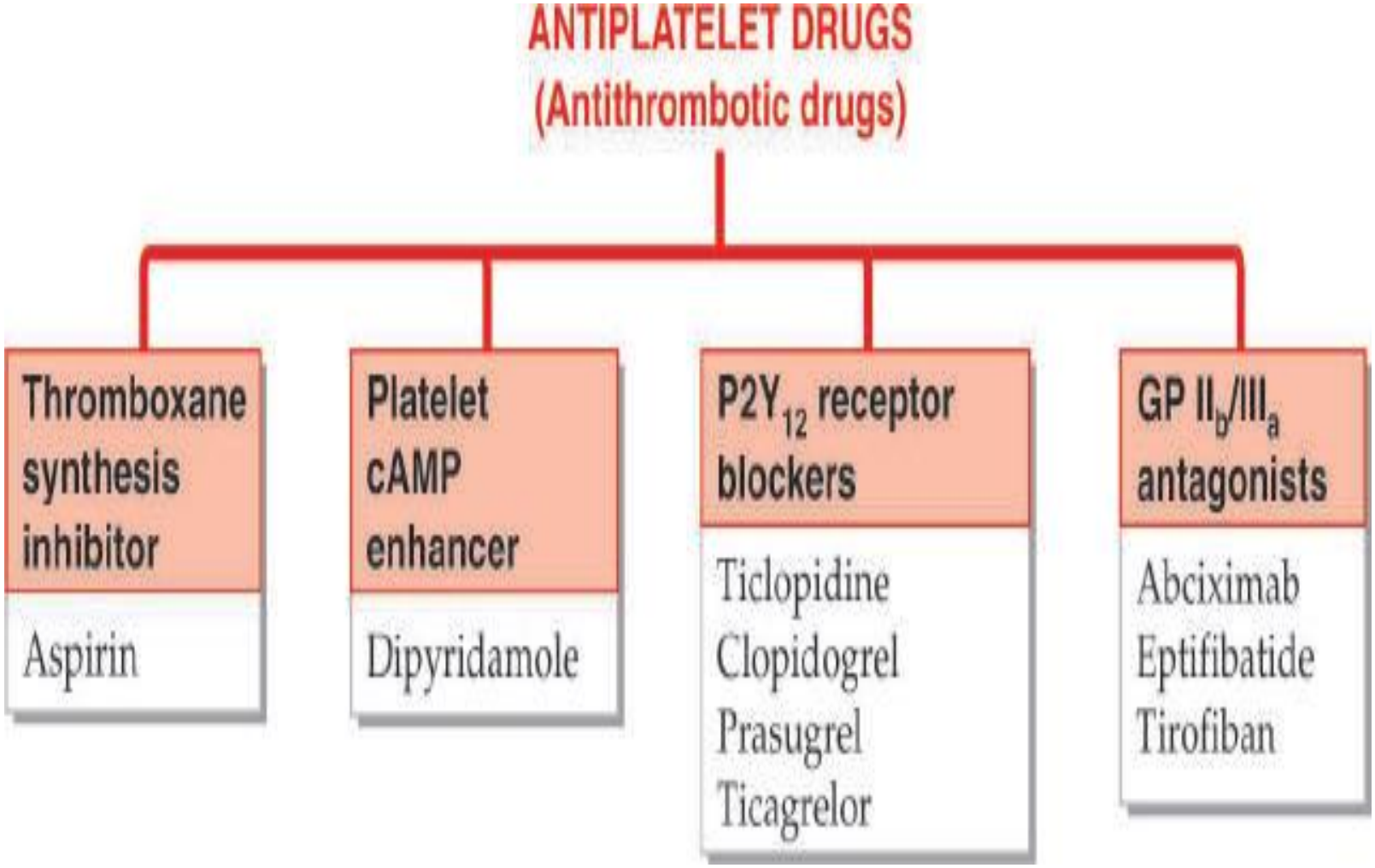
ANTIPLATELET DRUGS (Antithrombotic drugs)

- These are drugs which interfere with platelet function and are useful in the prophylaxis of thromboembolic disorders.

Mechanism of action

- Platelets express several glycoprotein **(GP)** integrin receptors on their surface.
- **Gp+Vwf or collagen** → releases **TXA2, ADP and 5-HT** conformational change favouring crosslinking of platelets **'platelet plug'** is formed.
- In arteries, platelet mass is the main constituent of the thrombus. Antiplatelet drugs are, therefore, more useful in arterial thrombosis

Classification of antiplatelet drugs



- Prostacyclin **(PGI2),** synthesized in the intima of blood vessels, is a **strong inhibitor** of platelet aggregation.
- A **balance** between **TXA2** released from platelets and PGI2 released from vessel wall appears to control intravascular thrombus formation.

Aspirin

- It **acetylates** the enzyme **COX1 and TX-synthase—inactivating them irreversibly**
- **Because platelets cannot synthesize fresh enzyme (have no nuclei**), TXA2 formation is suppressed at very low doses and till fresh platelets are formed.
- Thus, aspirin induced prolongation of bleeding time lasts for 5–7 days.

- The American (ACC/AHA)* guidelines recommend a dose of **75–162 mg/day** for long-term aspirin prophylaxis
- at low doses (75–150 mg/day or 300 mg twice weekly), TXA2 formation by platelets is selectively suppressed, whereas higher doses (> 900 mg/day) may decrease both TXA2 and PGI2 production.
- *Other NSAIDs*—are not clinically useful.

Dipyridamole

- It **inhibits phosphodiesterase** as well as **blocks uptake of adenosine to increase platelet cAMP which in turn potentiates PGI2 and interferes with aggregation.**
- used along with warfarin to **decrease** the incidence of **thromboembolism** in patients with prosthetic heart valves.
- also been used to enhance the antiplatelet action of aspirin. This combination may additionally lower the risk of stroke in patients with transient ischaemic attacks **(TIAs)**

Ticlopidine

- acts by **blocking the P2Y12 type** of purinergic receptors on the surface of platelets and **inhibits ADP-induced aggregation**.
- beneficial effects in **TIAs, stroke prevention, UA, secondary prophylaxis of MI**, and synergized with aspirin to **lower** the incidence of **restenosis after PCI and stent thrombosis**.

- However, it produced serious adverse effects like **neutropenia, thrombocytopenia, haemolysis, jaundice**, and has been superseded by other P2Y12 inhibitors (clopidogrel, etc.).

Clopidogrel

- **irreversibly blocks the P2Y12 type of purinergic receptor** on the surface of platelets.
- This Gi-coupled GPCR mediates ADP-induced platelet aggregation by **inhibiting adenylyl cyclase and decreasing cAMP**.
- Clopidogrel resembles ticlopidine in inhibiting platelet function irreversibly but is safer and better tolerated

- it is a **slow acting drug**; antiplatelet action takes about 4 hours to start and develops over days.
- The action of clopidogrel lasts for 5 days due to irreversible blockade of platelet P2Y12 receptors
- The most important adverse effect is **bleedin**g.
- neutropenia, thrombocytopenia and other bone marrow toxicity is **rare**.
- Side effects are diarrhoea, epigastric pain and rashes.

Prasugrel

- more potent and
- **faster acting P2Y12 purinergic receptor blocker**
- It is also more rapidly and more completely activated, resulting in faster and more consistent platelet inhibition.
- **Recovery, prasugrel-longer (7 days)**
- **clopidogrel (5 days)**

- Because of rapid action, prasugrel is particularly suitable for use in STEMI
- Prasugrel is **contraindicated**: Patients with history of **ischaemic stroke and TIAs** are at greater risk of intracranial haemorrhage.

Ticagrelor

- **blocks platelet aggregation by inhibiting binding of ADP to the P2Y12 receptor**
- Unlike clopidogrel and prasugrel the action of ticagrelor is **reversible**
- The risk of intracranial bleeding was higher with ticagrelor, but that of all major bleeds was similar.

- The European guidelines now recommend that all patients at high risk of ACS be given prophylactic ticagrelor.
- Side effects are dizziness, nausea, shortness of breath, tightness in chest and irregular pulse. Thus,
- ticagrelor is a faster, more potent and more consistent acting P2Y12 inhibitor antiplatelet drug.

Glycoprotein (GP) IIb/IIIa receptor antagonists

- The GPIIb/IIIa is an adhesive receptor (integrin) on platelet surface for fibrinogen and vWF through which agonists like collagen, thrombin, TXA2, ADP, etc. finally induce platelet aggregation.
- Thus, **GP IIb/IIIa antagonists block aggregation induced by all platelet agonists.** They are used only in patients with ACS and to cover PCI or coronary artery bypass grafting (CABG).

Abciximab

- **Fab fragment of a chimeric monoclonal antibody against GP IIb/ IIIa**, protein, but is relatively nonspecific and binds to some other surface proteins as well.
- Given along with aspirin + heparin during PCI it has markedly reduced the incidence of **restenosis, subsequent MI and death**.

- **Abciximab is nonantigenic**. The main risk is **haemorrhage**, incidence of which can be reduced by carefully managing the concomitant heparin therapy.
- **Thrombocytopenia is another complication**.

- **Constipation, ileus and arrhythmias** can occur
- It is **expensive**, but is being used in unstable angina and as adjuvant to coronary thrombolysis/PCI with stent placement.

Eptifibatide

- It is a synthetic cyclic peptide that selectively **binds to platelet surface GPIIb/IIIa receptor** and inhibits platelet aggregation.
- platelet inhibition reverses in a short time (within 6–10 hours) because it quickly **dissociates from the receptor**

- **Bleeding and thrombocytopenia are the major adverse effects**.
- Rashes and anaphylaxis are rare.
- **Tirofiban** is a **similar** drug.

Uses of antiplatelet drugs

- The aim of using antiplatelet drugs is to **prevent intravascular thrombosis and embolization**, with minimal risk of haemorrhage

- Those with **CAD or risk factors** for stroke are generally given a **single drug** (aspirin/clopidogrel).
- For indications like ACS, maintenance of vascular recanalization, stent placement, vessel grafting, etc. potent inhibition of platelet function is required. This is provided by **combining two** antiplatelet **drugs** which act by different mechanisms**(dual antiplatelet therapy).**

1. ***Coronary artery disease***

- **Primary prevention of ischaemia** with **aspirin** is of no proven benefit. It reduces the incidence of fatal as well as nonfatal MI, but increases the risk of cerebral haemorrhage.
- **Clopidogrel is an alternative** to aspirin in symptomatic patients of ischaemia.
- Continued aspirin/clopidogrel prophylaxis in
- post-MI patients clearly **prevents reinfarction**
- **and reduces mortality.**

2. ***Acute coronary syndromes (ACSs)***

- unstable angina **(UA)** to non-ST elevation myocardial infarction **(NSTEMI) to STEMI**
- Unstable angina (UA) Aspirin reduces the risk of progression to MI and sudden death.
- **Clopidogrel is generally combined with aspirin, or may be used as alternative if aspirin cannot be given.** For maximum protection the antiplatelet drugs are **supplemented with LMW heparin followed by warfarin**.

NSTEMI

- Patients of NSTEMI who are managed without PCI/thrombolysis are generally put on a combination of **aspirin + clopidogrel or ticagrelor,** which is continued for **upto one year**

STEMI

- **Primary PCI with or without stent placement** is the procedure of choice for all STEMI as well as high risk NSTEMI patients who present within 12 hours.
- **Prasugrel or ticagrelor + aspirin** is the antiplatelet regimen most commonly selected for patients who are to undergo PCI.
- Prasugrel is also preferred over clopidogrel in diabetics

- **Abciximab/eptifibatide/tirofiban infused i.v. along with oral aspirin** and s.c. heparin markedly **reduce** incidence of **restenosis** and subsequent MI after coronary angioplasty. Aspirin and/or clopidogrel/ticagrelor are routinely given to ACS patients treated with thrombolysis.

  Coronary artery bypass surgery is

- also covered by intensive antiplatelet regimen including **aspirin + GPIIb/IIIa antagonists/prasugrel**
- The patency of recanalized coronary artery or implanted vessel is improved and incidence of reocclusion is reduced by **continuing aspirin + clopidogrel/prasugrel/ticagrelor for upto 12 months**.
- Dual antiplatelet therapy (DAPT) is recommended after stent placement.
- Prasugrel is used when stent thrombosis occurs during clopidogrel treatment.

3. ***Cerebrovascular disease***

- **aspirin** has **reduced** the incidence of **TIAs** and of stroke in patients with TIAs
- Aspirin or clopidogrel is given to all patients of TIAs who are not to be treated with anticoagulants.
- Though short-term use of aspirin + clopidogrel DAPT may be beneficial, long-term use of the combination increases the risk of *haemorrhage*.

4. ***Prosthetic heart valves and arteriovenous shunts***

- Antiplatelet drugs, used with warfarin reduce formation of **microthrombi** on artificial heart valves and the incidence of **embolism**.
- Aspirin is clearly effective but increases risk of bleeding due to warfarin.
- Dipyridamole does not increase bleeding risk, but incidence of thromboembolism is reduced when it is combined with an oral anticoagulant.

5. ***Venous thromboembolism***

- Trials have shown antiplatelet drugs also to have a **prophylactic effect**, but their relative value in comparison to, or in addition to anticoagulants is not established

6. ***Peripheral vascular disease***

- Aspirin/clopidogrel may produce some **improvement in intermittent claudication** and **reduce** the incidence of **thromboembolism**.

Thank you!!!