# ANTIPLATELETS

DR. JAVAID NAZIR

subsequent release of platelet aggregating agents.

- Damaged endothelial cells synthesize less prostacyclin than healthy cells resulting in lower prostacyclin levels. Since there is less prostacyclin to bind platelet receptors, less intracellular cAMP is synthesized which leads to platelet aggregation.
- Platelet membrane also contains receptors that can bind thrombin and thromboxanes esp. thromboxane $A_2$
- In the normal vessel, circulating levels of thrombin and thromboxanes are low so platelet receptors are unoccupied & remain inactive so platelet activation and aggregation not initiated.

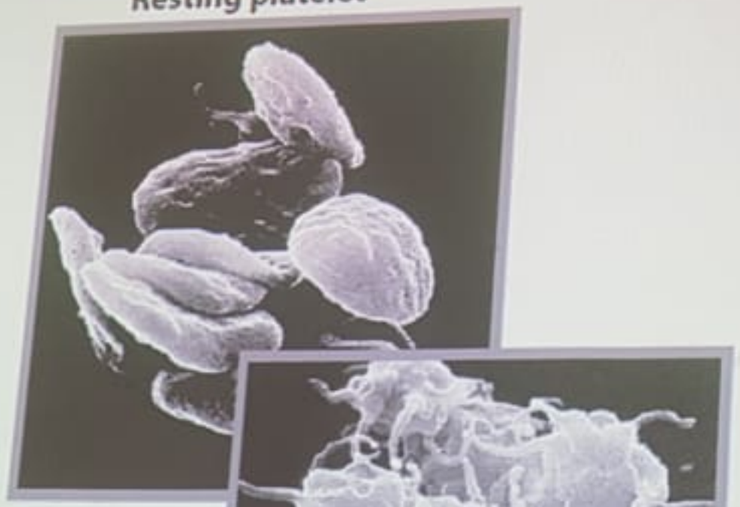
**Mechanism of PLT aggregation:** The ↑ in cytosolic $Ca^{++}$ accompanying activation is due to a release of sequestered stores within the platelet.

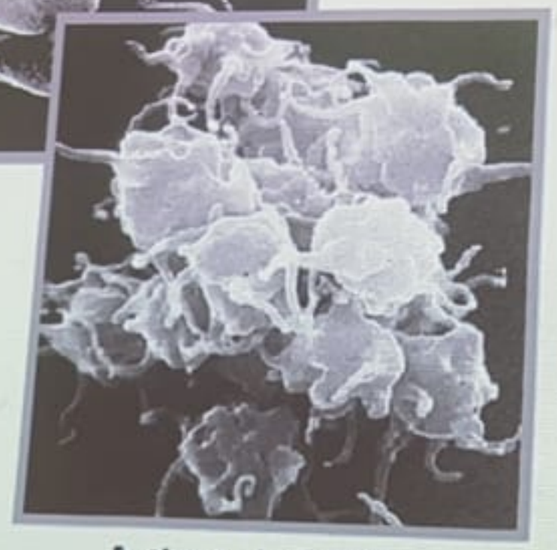
*This leads to*

- release of PLT granules containing mediators such as ADP & serotonin that activate other PLTs.
- activation of thromboxane $A_2$ synthesis &
- activation of glycoprotein(GP) IIb/IIIa receptors that bind fibrinogen & ultimately regulate PLT–PLT interaction & thrombus formation.

*Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate PLT resulting in platelet cross-linking & PLT aggregation.*

Resting platelet





Activated platelet

# ANTI PLATELET AGENTS

- Inhibition of prostaglandin metabolism:

  ASPIRIN

- Inhibition of ADP induced platelet aggregation

  CLOPIDOGREL, PRASUGREL, TICAGRELOR & TICLOPIDINE

- Blockade of IIb/IIIa receptors on platelets:

  THIENOPYRIDINES

  ABCIXIMAB, EPTIFIBATIDE & TIROFIBAN

- Additional:

  DIPYRIDAMOLE & CILOSTAZOL

# ASPIRIN

- $TXA_2$ is derived from $PGH_2$ which causes PLT to aggregate. Drugs that antagonise this pathway interfere with PLT aggregation in vitro & prolong BT in vivo.
- ASPIRIN inhibits synthesis of $TXA_2$ by irreversible acetylation of COX.
- FDA has approved use of 325 mg/d for primary prophylaxis of MI. (LOPRIN 75mg/d)

- Effect of ASPIRIN on PLTs lasts for whole of their life ie up-to 7 days.

# CLOPIDOGREL AND TICLOPIDINE

- They ↓ PLTs aggregation by inhibiting the binding of ADP to its receptors on PLTs & thus inhibit the activation of GP IIb/IIIa receptors required for PLTs to bind to fibrinogen & to each other.
- Clopidogrel, prasugrel & ticlopidine are converted in liver to active metabolites that irreversibly bind with PLT ADP receptor & so prevent ADP-mediated aggregation. Ticagrelor, newer drug that does not require activation & reversibly inhibits PLT ADP receptor.

USES: TIAs, Strokes & unstable angina, To prevent thrombosis in pts. undergoing placement of the CORONARY stent

- Ad. effects of TICLOPIDINE: N,D, DYSPEPSIA in 20% of Pts, hemorrhage in 5% & most serious LEUKOPENIA in 1%. Thrombotic thrombocytopenic purpura (TTP) is associated with TICLOPIDINE.
- DOSAGES: 250 mg twice daily.
- CLOPIDOGREL has fewer A/E than TICLOPIDINE & is rarely associated with NEUTROPENIA.

TPP rarely reported so preffered over TICLOPIDINE.

Anti-thrombotic effects of CLOPIDOGREL are dose dependent. Within 5 hrs after an oral dose of 300 mg, 80% of platelet activity is inhibited.

Maintainance dose is 75 mg/d which achieves max. PLTs inhibition & duration of anti-PLT effect is 7-10 days

# BLOCKADE OF PLT GP IIB/IIIA RECEPTORS

They are used in pts. with ac. coronary synd. They target PLT IIB/IIIA receptors complex which functions as receptor mainly for fibrinogen & vitronectin. Activation of this receptor complex is the final common pathway for PLT aggregation. There are about 50,000 copies of this complex on PLT surface. Persons lacking this have a bleeding disorder called GLANZMANN'S THROMBASTHENIA.

- ABCIXIMAB: A humanized monoclonal antibody directed against this complex. Approved for use in cutaneous coronary intervention & in ac. coronary synd.
  EPTIFIBATIDE: Cyclic PEPTIDE that binds FIBRINOGEN to receptors.
- TIROFIBAN: Not a peptide but has similar properties. Both inhibit ligand binding to IIb/IIIa receptors by their occupancy of receptors.
- All 3 dugs are given parentally. Oral forms of IIb/IIIa antagonists developed but lack of efficacy & significant THROMBOCYTOPENIA have prevented progress with oral analogs.

- Dipyridamole has variable bioavailability following oral administration. $t_{1/2}$- 12HRS. Highly protein bound. Undergoes hepatic metabolism as well as glucuronidation & is excreted mainly in the feces.

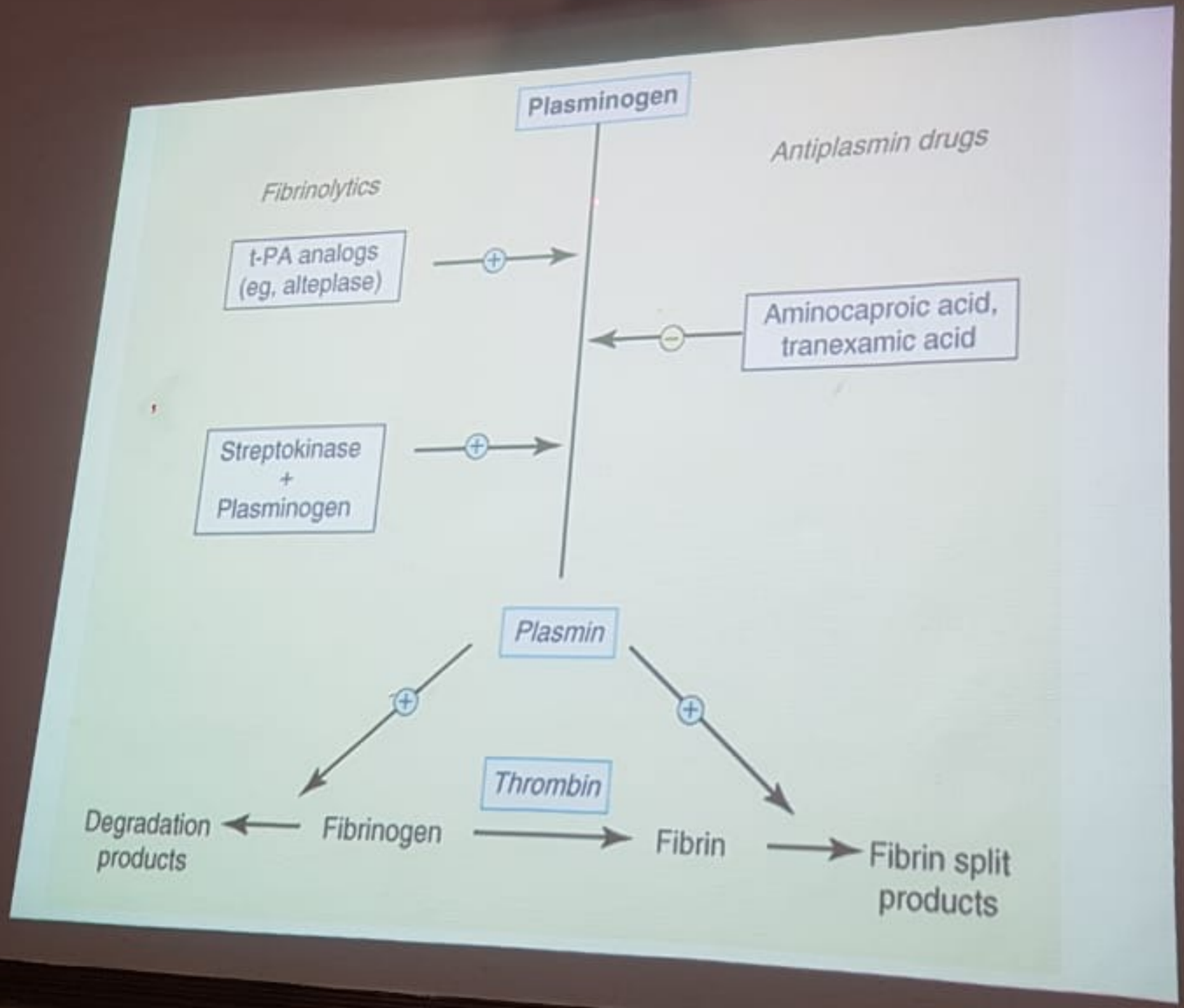
Pts with unstable angina should not use dipyridamole b/o its vasodilating properties which may worsen ischemia (coronary steal phenomenon).

Dipyridamole commonly causes headache & can lead to orthostatic hypotension esp. if administered IV.

- CILOSTAZOL: New phosphodiesterase inhibitor that promotes vasodilatation and inhibition of PLT aggregation. Used primarily to treat intermittent claudication.

- Fibrinolysis refers to the process of fibrin digestion by the fibrin specific protease, plasmin.
- In fibrinolytic system, the precursor form of the plasmin circulates in plasma in an inactive form as plasminogin.
- Plasminogen is a single chain glycoprotein with 790 amino acid residues. Its concentration in plasma averages 2µMole.

- In response to injury, endothelial cells synthesize and release t-PA which converts plasminogen to plasmin.
- This plasmin degrades fibrin, remodels the thrombus and limits its extension by proteolytic digestion of fibrin thereby dissolving the clot.


Plasminogen
Fibrinolytics
Antiplasmin drugs
t-PA analogs
(eg, alteplase)
Aminocaproic acid,
tranexamic acid
Streptokinase
+
Plasminogen
Plasmin
Thrombin
Degradation
products
Fibrinogen
Fibrin
Fibrin split
products

- Fibrinolytic Drugs rapidly lyse Thrombi by catalyzing the formation of serine protease plasmin from its precursor, plasminogen.

- These drugs create a generalised lytic state when given I/V so both protected hemostatic thrombi and target thromboemboli are broken down.

## Fibrinolytic Drugs are:

- 1st generation:

  Streptokinase & Urokinase

- 2ND GENERATION:

  Alteplase(formerly known as tPa)

  Anistreplase

  Reteplase

  Tenecteplase & duteplase

**MOA:** The thrombolytic agents share some common features. All act either directly or indirectly to convert plasminogen to plasmin, which in turn cleaves fibrin thus lysing thrombi.

Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately increased local thrombi may occur as the clot dissolves leading to enhanced platelet aggregation and thrombosis.

- Strategies to prevent this include administration of antiplatelet drugs such as aspirin or antithrombotics such as heparin.

# Streptokinase

- It's a protein synthesized by β-hemolytic Streptococci. By itself it has no intrinsic enzymatic activity. It combines with proactivator plasminogen.
- This enzymatic complex catalyses the conversion of inactive plasminogen to active plasmin.
- SK therapy is started within 04 hrs of MI & is infused for 01hr.On discontinuation of treatment,either heparin or oral anticoagulant may be administered.
- $t_{1/2}$ is 80 min.
- Antistreptococcal antibodies present in blood b/o previous streptococcal infections inactivate a large

amount of SK.

- SK is antigenic so can cause hypersensitivity as major ad. effect alongwith bleeding. So if thrombolytics are required during this period then tPa or urokinase should be used.

# Urokinase

- Human enzyme synthesized by kidney(1st isolated from human urine hence the name) that directly converts plasminogen to active plasmin.
- Plasmin itself cannot be used because naturally occurring inhibitors in plasma prevents its effects. However the absence of inhibitors for Urokinase and Streptokinase-proactivator complex permit their use clinically.
- Plasmin formed inside a thrombus by these activators is protected from plasma antiplasmins which allows it to lyse the thrombus from within.
- $t_{1/2}$ is 15 min.

# ANISTREPLASE

Anisoylated plasminogen streptokinase activator complex(APSAC).

Preformed complex of plasminogen & streptokinase & is considered to be a prodrug. Streptokinase must be released & only plasminogen to which it is associated will get converted to plasmin.

Long acting & injected in a single IV bolus of 30 units in 3-5 minutes so more convient to use.

# ALTEPLASE (Formerly t-PA)

Produced by DNA recombinant technology.

Plasminogen can be activated endogenously by t-PAs.Has low affinity for free Plasminogen. These activators rapidly activate plasminogen that is bound to fibrin in a thrombus or a hemostatic plug so said to be fibrin selective & at low doses has the advantage of lysing only fibrin without unwanted degradation of other protein notably fibrinogen.

This contrasts with SK which acts on free plasminogen & induces a general fibrinolytic state. $t_{1/2}$ 05min. Bleeding is major ad. effect including GI & CEREBRAL HEMMORAGE.

# Reteplase

- It is less fibrin specific than t-PA produced by recombinant DNA technology from which several amino acid sequences have been deleted.
- Less expensive than t-PA.
- Advantage: Faster reperfusion & bleeding tendency negligible.
- **TENECTEPLASE** mutant form of t-PA that has a longer $t_{1/2}$ and can be given as I/V bolus.
- It is slightly more fibrin specific than t-PA

## Indications

- Pulmonary embolism
- Severe DVT such as superior vena caval syndrome
- Ascending thrombophlebitis of iliofemoral vein
- Peripheral vascular disease in which these drugs are given intra-arterially.
- t-PA has also been approved for use in acute ischmic stroke within 3 hours of symptom onset. Dose is 0.9mg/Kg

## Contra Indications

- Surgery within 10 days
- Serious GIT bleeding within 3 months
- H/O hypertension
- Active bleeding disorder
- Previous H/O CVA.
- Pregnancy
- pts. with healing wounds
- Head trauma, brain tumor, intracranial bleeding

**Adverse effects:** **The thrombolytic agents do not distinguish** between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus hemorrhage is a major side effect.

For example a previously unsuspected lesion such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent.

Hypersensitivity with SK.

# Dosage

- Dosage of Streptokinase administered by I/V infusion in a loading dose of 250,000 units followed by 100,000 units per hour for 24 to 72 hours. Pts with streptococcal antibodies can develop fever, allergic reactions and therapeutic resistance.
- Streptokinase has been associated by increased bleeding risk in acute ischemic stroke when given at a dose of 1.5 million units, so not recommended in this setting.
- Urokinase requires a loading dose of 300,000 units given over 10 minutes and a maintenance does of 300,000 units per hour for 12 hours.

- Alteplase (t-PA) is given by I/V infusion of 60mg over the first hour and then 40mg at a rate of 20mg/h.
- Reteplase given as 2 I/v bolus injections of 10 units each at 30min interval.
- Tenecteplase is given as single I/V bolus of 0.5mg/Kg.
- Anistreplase is given as a single I/V injection of 30 units over 3-5min.
- A single course of fibrinolytic drugs is very expensive.