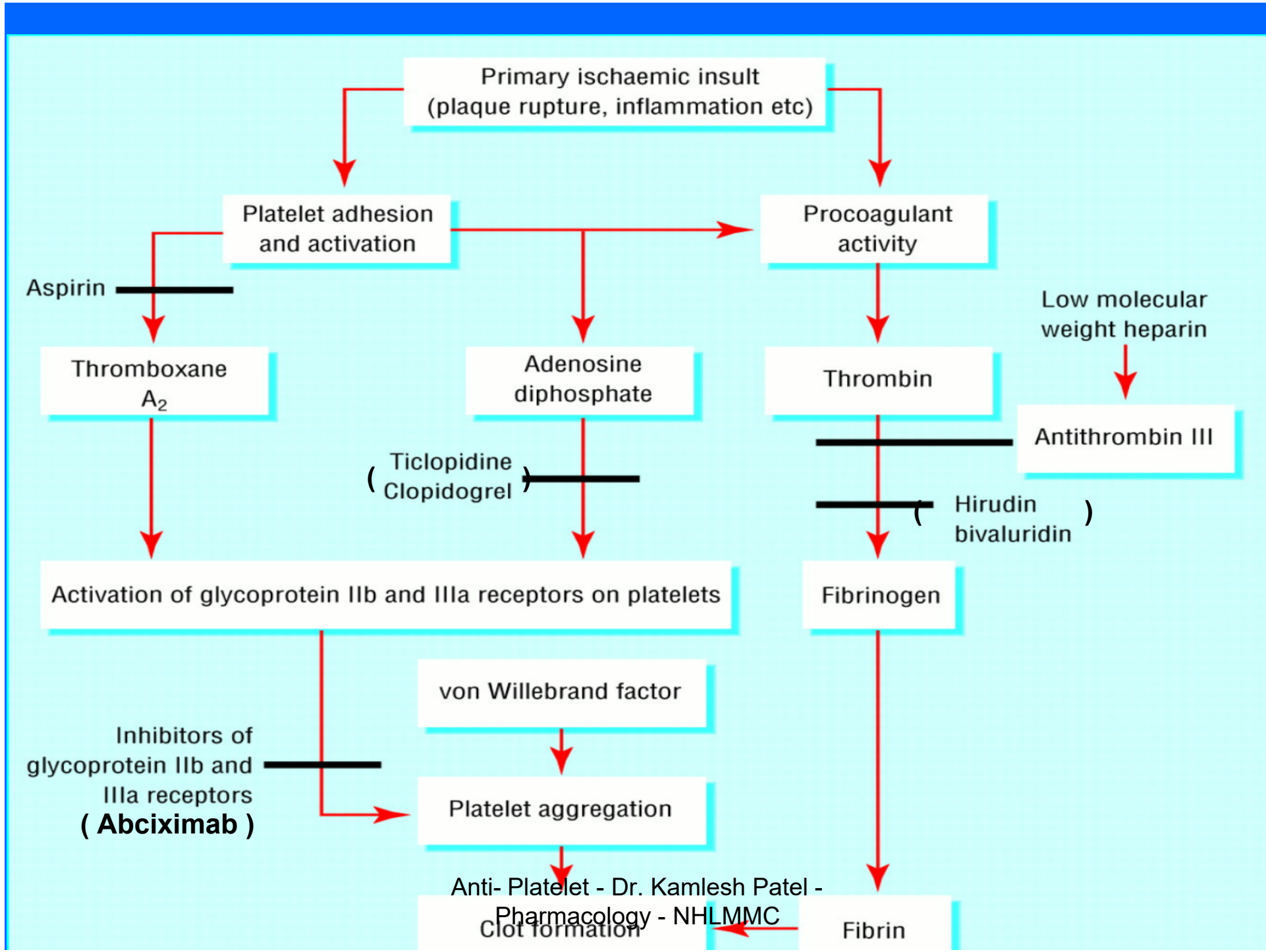


ANTI-PLATELET DRUGS

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Anti- Platelet - Dr. Kamlesh Patel -
Pharmacology - NHLMMC



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- **Antiplatelets interfere with platelet function – useful in prophylaxis of thrombo -emboloic disorders**
- **TXA₂ (platelets) – promote platelet aggregation – is a potent vasoconstrictor**
- **PGI₂ (vas.endothelium) – Inhibit platelet aggregation – is a potent vasodilator**
- **Balance between TXA₂ & PGI₂ controls intravascular thrombus formation**

Platelet Adhesion to Damaged Vessel Wall



Platelet activation



Arachidonic acid generation



↓ **Cox - 1 β** -----inhibits-----**Low Dose Aspirin**

ADP Release

PGG2, PGH2 (Unstable PG Intermediates)



TXA2 Production



Activation of Glycoprotein(GP) I b / III a Receptors on Platelets

• **Ticlopidine**

• **Clopidogrel**

Prasugrel

----- inhibits à



β ---Inhibits ----GP I b /III a Receptor Antagonists

(**Abciximab, Eptifibatide, Tirofiban**)



Binding of Fibrinogen & von Willebrand Factor to GP I b / III a Receptors and linking of platelets



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Inhibits Platelet Aggregation

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ANTIPLATELET DRUGS

1) Thromboxane A₂ synthesis Inhibitors :-

Low dose aspirin

2) ADP Receptor (P₂Y₁₂) Receptor Blockers :-

a) Irreversible : **Clopidogrel, Prasugrel, Ticlopidine**

b) Reversible : **Ticagrelor**

3) Phosphodiesterase Inhibitors :-

Dipyridamole, Cilostazol

4) Prostacycline Analogues :-

Epoprostenol, Iloprost

5) Glycoprotein IIb /IIIa receptor antagonists :-

Abciximab, Eptifibatide, Tirofiban

6) Protease activated receptor (PAR -1) antagonists :-

Vorapaxar

LOW DOSE ASPIRIN

MOA :

Selectively irreversibly inhibits & acetylates COX-1 & TX-synthetase in Platelets



↓ cyclic endoperoxides (PGG₂ / H₂)



↓ TXA₂ Production



Inhibits Platelet aggregation



↓ Thromboembolism

Low Dose Aspirin

- Action on COX is permanent lasting for the life span of platelets (5 – 7 days)
- Platelets have no nuclei, hence cannot synthesize new / fresh enzyme
- Dose : Aspirin antiplatelet effect :
50-150 mg once a day

Low Dose Aspirin

- Platelet COX is more sensitive
- TXA₂ level is more than PGI₂ in thromboembolism.
- Inhibits COX-1 & TXA₂ in platelets irreversibly & hence cannot synthesize fresh enzyme upto 7 days
- Inhibits COX-1 & PGI₂ reversibly in blood vessels & hence can rapidly resynthesize fresh enzyme.

PREPARATIONS

Aspirin

Tab : 50, 75, 100, 150 mg

Dose : 50 - 150 mg o.d

CLOPIDOGREL

- **Thienopyridine compound**
- **Prodrug**
- **Irreversible antagonists of ADP (P2Y₁₂) Receptors**

MOA of CLOPIDOGREL

Activated by CP-450 enzymes



Inhibits irreversibly the binding of ADP to its platelet receptors



Suppresses the ADP mediated activation of GP IIb / IIIa receptors



Inhibition of platelet aggregation
(Effects persists for 6 Days)

CLOPIDOGREL

- **OOA: Slow - 4hrs**
- **Absorption not affected by food / antacids**
- **Excreted in urine & faeces**
- **Preferred over Ticlopidine – less chances of neutropenia**
- **Dose : 300 mg Loading Dose initially, then, 75 mg OD daily**

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ADRs of Clopidogrel

- **Rashes**
- **Pruritus**
- **Abd. Pain**
- **Diarrhoea**
- **Dyspepsia**
- **Rarely neutropenia & thrombocytopenia**

Preparations

- **Tab: 75mg of Clopidogrel**
- **Combination: Aspirin 75mg+ Clopidogrel 75mg**
- **Aspirin 150mg+ Clopidogrel 75mg**
- **Dose: 1tab o.d.**

PRASUGREL

- Is a Prodrug
- Rapidly converted to active metabolite (t_{1/2} 7 h)
- More potent irreversible P₂Y₁₂(ADP) receptor blocker
- Has rapid onset of action, more consistent and greater antiplatelet action (than clopidogrel)
- More effective and safer (than Clopidogrel)
- PPI (omeprazole) does not reduce its effect (unlike clopidogrel)
- Is preferred in Diabetics, ACS undergoing PCI
- Lesser ischaemic episodes (than clopidogrel)
- C/I in Ischaemic stroke, TIA, Peptic ulcer Pts
- Dose : Loading Dose 60 mg initially
- 10 mg / day ; 5 mg/day < 60 kg, elderly >75yrs

TICLOPIDINE

- Is a Prodrug → converted to active metabolite
- Alters surface receptors on platelets (t_{1/2} 8h)
- Inhibits irreversibly ADP (Purinergic P₂Y₁₂) receptors and Fibrinogen – induced platelet aggregation without modifying GPIIb/IIIa receptor
- Peak anti-platelet action after 8-10 days
- Synergistic effect with Aspirin due to different action

USES & ADRs of Ticlopidine

1. Used in Stroke prevention, TIAs, Unstable angina, Intermittent claudication, PCI, CABG & post MI.
2. ADRs are : GIT : N,V,abd. Pain, Diarrhoea
3. Headache , Tinnitus, skin rashes, Bleeding
4. Neutropenia, thrombocytopenia , jaundice. (requires WBC monitoring)

DIPYRIDAMOLE

MOA :

Inhibits PDE & / or blocks the uptake of adenosine



Acts at adenosine -2 receptors & stimulates PI. adenyl cyclase



↑ platelet cAMP



Potentiates PGI₂ action



Inhibition of Platelet aggregation

DIPYRIDAMOLE

- * Inhibits Phosphodiesterase (PDE)
- No action on the level of TXA₂
- Alone not useful much
- Usually combined with Warfarin for Prophylaxis of Thromboembolism in patients with prosthetic heart valve.
- Reduces incidence of stroke in pts with prior history of stroke

PREPARATIONS

Tab : 25, 75, 100 mg of Dipyridamole

Combination :

Dipyridamole 75 + Aspirin 60 mg

Dipyridamole 75 + Aspirin 100 mg

Dose : 1 o.d

CILOSTAZOL

- Newer PDE3 inhibitor similar to Milrinone (inodilator)
- Potent antiplatelet agent
- Also facilitates vasodilatation
- Suitable agent for prevention of intermittent claudication in PVD
- Avoided in CHF pts, enzyme inhibitors
- Ses ; ventricular ectopic beats, palpitation
- Dose : 100 mg BD ½ hr before meals.

EPOPROSTINOL

- Prostacycline analogue
- Blocks all the pathway of platelet activation
- Inhibits expression of GP lib/IIIa receptors
- Directly inhibits Platelet aggregation
- Has short duration of action (3 minutes)
- Used by I.V. infusion to prevent platelet loss during Hemodialysis and Hemofiltration
- Also used for Pulmonary Hypertension
- S/Es : Vasodilatation – Headache, Flushing

GLYCOPROTEIN IIb / IIIa (GP IIb/IIIa) receptors blockers

- * Also known as α IIb β 3 receptor inhibitor
- Are Integrins (cell surface) glycoproteins that work as adhesion receptor in final pathway of platelet aggregation
- Are receptors for Fibrinogen, Vitronectin, Fibronectin and von Willebrand Factor(vWF)
- Blockage of GP IIA/IIb receptors prevents binding of fibrinogen and vWF causing inhibition of platelet aggregation.

GP IIb / IIIa Inhibitors

- 1. Abciximab (monoclonal antibody)**
- 2. Eptifibatide (synthetic drug)**
- 3. Tirofiban (non-peptide drug)**

ABCIXIMAB

- **Is a Fab fragment of monoclonal antibody against GPIIb/IIIa. Is nonantigenic**
- **It is an adhesive receptor for fibrinogen & VWF (von Willbrand Factor) through which agonists like TXA₂, ADP, Collagen, thrombin induce Platelet aggregation**
- **Hence, GP IIb/IIIa Antagonists block platelet aggregation induced by all platelet agonists.**

ABCIXIMAB

- **DOA** : 12 – 24 hrs (long platelet binding) ,
t_{1/2} : 30 mins
- **Inj** : 2mg / ml I.V inj
- **Dose** : Bolus dose of 0.25 mg/kg i.v. infusion over 10-60 min before PCI followed by 10 mcg/min for 12 hr.
- **ADRs** :
 - . Haemorrhage – give Heparin
 - . Thrombocytopenia, hypotension, bradycardia, cardiac arrhythmias

USES : - Unstable angina, adjuvant to coronary thrombolysis, PCI with stent placement

EPTIFIBATIDE

- Is cyclic heptapeptide (synthetic)
- Selectively inhibits KGD (Amino acid sequence Lys-Arg-Gly-Asp) binding site on GP Iia/IIIb (α IIb β 3) receptor.
- Long Duration of Action (2.5hrs) but effect is short due to short platelet binding and rapid dissociation from receptor.
- Less effective than Abciximab, as it does not bind to Vitronectin receptors
- Uses : Unstable angina & coronary angioplasty
- S/Es : Thrombocytopenia, Bleeding
- Dose : Bolus 180 mcg/kg followed by 2 mcg/kg/min for 72-96 hrs but upto 12-24 hrs after angioplasty.
- Used with Aspirin and heparin.

TIROFIBAN

- Is Nonpeptide
- Selectively blocks RGD amino acid sequence (Arg-Gly-Asp) binding site on GP IIa/IIIb receptors.
- No effect on Vitronectin receptors
- Uses: Unstable angina, Non-Q wave MI
- Long duration (2.5hrs)
- Dose : Bolus I.V 0.4 mcg/kg for 30 min followed by 0.1mcg/kg/min for 48 hrs
- Used with aspirin, heparin
- S/Es : Thrombocytopenia, Bleeding

USES OF ANTI-PLATELETS

1. CAD and ACS :

- Acute MI – Low dose aspirin
- Unstable angina, NSTEMI – Aspirin + Clopidogrel +/- Heparin
- Primary & secondary prevention of STEMI
- Prevent Restenosis & MI after Angioplasty with GP IIb/IIIa receptor antagonists + Aspirin + Heparin
- Antiplatelet combination in Pts with stent placement

USES OF ANTIPLATELET

2. CEREBROVASCULAR DISEASE :

- ? TIAs & strokes – Aspirin (75 mg daily) or Clopidogrel (75mg daily) or Cilostazol (less hemorrhage) to prevent cerebrovascular events.

3. Prosthetic Heart valve and AV shunt :

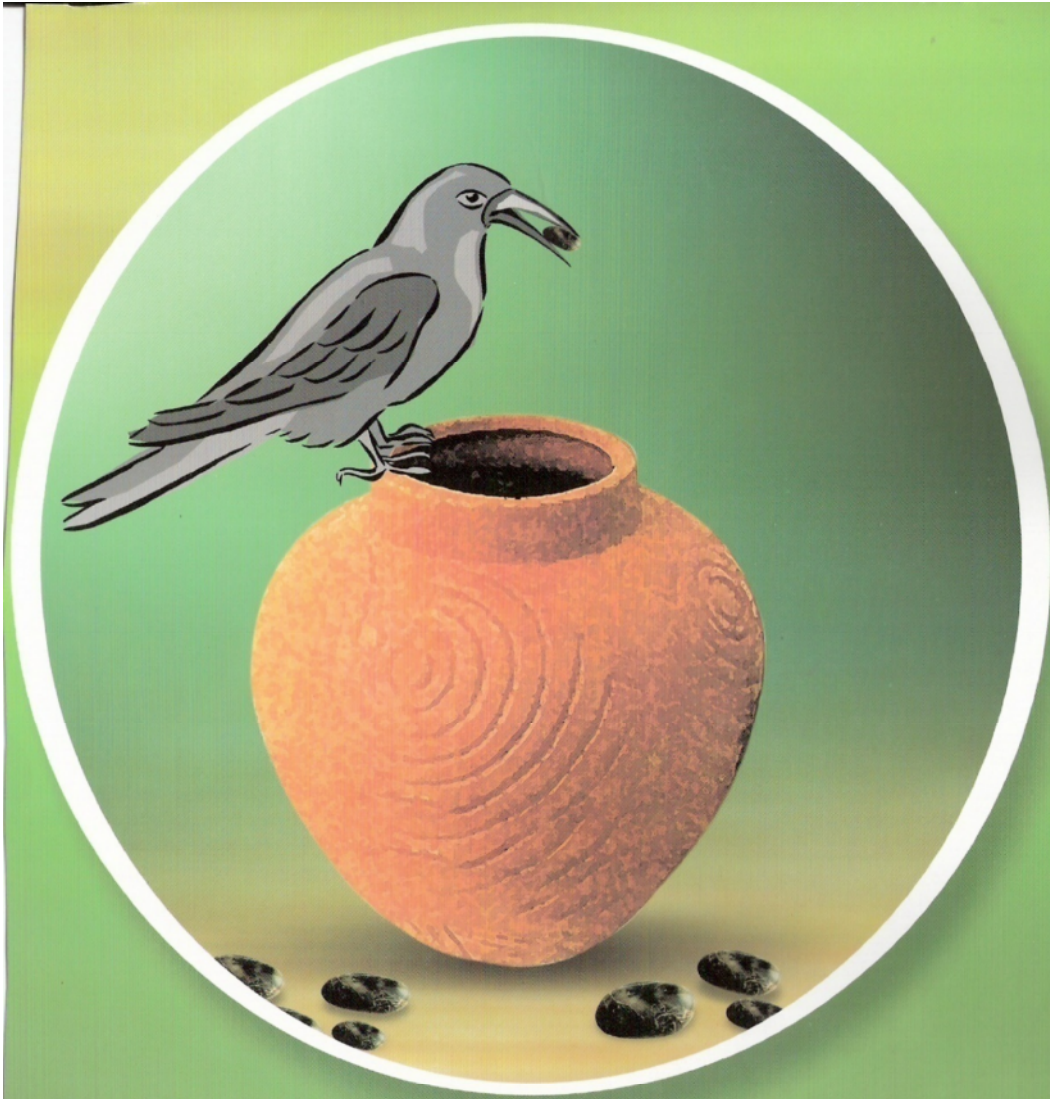
Aspirin + warfarin reduces incidence of embolism (more bleeding) or Dipyridamole + warfarin (less bleeding).

Antiplatelets maintain patency of AV shunt planted for hemodialysis or vascular grafts.

4. In PVD : Aspirin / Clopidogrel reduces intermittent claudication

5 Primary prevention in pts.with

- **DM**
- **Family H/O CA D**
- **Smoking**
- **HBP**
- **Obesity**
- **Albuminuria**
- **LDL > 130, HDL < 40,
TG >250mg / dl**



Look Around,
Think and
Solve Your
PROBLEMS
with

imagination

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