Antiplatelet Drugs

NSAIDs
MOA: (–)COX → ↓TXA2 → ↓platelet activation/aggregation
Trials: IST, CAST

ASPIRIN
- Clinical use
  - Acute ischemic stroke
  - Myocardial infarction
  - Acute coronary syndromes
- Adverse effects: GI problems
- Contraindications: hypersensitivity, bleeding

ADP ANTAGONISTs
MOA: irreversible binding of active metabolite to ADP receptors on platelet
Trials: CURE, COMMIT, CAPRIE

CLOPIDIGREL
- Prodrug: CYP2C19 forms active metabolite
- Pharmacokinetics: fast absorption, t½ 6hrs, metabolite t½ 30mins, dose dependent onset of action
- Reduced efficacy: renal impairment, concomitant use with PPI’s
- Boxed warning: poor metabolizers of *2 and *3 alleles → higher CV events
- Clinical use
  - Acute coronary syndrome
  - Recent MI, stroke, or peripheral artery disease
- Adverse effects: bleeding, thrombotic thrombocytopenic purpura
- Contraindications: hypersensitivity, bleeding

TICLOPIDINE
- Boxed warning: may cause life-threatening like neutropenia, agranulocytosis, TTP, aplastic anemia
- Pharmacokinetics: rapid absorption, heavily metabolized by liver, high plasma protein binding
- Clinical use
  - 2° prevention of thrombotic strokes who can’t take ASA
  - Adjunct therapy with ASA to reduce risk of stent thrombosis
- Adverse effects: GI problems, skin rash, neutropenia
- Contraindications: hypersensitivity, active bleeding, hematopoietic disorders, liver impairment

PRASUGREL
- Prodrug converted by CYP450
- Pharmacokinetics: rapidly absorbed
- Significantly reduces total endpoint events compared to Plavix
- Clinical use
  - Acute coronary syndrome
- Boxed warning: bleeding risk for pts with active bleeding or hx of TIA or stroke; discontinue use before surgery; not for older or smaller pts with concomitant antiplatelet therapy
- Contraindications: active bleeding, prior transient ischemic attack or stroke
**GP 2b/3a RECEPTOR BLOCKERS**

MOA: blocks fibrinogen binding to receptors on platelet cell membrane

*Tribes: TARGET, PURSUIT*

Contraindications: active bleeding, thrombocytopenia, prior stroke, major surgery/trauma, severe hypertension

**TIROFIBAN & EPTIFIBATIDE**

- From rattlesnake venom protein
- Reversible, binds only to activated platelets
- Concentration dependent, shorter t½
- Recommended for NSTE ACS pts undergoing PCI, or with continuing ischemia
- Renal impaired pts: ½ maintenance dose

**ABCDIXIMAB**

- Fab of monoclonal mouse Ab
- Recommended for PCI after STEMI, for heart stent implantation during PCI
- Reduces risk of another MI and repeated PCI

**PHOSPHODIESTERASE INHIBITOR**

MOA:

CAMP is a very important 2nd messenger in regulating platelet function. In slide 20, it shows that activation of CAMP pathway in platelets by adenosine via the A2-receptor will suppress the release of Ca2+ from ER. This reduces the intracellular Ca2+ level thereby reducing platelet activation since elevated intracellular Ca2+ level plays a critical role in platelet activation.

In platelet, CAMP is broken down to AMP by the enzyme CAMP-dependent phosphodiesterase (PDE3). Therefore the inhibitory effect of CAMP on Ca2+ release from ER is removed.

The phosphodiesterase inhibitor will prevent platelet activation in the following way:

1) Inhibiting CAMP degradation: Phosphodiesterase inhibitor will inhibit the PDE3 activity inside platelet, thus increasing the intracellular CAMP levels. This will further inhibit the release of Ca2+ from ER, therefore preventing platelet activation.

2) Stimulate CAMP synthesis: Phosphodiesterase inhibitor will also potentiate the inhibitory effects of adenosine on platelets by inhibiting the adenosine uptake from surrounding endothelial cells and even platelets itself. This will increase the adenosine levels around platelets therefore more adenosine could activate the CAMP 2nd messenger via the A2-receptor. More CAMP means greater inhibition on Ca2+ release from ER in platelet, therefore platelet activation is inhibited.

One of the side effects of using phosphodiesterase inhibitor (such as dipyridamole) as antiplatelet agent is the hypotension. Dipyridamole cause vascular smooth muscle relaxation by increasing the intracellular CAMP level via inhibition of PDE3 inside the vascular smooth muscle cell. Increased CAMP inhibits the myosin light chain kinase (an enzyme responsible in phosphorylating myosin during smooth muscle contraction); thus, relaxation occurs.

**DIPYRIDAMOLE**

- Dose dependent vasodilation: (−)cGMP-PDE → ↓↑cGMP
- Pharmacokinetics: long t½, highly bound, metabolized in liver, excreted in bile
- Clinical use
  - Thromboembolic prophylaxis: as adjunct to warfarin, protect against complications of cardiac valve replacement
  - Dose: 75-100mg po tid w/warfarin
- Contraindications: hypersensitivity, angioedema
- Adverse effects: (minimal) hypersensitivity reactions, larynx edema, fatigue, arthritis, dyspepsia, etc.