

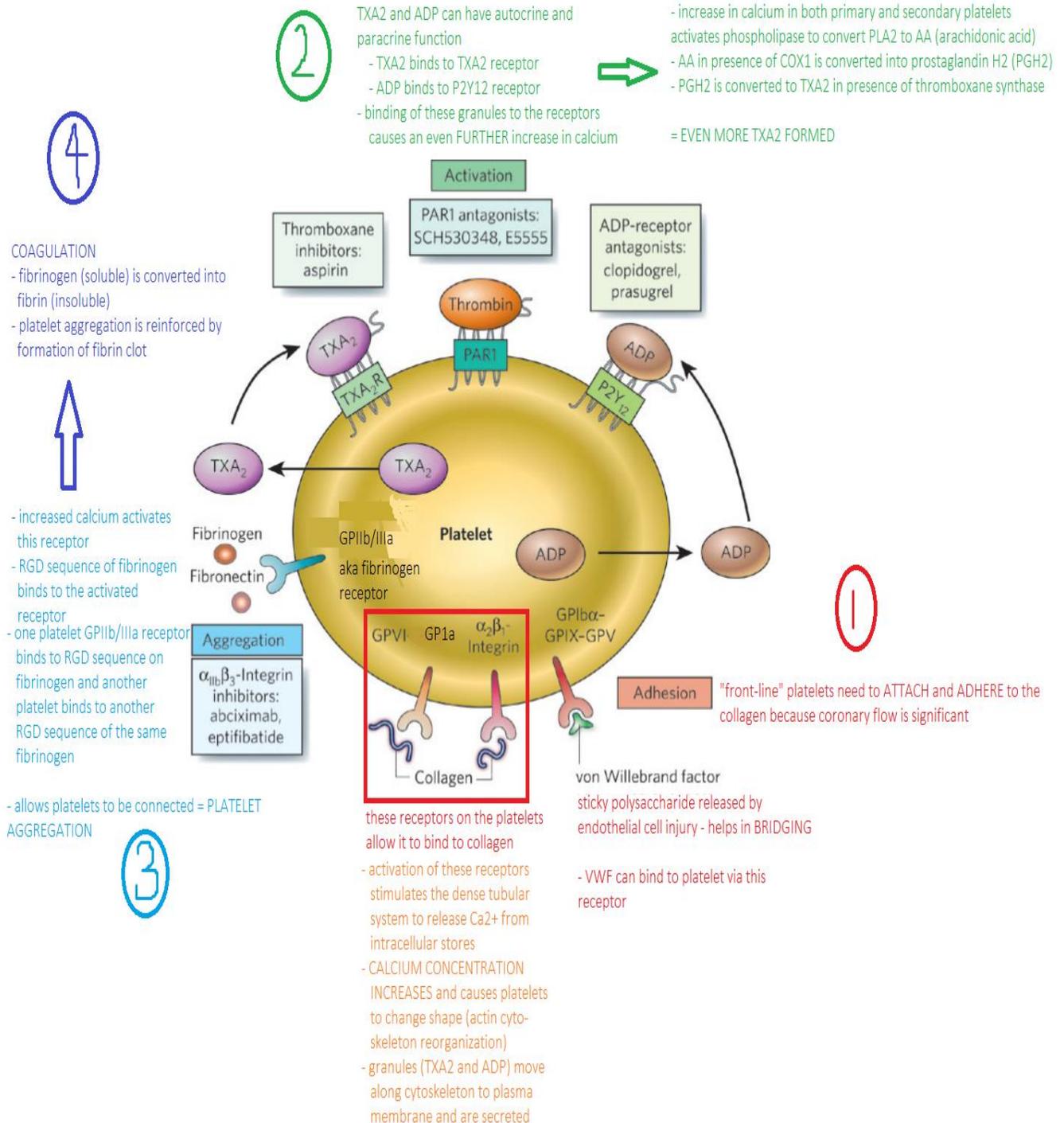
ALLEVIATION OF ANGINA SYMPTOMS:

- Immediate relief: Nitroglycerin – tablets or spray for immediate relief and before activities known to bring an angina
 - Decreases oxygen demand (decreasing pre- and after- load)
- Slowing progression of disease: B-blockers or CCBs
- Preventing new vascular events: long-term anti-platelet therapy
 - Increase oxygen supply (increase coronary flow)

ARTERIAL THROMBI:

- Pale, granular, lower cell content
- Made up of platelets
 - Platelets: negative charge repels negative charge of endothelial cells, so doesn't stick to blood vessels

EVENTS LEADING TO THROMBUS FORMATION:



ANTIPLATELET THERAPY:

ASPIRIN:

LOW-DOSE ASA:

- Low-dose aspirin is more effective in inhibiting platelet COX (*irreversible acetylation*)

COX in vascular smooth muscle	COX in platelets
Inhibits conversion of AA to PGH2	
<ul style="list-style-type: none"> • Prevents conversion of PGH2 to prostacyclin 	<ul style="list-style-type: none"> • Prevents conversion of PGH2 to TXA2
<ul style="list-style-type: none"> • Prostacyclin unable to stimulate cAMP synthesis in platelets (which inhibits platelet aggregation) • Prostacyclin also unable to relax vascular smooth muscle (aka prevents vasodilation) 	<ul style="list-style-type: none"> • Prevents TXA2 from decreasing cAMP, thus preventing the increase in calcium • Prevents TXA2 from moving into vascular smooth muscle, thus preventing the decrease in cAMP there (which would cause vasoconstriction)
DON'T WANT TO BLOCK COX HERE	WANT TO BLOCK COX HERE

PK:

- Platelets are anucleate = cannot synthesize new enzyme
 - Remain inactive for life span (7-10 days)
- Onset of platelet action quick (< 60 mins)

ADVERSE EFFECTS:

- Prolongs bleeding time
- Hemorrhagic stroke (bleeding in brain)
- GI bleeding (blocking COX1 in gut which is forming protective prostaglandins)
- Aspirin resistance (controversial – too low dose or polymorphisms in COX1?)

ADP INHIBITORS: Clopidogrel, Prasugrel, Ticagrelor - *can be given with aspirin*

MOA:

1. Inhibit binding of ADP to P2Y12 receptor
2. Prevents decrease in cAMP that usually occurs with P2Y12 activation
3. Increase in calcium prevented
4. Decreased:
 - a) Fibrinogen receptor activation
 - b) TXA2 generation

ADVERSE EFFECTS:

- Events of bleeding
- Clopidogrel resistance
 - Genetic polymorphisms of CYP450 (ex// CYP2C19)

- Clopidogrel – *prodrug*
 - Takes time (several days) to show effects
 - 85% is converted by esterases in the intestine to inactive metabolites
 - 15% is converted into active metabolites by hepatic enzymes
 - Loading dose: 300 mg, maintenance dose: 75 mg
- Prasugrel – *prodrug*
 - More potent (10x)
 - More efficient metabolism = more rapid action
 - Converted by esterases into intermediate metabolite
 - Intermediate metabolite forms active metabolite in liver (CYP3A4, CYP2B6)
 - Loading dose: 60 mg, maintenance dose: 10 mg
- Ticagrelor
 - Direct and REVERSIBLE ACTION
 - Does not require metabolic transformation

GP IIb/IIIa RECEPTOR ANTAGONISTS: only used in hospital settings **IV**

Abiciximab	Monoclonal Ab	By blocking GPIIb/IIIa receptor, fibrinogen is unable to bind and platelets cannot aggregate
Eptifibatide	Small molecule synthetic peptide (RGD)	By resembling the RGD sequence, it can occupy the GPIIb/IIIa receptor, so that the actual RGD sequence of fibrinogen can't bind
Tirofiban	Smaller synthetic non-peptide molecule (RGD)	

PDE INHIBITORS: Dipyridamole and Pentoxifyline (different drugs but same MOA)

- PDE converts cAMP to AMP (remember decrease in cAMP in platelets = increase in calcium)
- Blocking PDE prevents this conversion, which increases cAMP levels = decrease in calcium

THROMBOLYTICS:**USE:**

- Administered IV and early
- Minimize needle punctures and discontinue parenteral medications
- For unwanted bleeding, whole blood or Aminocaproic acid (plasmin inhibitor) administered

DRUGS:

- Alteplase: 3-4 minutes
- Tenecteplase: 14-45 minutes
 - Longer half-life
 - More specific to fibrin

TISSUE PLASMINOGEN ACTIVATOR (t-PA):

- t-PA is normally secreted from the endothelial cell but is also a drug (hospital setting, IV)
- t-PA is a protease that binds to plasminogen, breaking it down to plasmin
 - Plasmin is thus activated and can digest fibrin
- This reaction is fibrin specific = only forms plasmin in presence of fibrin (therefore only digest the clot)

NITROVASODILATORS:**NITRIC OXIDE:**

1. Nitric oxide released from endothelial cell
2. NO activates guanylyl cyclase (GTP → cGMP)
3. cGMP activates cGMP-specific protein kinase
 - a. Increased Ca storage in SR
 - b. Stimulates K⁺ channel = hyperpolarization = less calcium entry
4. NET: decrease in Ca = smooth muscle relaxation (vasodilation)

SODIUM NITROPRUSSIDE:

- Releases NO in circulation
- Relaxation of both arteries (reduce afterload) and veins (reduce preload)
- Tx of hypertensive crisis
- Especially sensitive to light
- Cyanide poisoning (SNP → cyanide in RBCs)
 - Cyanide → thiocyanate (inactive) IN PRESENCE OF SODIUM THIOSULFATE
 - Therefore give sodium thiosulfate with sodium nitroprusside

ADVERSE EFFECTS:

- Headache
- Facial flushing
- Orthostatic hypotension
- Reflex tachycardia
- Tolerance
- **Potential fatal interaction** with PDEV inhibitors (i.e. Viagra)
 - Both drugs stimulate cGMP which results in synergistic effects on lowering blood pressure
 - Potentiate hypotensive effects of nitrates

OTHER NITRATES: nitroglycerin, isosorbide dinitrate, isosorbide 5-mononitrate

- Tx for immediate relief of angina
- Very high first pass metabolism (given sublingual, spray, transdermal, buccal)
- Require metabolic transformation in tissues (smooth muscles) to reduce the nitrate into S-nitrosothiol, which is then further reduced into NO
 - Does not release NO spontaneously

HEMODYNAMIC EFFECTS:

1. Venous vasodilation: decreases preload
 - a. Decrease ventricular size
 - b. Decrease ventricular wall stress
 - c. Decrease O₂ consumption
2. Coronary vasodilation: increase myocardial perfusion
3. Arterial vasodilation: decrease afterload → decrease BP

At therapeutic doses used, nitrates mainly work on VEINS (rather than sodium nitroprusside that works on BOTH)