ANTIPLATELET DRUGS

Antiplatelet drugs

- 1….Prostaglandin synthesis inhibitor(ASPIRIN)
- 2….ADP induced platelet aggregation inhibitors
- (Clopidogrel, Prasugrel , Ticlopidine)
- 3…blockade of platelet glycoprotein IIB/IIIA receptors (Abciximab, Eptifibatide, Tirofiban)
- 4…Additional drugs (Dipyridamole ,Cilostazol)

Introduction

- Arterial and venous thromboses are major causes of morbidity and mortality rates.

- Arterial thrombosis is the most common cause of acute myocardial infarction (MI), ischemic stroke, and limb gangrene.

- Deep-vein thrombosis (DVT) leads to pulmonary embolism (PE).

- Most arterial thrombi are superimposed on disrupted atherosclerotic plaque.

  (because plaque rupture exposes thrombogenic material in the plaque core to the blood).

- This triggers platelet aggregation and fibrin formation

- Leading to generation of a platelet-rich thrombus that can temporarily or permanently occlude blood flow

- In contrast , venous thrombi rarely form at sites of obvious vascular disruption.

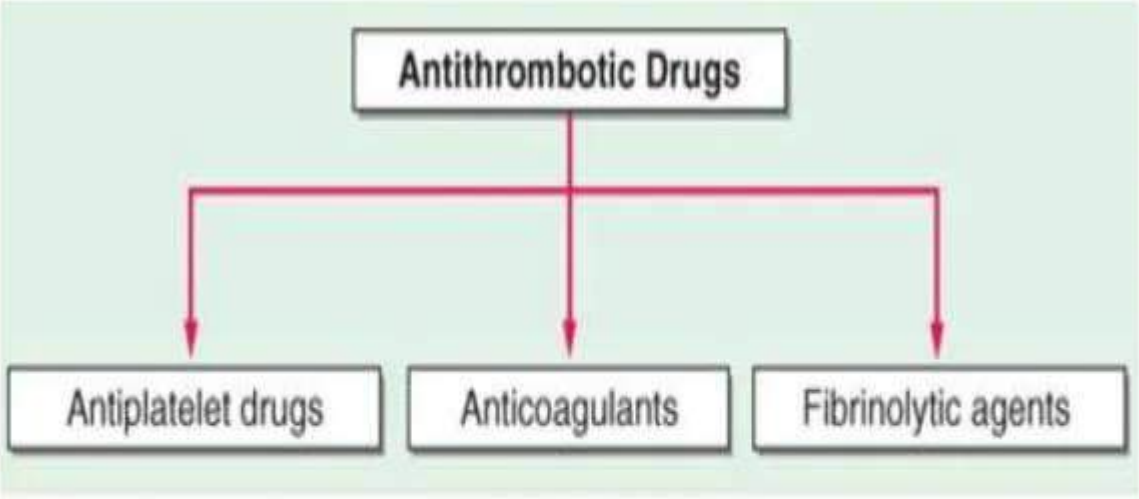
- Mostly they can develop after surgical trauma to veins or secondary to indwelling venous catheters.

- They originate in the valve cusps of the deep veins of the calf or in the muscular sinuses, where they are triggered by stasis.

- If the thrombi extend into more proximal veins of the leg, thrombus fragments can dislodge, travel to the lungs, and produce a PE

- Arterial thrombi are rich in platelets because of the high shear in the injured arteries.

- In contrast, venous thrombi (low shear condition) contain relatively few platelets and are predominantly composed of fibrin and trapped red cells.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Classification of antithrombotic drugs.

- Strategies to inhibit or treat arterial thrombosis focus mainly on antiplatelet agents.

  (although, in the acute setting, they often include anticoagulants and fibrinolytic agents)

- Anticoagulants are the mainstay of prevention and treatment of venous thromboembolism (because fibrin is the predominant component)

- Fibrinolytic therapy is used in selected patients with venous thromboembolism.(Massive PE)

Role of Platelets in Arterial Thrombosis

- In healthy vasculature, circulating platelets are maintained in an **inactive state**

HOW ?

- By nitric oxide (NO) and prostacyclin (PGI2) released by endothelial cells lining the blood vessels.

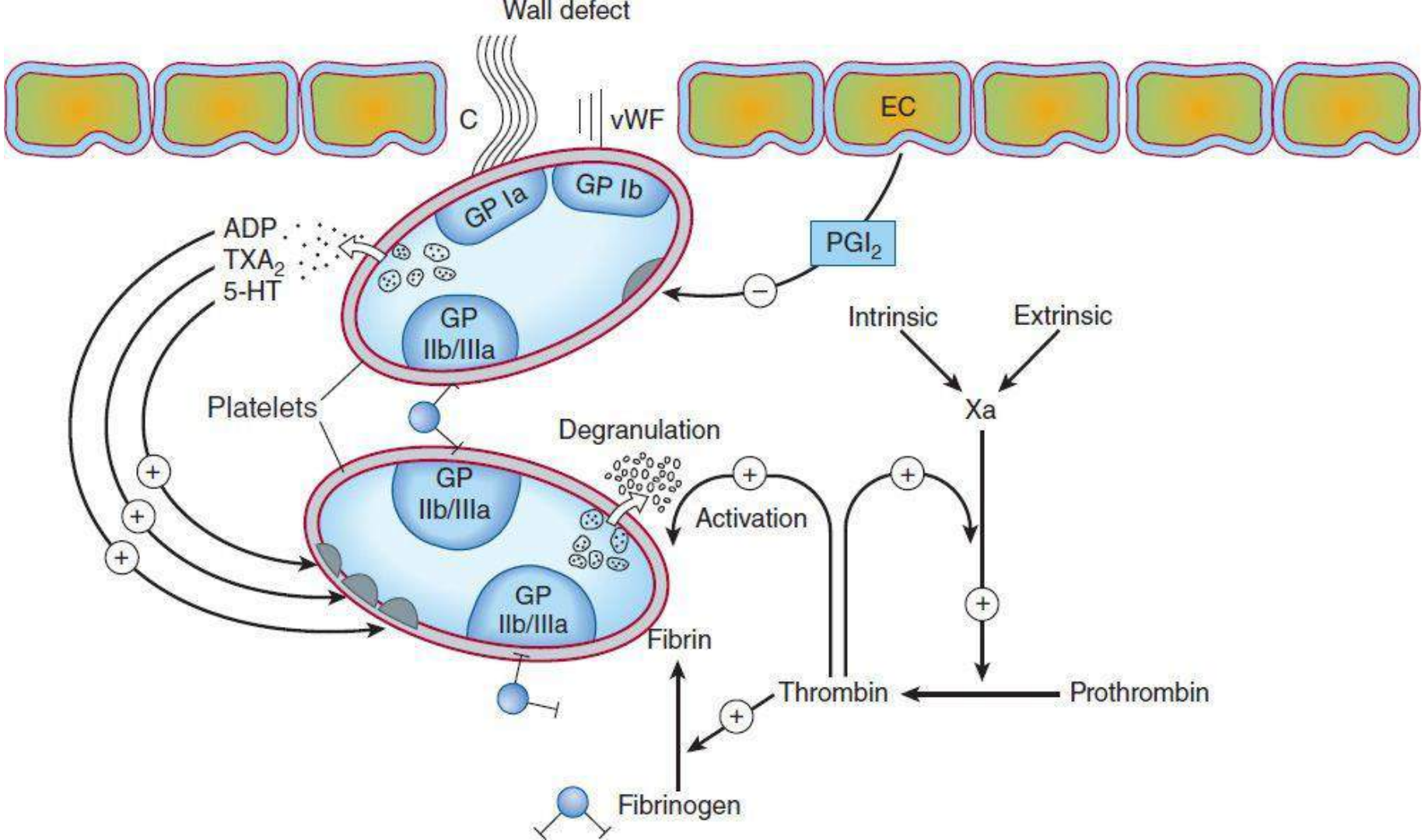
- In addition, endothelial cells also express ADPase that degrades ADP released from activated platelets.

- Prostacyclin (PGI2) activates PGI2 receptors on Platelets.
- This activation increases cAMP levels and inhibits Platelet aggregation.

How???

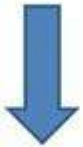
✓ cAMP inhibits release of ADP and 5HT from dense granules of Platelets.

"ADP and 5HT " is involved in Platelet aggregation !


Wall defect
C
vWF
EC
GP Ia
GP Ib
GP IIb/IIIa
ADP
TXA_2
5-HT
PGI_2
Intrinsic
Extrinsic
Xa
Platelets
Degranulation
GP IIb/IIIa
GP IIb/IIIa
Activation
Fibrin
Thrombin
Prothrombin
Fibrinogen

- When the vessel wall is damaged,,,

- Release of these substances is impaired and subendothelial matrix is exposed.



- Platelets adhere to exposed collagen via $\alpha_2 \beta_1$ and glycoprotein (GP)V1 (receptor on their surface)

- Platelets adhere to von Willebrand factor (present in subendothelial matrix) via GPIbα and GPIIb/IIIa ($\alpha_{IIb} \beta_3$)

- Adherent platelets undergo a change in shape

- Absence of Prostacyclin → ↓ cAMP

- Secretion ADP from their dense granules, and also there is synthesis and release thromboxane A_2.

- Released ADP and thromboxane A_2 are platelet agonists, activate ambient platelets and recruit them to the site of vascular injury

- Disruption of the vessel wall also exposes tissue factor(factor 3) present in subendothelieal region

- Tissue factor initiates coagulation.

- Also,,, the Activated platelets

✓ potentiate coagulation by binding clotting factors.

✓ supports the assembly of activation complexes.

- This will enhance thrombin generation.

- **MOST** potent platelet agonist , it activates and recruits more platelets to the site.

HOW ??

✓ Thrombin is a protease.

✓ Platelet activation by thrombin is mediated via Thrombin Receptors (on platelet surface) called PARs (protease-activated receptors) :

✓PAR-1 is the major human platelet receptor

✓It exhibits 10–100-times higher affinity for thrombin when compared with PAR-4.

- Thrombin also converts fibrinogen to fibrin.

After Recruitment,

- Divalent fibrinogen or multivalent vWF molecules bridge adjacent platelets together to form platelet aggregates.

- Fibrin strands then weave these aggregates together to form a platelet/fibrin **mesh**.

- Antiplatelet drugs target various steps in this process.

- **The commonly used drugs**

✓Aspirin

✓Thienopyridines : clopidogrel, prasugrel, and ticlopidine.

✓Dipyridamole.

✓GPIIb/IIIa antagonists : Abciximab, Eptifibatide, Tirofiban.

Newer Antiplatelets

✓Ticagrelor

✓Thrombin Receptor Blockers : Vorapaxar

Aspirin

- Low dose aspirin inhibits platelet TXA2 synthesis ,by irreversible acetylation of a serine residue in the active site of cyclo –oxygenase I
- Unlike nucleated cells ,platelets can not synthesise proteins ,so after aspirin ,TXA2 synthesis does not recover untill the affected cohort of platelets is replaced in 7-10 days

Aspirin

- The most widely used antiplatelet agent worldwide is aspirin.

Mechanism of Action

- Aspirin blocks production of TxA_2 by acetylating a serine residue near the active site of platelet cyclooxygenase-1 (COX-1).

- The action of aspirin on platelet COX-1 is permanent, lasting for the life of the platelet (7-10 days).

- Complete inactivation of platelet COX-1 is achieved with a daily aspirin dose of 75 mg.

- Note : Maximally effective at doses of 50-320 mg/day.

?? Higher the dose more EFFICACY ????

- At high doses (1 g/d), it also inhibits COX-2 (responsible for synthesis of prostacyclin, a potent inhibitor of platelet aggregation)

- So Higher doses are potentially less efficacious and also increase toxicity, especially bleeding.

Indications

- Secondary prevention of cardiovascular events in patients with coronary artery, cerebrovascular, or peripheral vascular disease.

- Compared with placebo, aspirin produces a 25% reduction in the risk of cardiovascular death, MI, and stroke.

- When rapid platelet inhibition is required, dose of at least 160 mg is given.

Clinical uses

- 75 mg once daily for thromboprophlaxis reserved for people at high CVS risk e.g survivors of MI in whom benefit of aspirin outweighs the risk of GIT bleeding

Side Effects

- Dyspepsia
- Erosive gastritis
- peptic ulcers with bleeding and perforation.

These side effects are dose-related

- Use of enteric-coated or buffered aspirin in place of plain aspirin does not eliminate the risk of gastrointestinal side effects.
- The overall risk of major bleeding with aspirin is 1–3% per year.

- Hepatic and renal toxicity are observed with aspirin overdose

- The risk of bleeding is increased when used with warfarin.

Contraindications

- History of aspirin allergy characterized by bronchospasm.

Dipyridamole

MOA

- It interferes with platelet function by increasing the cellular concentration of cAMP.

How ?

✓ By decreasing the metabolism of cAMP to 5' AMP

✓ By inhibiting cyclic nucleotide phosphodiesterases (involved in metabolism of cAMP)

✓ It also inhibits Adenosine deaminases

- **Other Properties** :

- Dipyridamole is a potent coronary vasodilator.

- It has minimal effect on BP and cardiac work.

Uses

- The drug has little or no benefit as an anti-thrombotic agent.
- So It is used in combination with warfarin.

✓ In the prophylaxis of coronary and cerebral thrombosis of post-MI and post-stroke patients.

✓ In patients with Prosthetic valves (it inhibits embolization).

Adverse Effects :

- Exacerbation of Angina
- Headache
- Tachycardia
- GI distress.

Ticlopidine

- Platelets contain two purinergic receptors, $P2Y_1$ and $P2Y_{12}$.
- both are GPCRs for ADP. I.e, it require ADP for its activation.
- $P2Y_1$- induces a shape change and aggregation.

- $P2Y_{12}$ - inhibits adenylyl cyclase. So causes Platelet activation
  - increases Adhesiveness of platelets

- Ticlopidine (thienopyridine) is a prodrug that inhibits the $P2Y_{12}$ receptor.

- It is converted to the active thiol metabolite by hepatic CYP .

- It is rapidly absorbed and highly bioavailable.

- It permanently inhibits the $P2Y_{12}$ receptor by forming a disulfide bridge in the extracellular region of the receptor.

- It has a short $t_{1/2}$ but a long duration of action, (Like aspirin) ("hit-and-run pharmacology“)

- Maximal inhibition of platelet aggregation is not seen until 8-11 days after starting therapy.

- Dose is 250 mg twice daily.

Adverse Effects

- The most common side effects are nausea, vomiting, and diarrhea.
- Severe neutropenia (absolute neutrophil count <500/microL)
- Fatal agranulocytosis with thrombopenia has occurred within the first 3 months of therapy;
- Rare cases of TTP-HUS (thrombotic thrombocytopenic purpura-hemolytic uremic syndrome) in 1 in 1600-4800 patients.

Therapeutic Uses

- Ticlopidine has been shown to prevent cerebrovascular events in secondary prevention of stroke.

- Because it is associated with life-threatening blood dyscrasias , it has largely been replaced by clopidogrel.

Clopidogrel

- It is closely related to ticlopidine.
- it is an irreversible inhibitor of platelet $P2Y_{12}$ receptors
- it is more potent and has a more favorable toxicity profile than ticlopidine.
- It is a prodrug with a slow onset of action.
- The usual dose is 75 mg/day.

Uses

- The drug is (somewhat) better than aspirin in the secondary prevention of stroke.
- The combination of clopidogrel plus aspirin is superior to aspirin alone (two drugs are synergistic)

✓ for prevention of recurrent ischemia in patients with unstable angina.

- After angioplasty and coronary stent implantation.

- Its been used to

✓ reduce the rate of stroke

✓ To reduce Myocardial infarction, and death in patients with recent myocardial infarction or stroke.

✓ Established peripheral arterial disease.

✓ acute coronary syndrome.

Clopidogrel Resistance :

- The capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects.

- This variability is because of genetic polymorphisms in the CYP isoenzymes involved in the metabolic activation of clopidogrel.

- Most important is *CYP2C19*.

- Clopidogrel-treated patients with the loss-of-function *CYP2C19*2* allele exhibit reduced platelet inhibition.

  (compared with those with the wild-type *CYP2C19*1)*

- So they experience a higher rate of cardiovascular events.

- This is important because 25% of whites, 30% of African Americans, and 50% of Asians carry the loss-of-function allele.

- This will render them resistant to clopidogrel.

- So to such patients , prasugrel or newer $P2Y_{12}$ inhibitors may be better choices.

Prasugrel

- This also is a prodrug that requires metabolic activation.
- However, its onset of action is more rapid than that of ticlopidine or clopidogrel.

- It produces greater and more predictable inhibition of ADP-induced platelet aggregation.

- Rapid and complete absorption of prasugrel from the gut.

- Virtually all of the absorbed prasugrel undergoes activation.

- (only 15% of absorbed clopidogrel undergoes metabolic activation)

- It has prolonged effect after discontinuation.
- This can be problematic if patients require urgent surgery.
- Risk for bleeding unless the it is stopped at least 5 days prior to the procedure

- The drug is **contraindicated** in those with a history of cerebrovascular disease. (high risk of bleeding).

- **Caution** : in patients weighing <60 kg or in those with renal impairment.

- **Dose :** loading dose is 60 mg, and is given once daily at a dose of 10 mg.

- *CYP2C19* polymorphisms appear to be less important determinants of the activation of prasugrel

Glycoprotein IIb/IIIa Inhibitors

- Glycoprotein IIb/IIIa is a platelet-surface integrin.
- There are about 80,000 copies of this dimeric glycoprotein on the platelet surface.
- Glycoprotein IIb/IIIa is inactive on resting platelets.

- It undergoes a conformational transformation when platelets are activated by thrombin, collagen, or TxA_2.
- This transformation endows GP with the capacity to serve as a receptor for fibrinogen and von Willebrand factor.
- This anchor platelets to foreign surfaces and to each other, thereby mediating aggregation.
- Thus, inhibitors of this receptor are potent antiplatelet agents.

Abciximab

- It is is the Fab fragment of a humanized monoclonal antibody directed against the α_{IIb} β_3 receptor.

- It also binds to the vitronectin receptor on platelets, vascular endothelial cells, and smooth muscle cells.

  (Vitronectin is a GP present in serum and in matrix. It promotes Adhesion)

Uses

- Patients undergoing percutaneous angioplasty for coronary thrombosis—

✓To prevent restenosis, recurrent myocardial infarction, and death

(in conjunction with aspirin and heparin)

- Plasma $t_{1/2}$ 30 minutes.

- But antibody remains bound to the $\alpha_{IIb}\beta_3$ receptor and inhibits platelet aggregation for atleast 18-24 hours after infusion.

- Dose : 0.25-mg/kg bolus followed by 0.125 g/kg/min for 12 hours or longer.

Adverse Effects

- The major side effect is bleeding.

- **Contraindications** :

  are similar to those for the fibrinolytic agents.

- **Like,** Prior intracranial hemorrhage

  Known structural cerebral vascular lesion

  Known malignant intracranial neoplasm

Eptifibatide

- Eptifibatide is a cyclic peptide inhibitor on $\alpha_{IIb}\beta_3$.
- Dose : as a bolus of 180 mcg/kg followed by 2mcg/kg/min for up to 96 hours.
- It is used to treat acute coronary syndrome and for angioplastic coronary interventions.

- It appears that its benefit is somewhat less than that obtained with the abciximab,

- ?? because it is specific for $\alpha_{IIb}\beta_3$ and does not react with the vitronectin receptor

- Platelet aggregation is restored within 6-12 hours after cessation of infusion.

- Eptifibatide generally is administered in conjunction with aspirin and heparin

Adverse Effects

- Bleeding
- Thrombocytopenia 0.5-1% of patients.

Tirofiban

- *It* is a nonpeptide, small-molecule inhibitor of $\alpha_{IIb}\beta_3$
- It appears to have a mechanism of action similar to eptifibatide.

Uses

- It has a short duration of action and has efficacy in non-Q-wave myocardial infarction and unstable angina.

Side effects :

- similar to eptifibatide.

- It does not react with the vitronectin receptor.

- The value in antiplatelet therapy after acute myocardial infarction is limited .

Dose :

- I.V at an initial rate of 0.4 g/kg/min for 30 minutes.

- Maintenance : at 0.1 mg/kg/min for 12-24 hours after angioplasty or atherectomy.

- It is used in conjunction with heparin

Newer Antiplatelet Agents

- Cangrelor and ticagrelor : direct-acting reversible $P2Y_{12}$ antagonists.

Current Status :

- Cangrelor : FDA Panel thumbs down for Cangrelor (feb 12, 2014)

- Ticagrelor : Approved (july 20 2011) for ACS

THROMBIN RECEPTOR ANTAGONISTS

- Vorapaxar (SCH530348) and Atopaxar (E5555)

Curent Status :

- Vorapaxar : **On May 05, 2014, obtained FDA approval.**

- Atopaxar : **in phase II clinical trial.**

Ticagrelor

- It is an orally active, reversible inhibitor of $P2Y_{12}$.
- It produces greater and more predictable inhibition of ADP-induced platelet aggregation (than clopidogrel) in patients with acute coronary syndrome
- It has a more rapid onset and offset of action.
- Dose : 90 mg tablets are available.

- When compared with clopidogrel, ticagrelor produced

✓ A greater reduction in cardiovascular death, MI, and stroke at 1 year.

✓ No differences in rates of major bleeding.

Vorapaxar

- It is an orally active, high-affinity, potent and competitive reversible antagonist of PAR-1 expressed on Platelets.

- So it blocks thrombin-mediated platelet activation.

- Bioavailability : 100 %

- **Indications :**

  To reduce thrombotic cardiovascular events in patients with H/O MI and PAD.

- **Dose :**

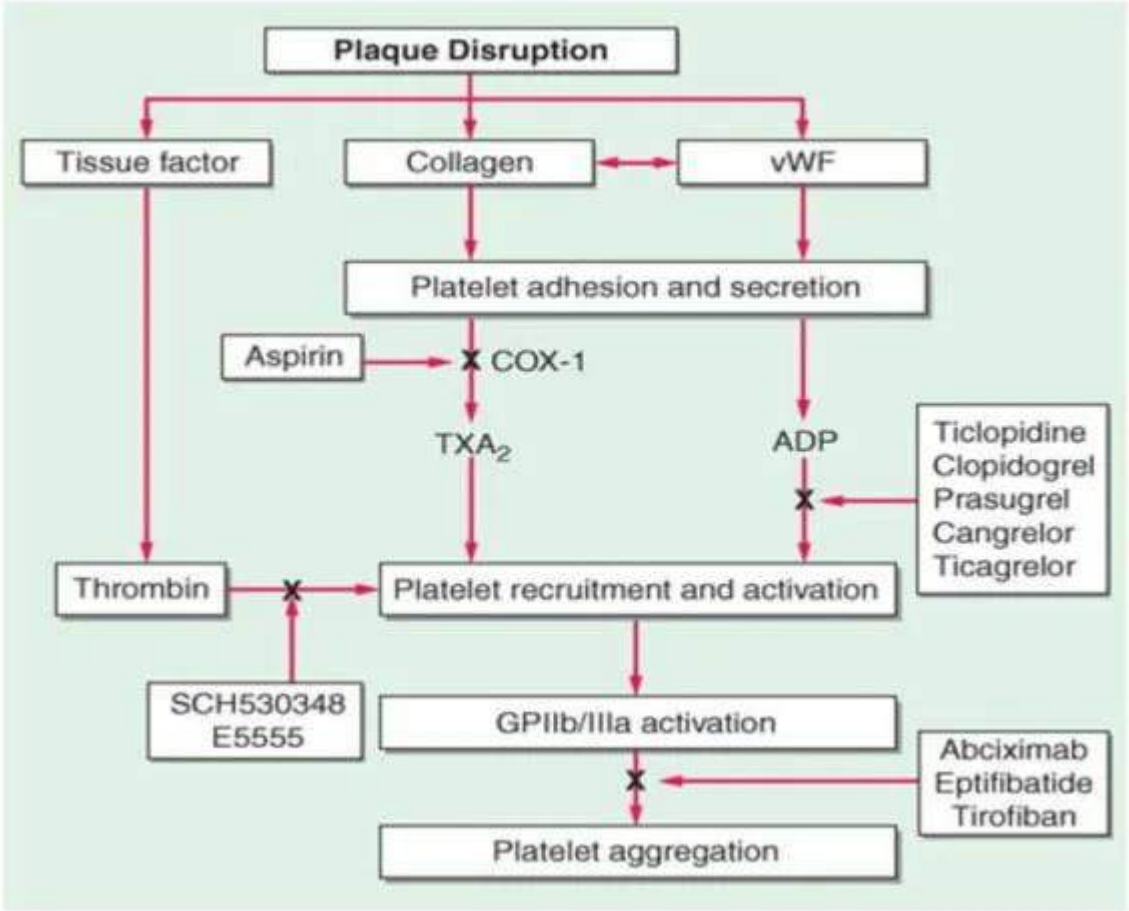
  Tablet 2.08 mg with Aspirin/ Clopidogrel daily.

Adverse Effects :

- Clinically significant bleeding (15.5 %)
- Anemia
- Depression
- Intracranial bleeding (0.4 %)

Contraindications

- H/O Stroke
- TIA and Intra Cranial Haemorrhage.


Plaque Disruption
Tissue factor
Collagen
vWF
Platelet adhesion and secretion
Aspirin
X COX-1
TXA2
ADP
Ticlopidine
Clopidogrel
Prasugrel
Cangrelor
Ticagrelor
Thrombin
Platelet recruitment and activation
SCH530348
E5555
GPIIb/IIIa activation
Abciximab
Eptifibatide
Tirofiban
Platelet aggregation

RESEARCH ARTICLE RELATED TO ANTIPLATELET DRUGS

Antiplatelet Therapy for Atherothrombotic Disease in 2022—From Population to Patient-Centered Approaches

https://www.frontiersin.org/articles/10.3389/fcvm.2022.805525/full


THANK
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