ANTICOAGULANTS

PRESENTED BY : ABDULLAH AJARMA
ABDELAZIZ ALARAJ
YAZAN DARAWI
SUPERVISED BY: DR. TAYSEER AL-TAWARAH

OBJECTIVES :

- INTRODUCTION “ HEMOSTASIS
- ANTI COAGULANTS
- ANTI PLATELETS

I.HEMOSTASIS

is the mechanism that leads to cessation of bleeding from a blood vessel.

It is a process that involves multiple interlinked steps. This cascade culminates into the formation of a “plug” that closes the damaged site of the blood vessel controlling the bleeding

THERE ARE TWO PRIMARY GOALS OF HEMOSTASIS

(1) TO PREVENT BLEEDING FROM DEFECTS IN VESSEL WALLS VIA THE TEMPORARY FORMATION OF A CLOT

(2) REPAIR OF INJURED VESSEL WALLS

HEMOSTASIS

blood stop

PRIMARY HEMOSTASIS

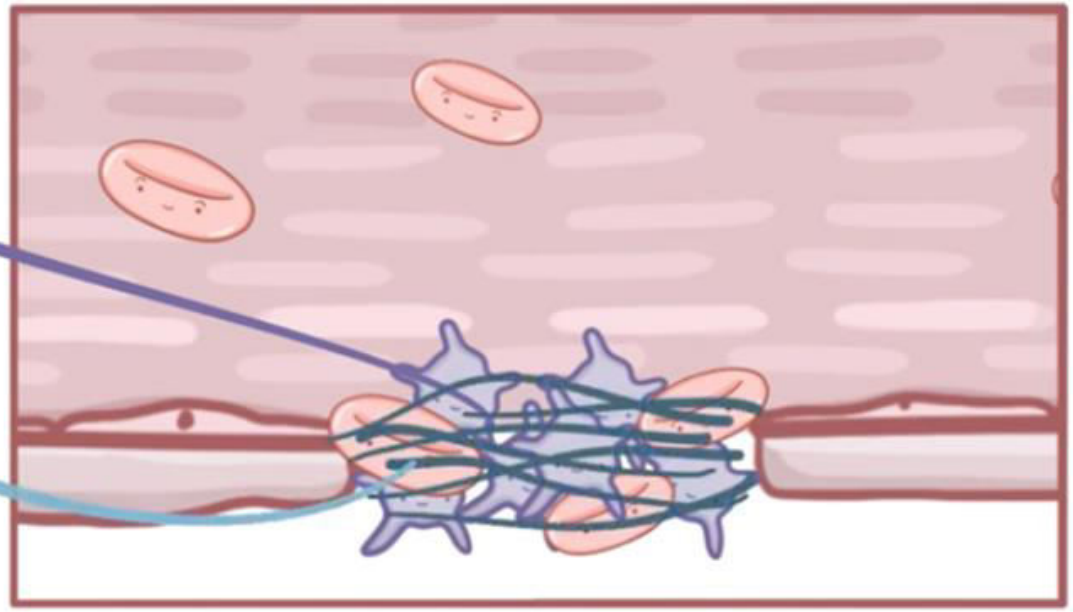
PLATELET PLUG

SECONDARY HEMOSTASIS

REINFORCES with PROTEIN MESH

↓

FIBRIN



PRIMARY HEMOSTASIS

~ 1ST STEP

STAGES

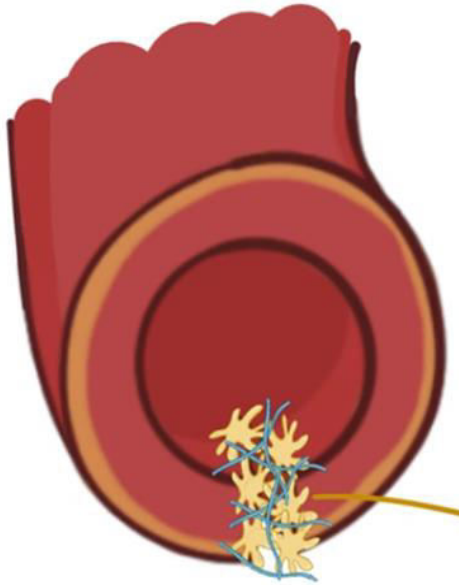
1) ENDOTHELIAL INJURY

2) EXPOSURE

3) ADHESION

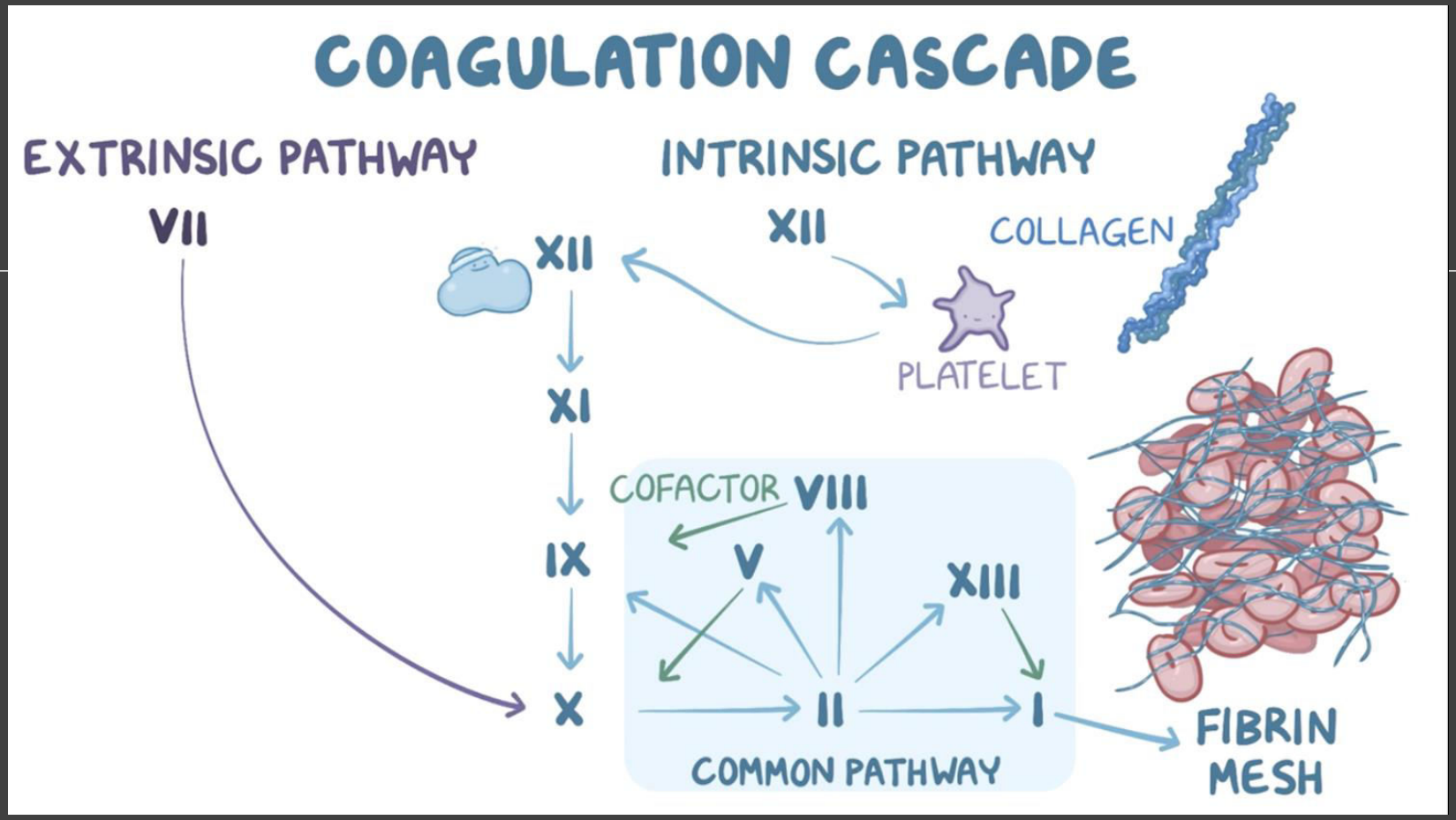
4) ACTIVATION

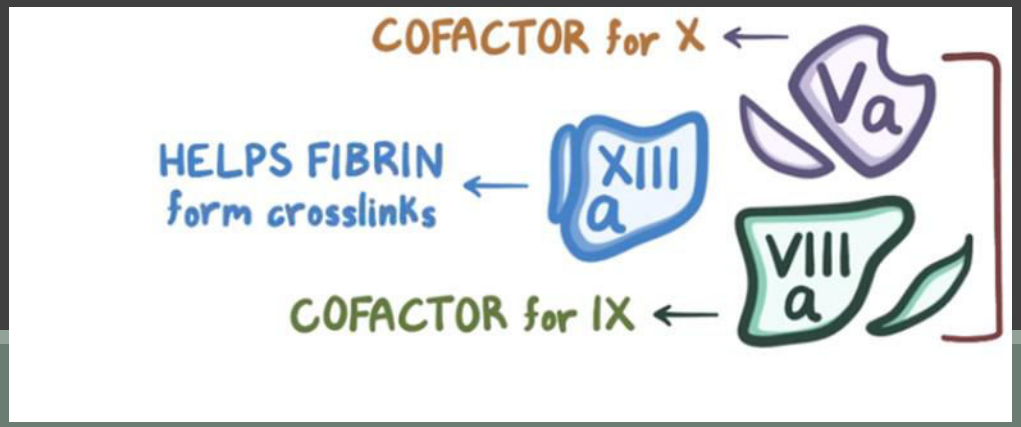
5) AGGREGATION



PREVENTS FURTHER BLOOD LOSS

PLATELET PLUG


COAGULATION CASCADE
EXTRINSIC PATHWAY
INTRINSIC PATHWAY
VII
XII
XII
COLLAGEN
PLATELET
XI
IX
X
COFACTOR VIII
V
XIII
II
I
COMMON PATHWAY
FIBRIN MESH


COFACTOR for X
Va
HELPS FIBRIN form crosslinks
XIII a
VIII a
COFACTOR for IX

2. ANTICOAGULANTS

Anticoagulants

They are drugs used to treat and prevent clot formation.

They inhibit either the action of coagulation factors or interfere with the synthesis of coagulation factors.

Common Anticoagulant agents

- Indirect thrombin inhibitors: Heparin
- Vitamin K Antagonist :Warfarin
- Direct Xa inhibitors
- Direct thrombin inhibitors

Anticoagulant Drugs

- *Heparin*
- *Warfarin*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*

Uses

Venous thromboembolism (VTE) prophylaxis.

- Deep vein thrombosis (DVT).
- Pulmonary embolism (PE).
- Myocardial infarction (MI).
- Acute coronary syndrome.
- Stroke or transient ischemic attack (TIA).

Heparin

It has two forms : unfractionated heparin and Low molecular weight (LMW) heparins

LMWHs include : Enoxaparin, Dalteparin

	Unfractionated heparin	LMWH
Metabolism & execration	metabolized in the reticuloendothelial system and the liver & excreted by the kidney	metabolized in the liver & excreted by the kidney
Dose adjustment in cases of renal impairment	not required	generally required
Dose	Unfixed dose (loading dose, followed by continuous infusion)	Fixed dose (once or twice daily)
Plasma levels	plasma levels following subcutaneous administration peak at 2-4h, & when administered intravenously , it has an instantaneous onset of action	Plasma levels peak at approximately 3-5h after subcutaneous administration and at approximately 2h after intravenous administration
half-life	45 minutes to one hour	3-7h if renal function is normal when given subcutaneously.
Price	cheap	expensive

1) **Bleeding**;
   - ***Major*** **adverse effect of heparin**.
   - ***Monitoring*** is **required** to minimize bleeding.
   - ***Excessive bleeding*** may be **managed** by **discontinuing** the drug ***or*** by ***treating*** with **protamine sulfate**.

2) **Hypersensitivity Reaction**;
   - ***Such as***; chills, fever, urticaria, and anaphylactic shock, ***due to***; heparin is of animal origin.
   - Heparin and LMWHs are ***contraindicated*** in patients who have hypersensitivity to heparin.

3) **Thrombocytopenia**;
   - **Heparin-induced thrombocytopenia** (**HIT**) is a serious condition that occurs in 1-4% of individuals treated with UFH for a minimum of 7 days.
   - The risk of HIT may be higher in individuals treated with UFH of bovine origin compared with porcine heparin and is lower in those treated exclusively with LMWH.
   - HIT is caused by the formation of abnormal antibodies (immune-mediated) that activate platelets.
   - Morbidity and mortality in HIT are related to thrombotic events (venous thrombosis occurs most commonly).
   - Heparin therapy should be discontinued when patients develop HIT.
   - In cases of HIT, heparin can be replaced by another anticoagulant, such as **Argatroban**.

4) ***Other Side Effects***;
   - **Osteoporosis** has been observed in patients on long-term therapy.
   - **Hair loss** and **alopecia** have been reported.

Protamine sulfate

- Strongly basic LMW protein
- 1 mg IV neutralizes 100 U of heparin
- Can act as weak anticoagulant in absence of heparin
- Rapid IV injection causes flushing and breathing difficulty

	Heparin	Warfarin
Synonyms		*Coumarin, Coumadin, Dicoumarol*
vivo vs vitro	Endogenous and Exogenous (in vivo & in vitro)	Exogenous only (in vitro only)
Origin	Basophils and mast cells	Plant
Mechanism of action	Stimulates antithrombin III (ATIII) --> inactivation of factors 2,7,9,10,11,12	Competes with vitamin K (prevents the activation of vitamin K via inhibiting the enzyme epoxide reductase) --> lack of gamma carboxylation of: • Factors II, VII, IX, X (pro-Coagulation) as well as: • Proteins C, S, Z (anti-Coag.)
Site of action	Blood	Liver
Onset	Rapid (within seconds)	Slow Peak effect 72-96 hours
Duration	Short (hours) $t_{1/2}$: 2 hours	Long (days) $t_{1/2}$: 40 hours
Administration	IV or SubQ IM (avoided, due to --> hematoma)	Orally (P/O)
Monitoring	aPTT (intrinsic coagulation pathway)	PT/INR (extrinsic coagulation pathway)
Antidote	Protamine Sulfate	Slow: Vitamin K (24 hours) Fast: Fresh Frozen Plasma (FFP) or Prothrombin Complex Concentrate (PCC)
Cross placenta	No	Yes
Teratogenic	-- (***Hep****arin* leaves the baby ***Happy***)	Yes (**War**farin declared **War** on the baby)

Recent Anticoagulant Drugs

Factor X inhibitors

Fondaparinux
- Synthetic polysaccharide that have the same mechanism like LMWH (i.e. selective inhibitor of factor Xa).
- It is given by **s.c.** injection **once daily** (has long t½).

Rivaroxaban
- Synthetic compound that have the same mechanism like LMWH (i.e. selective inhibitor of factor Xa).
- Given by the oral route

Direct thrombin (factor II) inhibitors

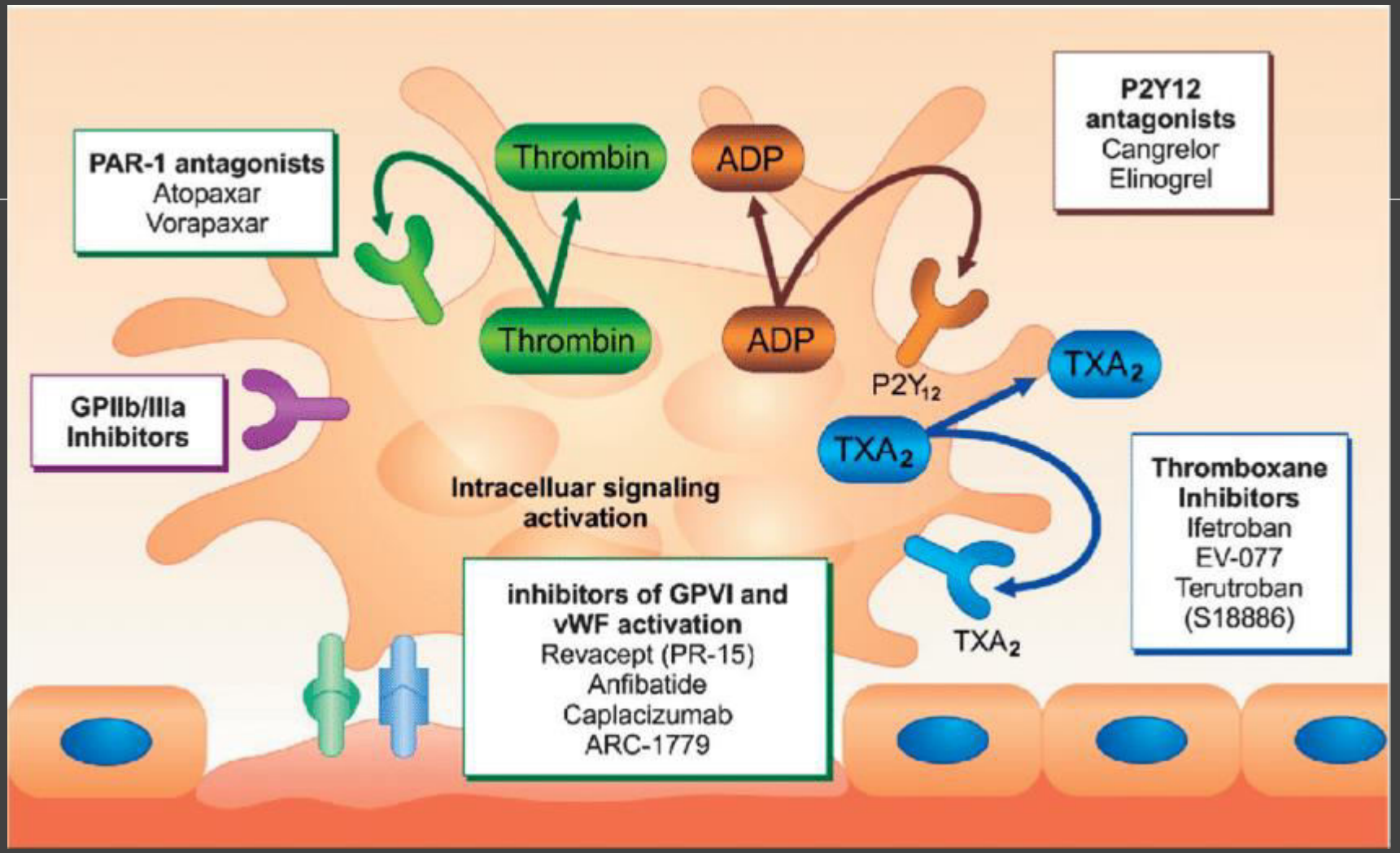
Argatroban
- Synthetic compound that acts as direct thrombin inhibitor.
- It can be used as alternative to heparin to treat patients with heparin-induced thrombocytopenia.
- It is given **i.v.** and has immediate onset of action.

Dabigatran
- Synthetic compound that acts as direct thrombin inhibitor.
- It can be used as alternative to heparin to treat patients with heparin-induced thrombocytopenia. Given by the oral route

There are two specific reversal agents (antidotes) approved for reversal of a DOA: idarucizumal is approved for reversal of the direct thrombin inhibitor dabigatran, and andexanet alfa is approved for reversal of the direct FXa inhibitors apixaban and rivaroxaban

Routine DOC monitoring in the laboratory is not recommended, except for particular clinical situations. The DTT and ecarin-based clotting assays show the best correlation with dabigatran plasma concentration. Anti-Xa provides the best correlation with anti-Xa DOC plasma concentration.

3. ANTI-PLATELET MEDICATIONS


PAR-1 antagonists
Atopaxar
Vorapaxar
Thrombin
Thrombin
ADP
ADP
P2Y12 antagonists
Cangrelor
Elinogrel
P2Y12
GPIIb/IIIa Inhibitors
TXA2
TXA2
TXA2
Intracelluar signaling activation
Thromboxane Inhibitors
Ifetroban
EV-077
Terutroban
(S18886)
inhibitors of GPVI and vWF activation
Revacept (PR-15)
Anfibatide
Caplacizumab
ARC-1779

Types of drugs

Aspirin- works on Arachidonic Acid and TXA2 to inhibit degranulation and platelet aggregation.

Dipyridamole- works on PDE inhibition and increase CAMP (**Cyclic adenosine monophosphate)**and thus VASP-P (**Vasodilator-stimulated phosphoprotein)** to prevent aggregation

P2Y12 blokers that work to antagonize ADP by inhibit the aggregation and degranulation.

G2b/3a antagonist- inhibit aggregation and the strongest ones.

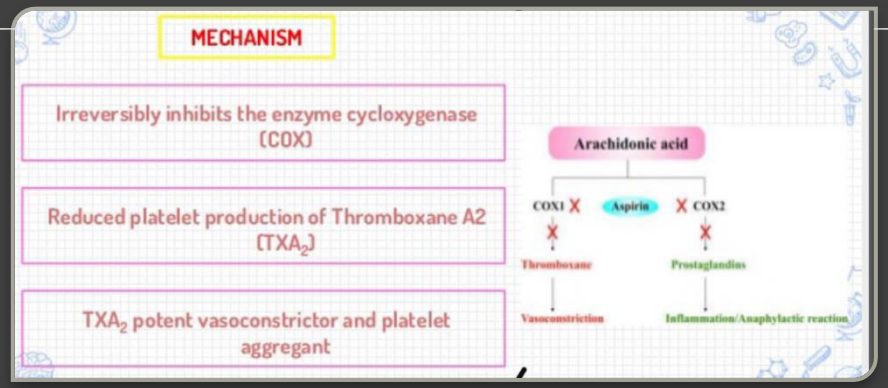
Aspirin

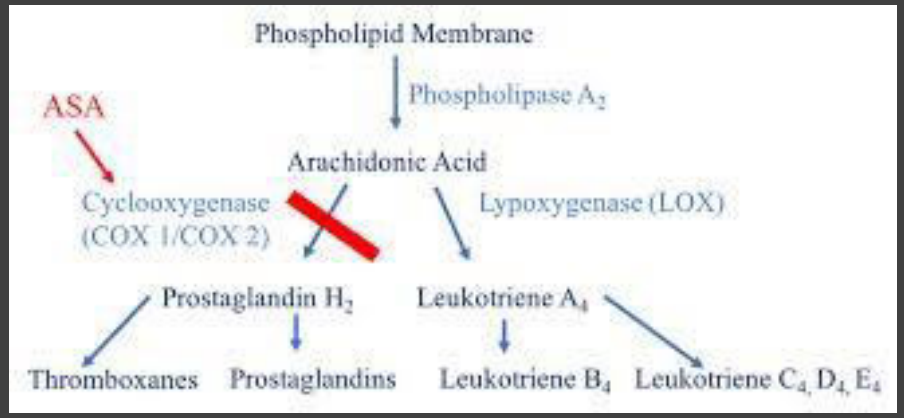
Prevent arachidonic acid that is released from the cell wall due to injury to be broken down into TXA2 by COX1,2 irreversible inactivation thus prevent further degranulation of ADP,Seratonin and TXA2.

Prolonged bleeding time 5-7 days

SE:upset stomach, stomach ulcers, stomach bleeding, worsening asthma

Don’t give it to children because of the risk of Reye syndrome.





Cilastazole/Dipyridamole

PDE inhibitor leading to increase in the cAMP conc.

inhibit the aggregation of platelets together and forming clots.

Potentiate Warfarin and Aspirin effects.

Metabolized in the liver and excreted in bile.

Preferred in cases of PAD with Aspirin.

Thienopyridine derivates

Inhibit ADP and fibrinogen induced platelets aggregation.

Ticlodipine is the 2nd in potency but carries more risk of thrombocytopenia and neutropenia.

Clopidogrel is the newer form of Ticlodipine but thrombocytopenia and neutropenia are rare effect ot it.

Prasugrel is the newest, fastest and most potent one of them.

SE:severe neutropenia, bleeding, nasuea, dyspepsia, diarrhea.

G2b/3a antagonist

Absciximab,Tirofiban and eptifibtide block the G2b/3a receptor and inhibit the platelet aggregation, they are the most potent among all antiplatelet agents and thus used only in severe cases-indications are mentioned next.

Uses of antiplatelets.

1. ACS (acute coronary syndrome): unstable angine/NSTEMI/STEMI, we use Aspirin in combination with one of the thienopyredine derivates as clopidogrel if post PCI(percutanous coronary intervention) and prasugrel if pre PCI, we use Aspirin + G2b/3a antagonist only in severe cases where we have lung edema, ST deviations,LVEF(left ventricular ejection fraction)<40% and very high troponin, otherwise It may cause serious bleeding.
2. CVAs: after the window of 3-4.5 hours we can give aspirin+Clopidogrel
3. CAD prophylaxis: Aspirin 71gm

Patients with Increased Thrombosis Risk

Elderly (older than 70)

Immobile patients

History of DVT/PE

Critical ill patients admitted to the intensive care unit

Stroke with lower extremity paralysis

Advanced congestive heart failure

Active cancer

Acute respiratory failure

Thrombophilia

Recent surgery or trauma

Obesity

Ongoing hormonal therapy

Cont.

Based on thrombosis risk, patients are classified into low risk, moderate risk, and high risk for VTE.

Low-risk patients: Young patients with no risk factors for VTE. No need for prophylaxis.

Moderate-risk patients: With at least one risk factor, pharmacological prophylaxis is preferred with or without mechanical prophylaxis.

High-risk patients: With multiple risk factors, pharmacological prophylaxis is preferred with mechanical prophylaxis.

Cont.

Commonly used pharmacological agents for prophylaxis in hospitalized patients are:

Low-molecular-weight heparins (LMWH)

Unfractionated heparin (UFH)

LMWH is preferred to UFH due to ease of administration (once daily versus 2 to 3 times per day) and decreased incidence of DVT. A number of LMW heparin preparations are available, all of which have almost equal efficacy against VTE.

DVT Prophylaxis in Hospitalized Cancer Patients

Patients with active cancer but no additional thrombosis risk factors do not need DVT prophylaxis in outpatient settings. If they have additional risk factors), either LMWH or UFH is used.