Drugs for coagulation disorders part II

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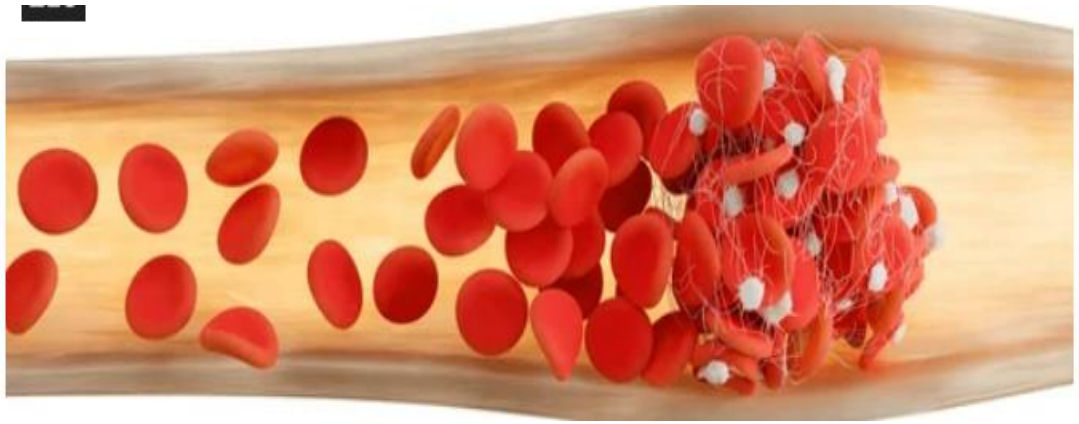
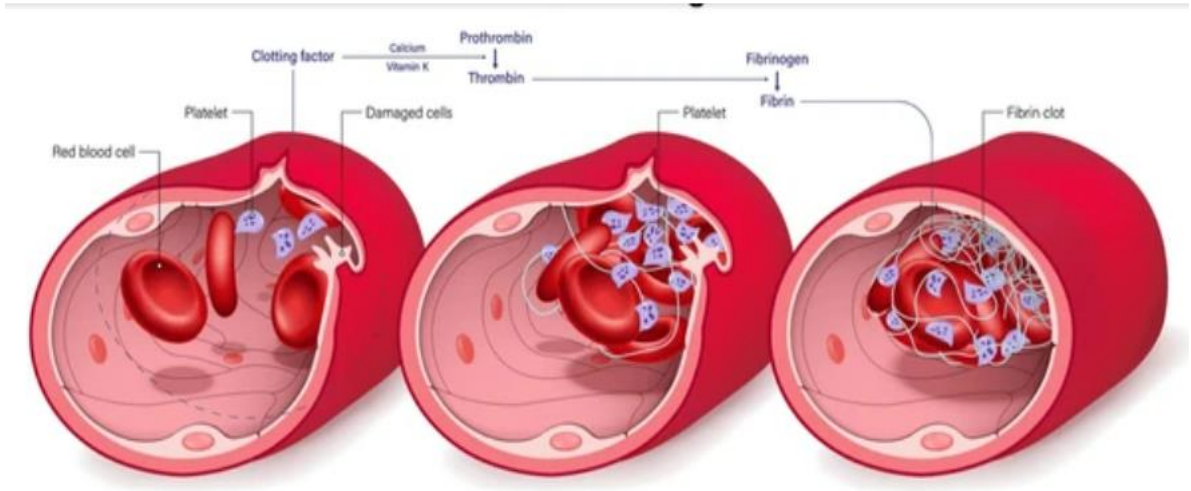
II- Anti-platelets

- **Principal components of thrombi include fibrin, platelets, red blood cells (RBCs),**
- Thrombus may block arteries or veins causing partial or complete obstruction resulting in MI, pulmonary embolism, cerebral stroke or DVT.



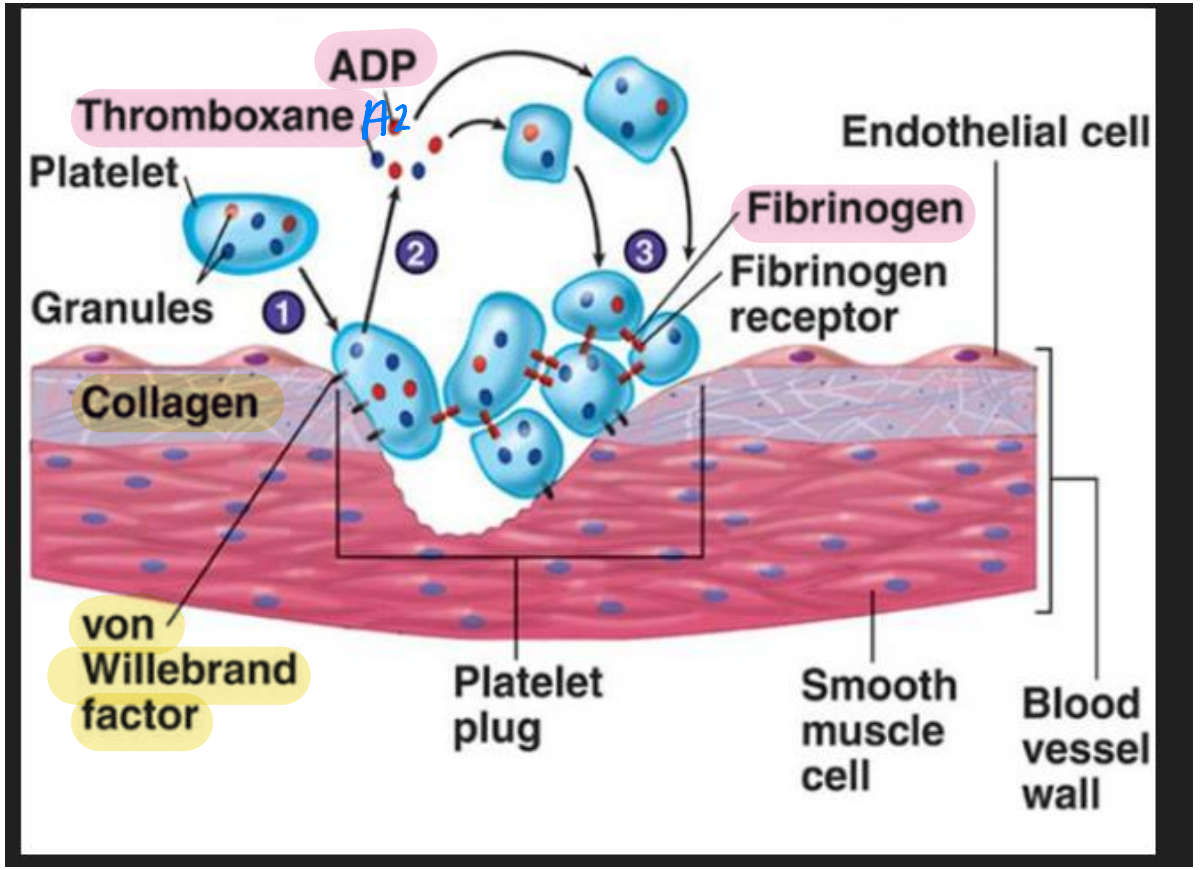


Classification of antiplatelet drugs (antithrombotic):

1- Platelet aggregation inhibitors: (eg, aspirin, clopidogrel, dipyridamole,ticlopidine)

2- Glycoprotein platelet inhibitors: (eg, abciximab, eptifibatide, tirofiban)

3- Protease-activated receptor-1 antagonists: vorapaxar



Platelet aggregation inhibitors:

1- Aspirin

Mechanism of antiplatelet effect of aspirin:

* **Thromboxane A_2 (platelet aggregating agent).**
* The **low dose aspirin (75-150 mg, 81 mg) irreversibly inhibits thromboxane A2 synthesis** through **inactivation of platelet COX-1** resulting in: **suppression of platelet aggregation last for the life of the platelets "approximately 7 to 10 days" .**
* **The anti-platelet effect is cumulative with 'low dose' aspirin.**

Low Dose Aspirin - Major Uses: (prophylaxis)

- Secondary prevention of transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction.
- Prevention of MI in patients with angina pectoris.
- Prevention of coronary artery bypass graft (CABG) occlusion.

Aspirin adverse effects

- Risk of GI adverse events (ulceration and bleeding)
- Allergic reactions and intolerance in some asthmatics
- Lack of response in some patients (aspirin resistance).
- Advantages of aspirin:
- Although it is not very effective antithrombotic drug, it is widely used because of its ease of use, low cost and availability

Precautions:

i. Aspirin must be stopped (7-14 days) before surgical operation to avoid bleeding.

ii. NSAIDs e.g., Ibuprofen, if taken concomitantly with, or 2 hours prior to aspirin, can obstruct the access of aspirin COX 1 and antagonize the platelet inhibition by aspirin. Therefore, aspirin should be taken at least 30 minutes before other NSAIDs as ibuprofen or at least 8 hours after ibuprofen.

race to COX 1

iii. COX-2 inhibitors (Coxibs e.g., celecoxib) do not have antiplatelet effects and may contribute to cardiovascular events by increasing activity of thromboxane A_2 (prothrombotic) i.e., the patients taking coxibs still need low-dose aspirin for cardiovascular protection.

Dose of Aspirin:

the dose 75-150 mg per day.

81 average

2) Ticlopidine

3) Clopidogrel (Plavix) >>

Mode of action:

- **Irreversible blocking of ADP (adenosine diphosphate) receptors on platelets and the subsequent inhibition of ADP activation of the GP IIb/IIIa receptors required for platelet aggregations, thereby preventing platelets aggregation.**

Adverse effects

1. **Prolonged bleeding for which there is no antidote.**
2. **Inhibition of cytochrome P450 (enzyme inhibitor) → interfere with the metabolism of drugs such as phenytoin, tolbutamide, warfarin, and tamoxifen if taken concomitantly.**
3. **Serious hematological adverse effects "neutropenia, thrombocytopenia, and aplastic anemia) limit ticlopidine usefulness.**

w/ heparin

Uses:

1) **Prevention of coronary stent occlusion (usually combined with aspirin).**
2) **In combination with aspirin to prevent MI and stroke.**

- **Clopidogrel is the preferred agent - Why?**
  - **Clopidogrel is more effective in ischemic heart disease events (evidence-based).**
  - **Clopidogrel is safer than Ticlopidine due to haematological side effects of Ticlopidine " *neutropenia*, thrombocytopenia and aplastic anemia" although clopidogrel still causes thrombocytopenia.**
  - **Food interferes with the absorption of ticlopidine but not with clopidogrel.**

New ADP antagonists: Clop too old..

Prasugrel

- **More rapid onset of action than clopidogrel**

4- Phosphodiesterase inhibitors

Dipyridamole

- **Coronary vasodilator with weak antiplatelet effect.** how to benifit from this?
- **Given in combination with aspirin or warfarin in coronary ischemia (not used alone).** * too weak
- **Mechanism of action:**
- **Increases intracellular levels of cAMP by inhibiting phosphodiesterase → ↓ thromboxane A_2 synthesis.**
- **It is also suggested that dipyridamole increases the level of adenosine which prevent platelet aggregation by stabilizing platelets.**

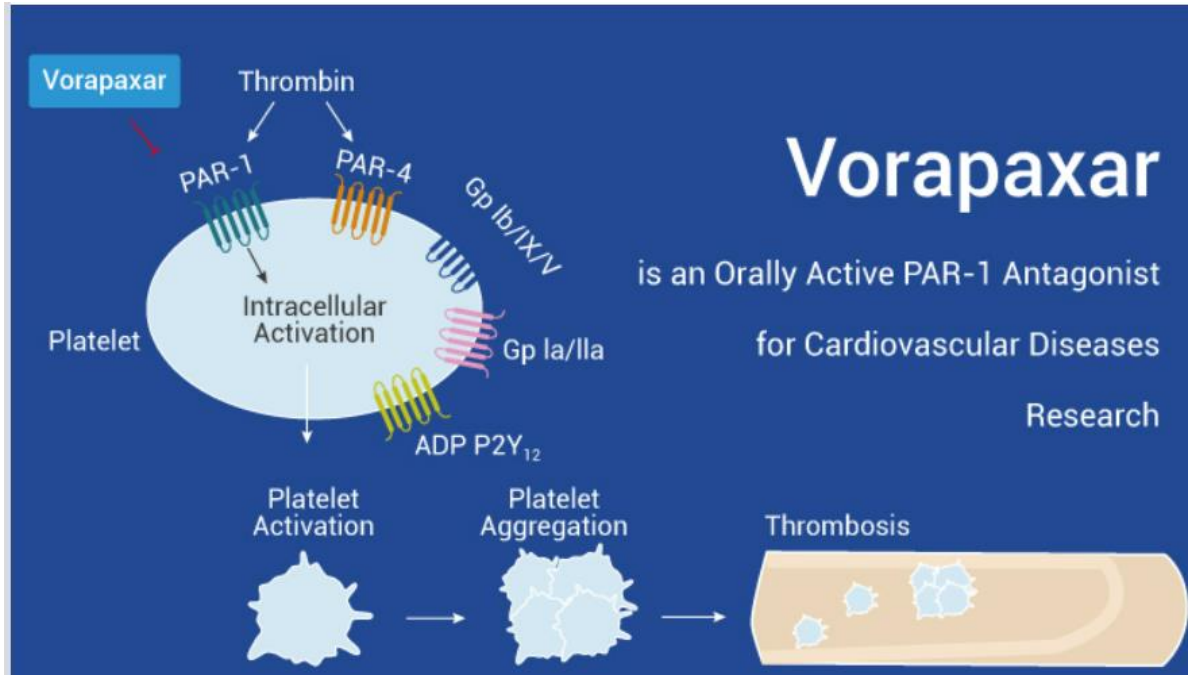
GP IIb/IIIa Antagonists

- **Mechanism of action:**
- **Glycoprotein IIb/IIIa is a platelet surface receptor for fibrinogen needed for platelet aggregation.**
- **Stimulation of GPIIb/IIIa receptors produces platelet aggregation while blocking of these receptors prevents platelet aggregation.**
- **Available only for intravenous administration.**
- **GP IIb/IIIa blockers:**

1. **Monoclonal antibody: abciximab**
2. **Peptide Antagonists :Eptifibatide**
3. **Non-peptide Antagonists Tirofiban**

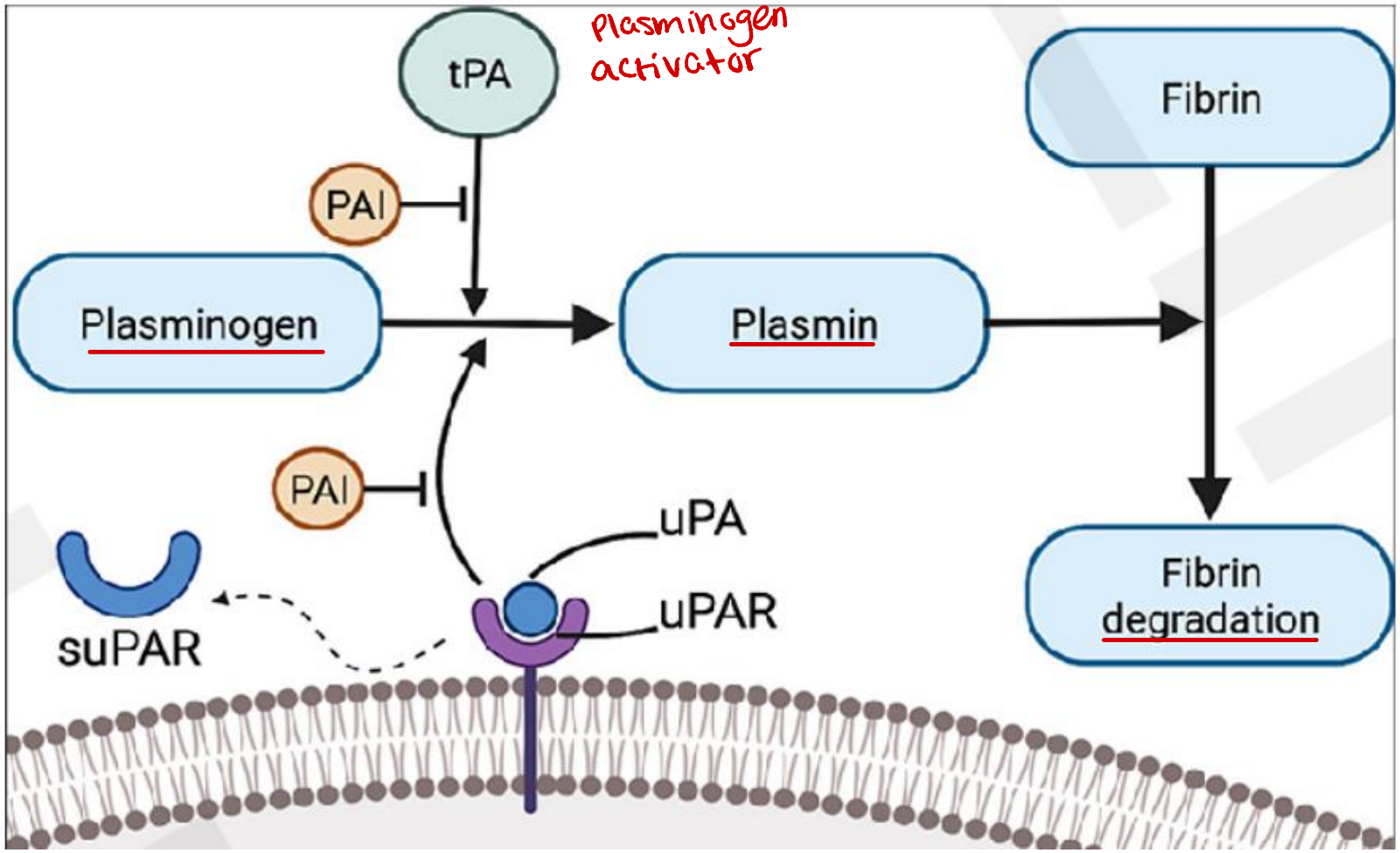
Protease-activated receptor-1 (PAR 1) antagonists

- **Mechanism of action:**
- antiplatelet effect by inhibiting **thrombin-related platelet aggregation**.
- Vorapaxar: **oral** potent PAR 1antagonists
- **For prevention of MI in ischemic heart diseases**



after already formed clot

Iii- Thrombolytic Agents (Fibrinolytic)



small clots often

immediate emergency → all IV → protein ⊗ oral

- **Thrombolytics:**
- **are agents that can dissolve the already formed intravascular thrombi in acutely occluded vessels.**

Classes:

1st generation: Streptokinase & Urokinase

2nd generation: tissue plasminogen activator (tPA- Alteplase); prepared by recombinant techniques.

3rd generation: recombinant variants of t-PA (comparable efficacy with t-PA) but with longer half-lives

e.g., Reteplase and Tenecteplase

a) Streptokinase

- **Produced by β-hemolytic streptococci.**

Mechanism of action:

- **When given I.V., it forms a stable complex with plasminogen → conformational changes of plasminogen forming active plasmin. Active plasmin dissolve already formed clot.**

not site specific

any plasminogen = bleeding

ADRs: Hypotension, Allergic reactions (immunogenic) and bleeding tendency (non-fibrin specific).

Advantages:

- **Decreases mortality and morbidity associated with thromboembolic disorders.**
- **Relatively inexpensive to other thrombolytics.**

b) Urokinase:

- **The same action of streptokinase but differs in:**
  - **Originally isolated from human urine**
  - **More expensive than streptokinase.**
  - **Non allergic (Non-immunogenic).**
  - **Lower recurrence rate of thrombosis.**

c) Intrinsic or tissue-plasminogen activators (t-PA)

- **Newly advanced agents & fibrin specific.** ⊗ bleeding tendancy
- **Include:**
  - **Alteplase: short-acting: IV infusion** (first one)
  - **Reteplase: Rapid with longer duration: IV bolus injection, 2 doses: 30 min. apart** (تعديل)
  - **Tenecteplase: The fastest lytic IV bolus injection used in MI, single dose** (best)
- **They activate plasminogen bound to fibrin forming plasmin.**
- **Plasmin dissolves fibrin clot, so called fibrin-specific.**
- **Both Reteplase and Tenecteplase are:**
  - **Longer half-lives than alteplase.**

* **All drugs are similar in efficacy & safety.**

* **They are very expensive.**

Clinical Indications of Thrombolytics

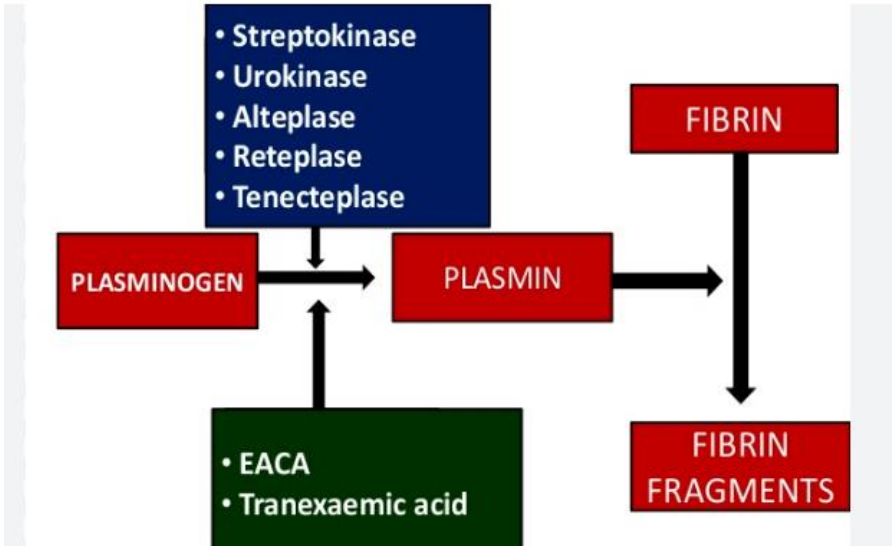
1. **Acute myocardial infarction (acute MI):**
   - **within 6-12 h of starting infarction.**
   - **Best results if intervention within 1-1.5 H**
   - **The use of small dose of aspirin (75-150 mg) with thrombolytics improves their efficacy.**
   - **Angioplasty with or without stent placement is superior to thrombolytic therapy: (PCI) percutaneous coronary intervention.**
   - **The shorter the door-to- needle time (DNT), the better the prognosis**
2. **Acute Pulmonary embolism:**
   - **Thrombolytics improves pulmonary embolism if used within the first 24 h of embolism.**
3. **Acute arterial thrombosis**
4. **Acute deep vein thrombosis**
5. **Acute ischemic stroke (not haemorrhagic).**
   - **Contraindications of thrombolytic drugs**

- **Internal bleeding: active bleeding in brain, eye,…**
- **Hemorrhagic Stroke or history within 3 months**
- **Uncontrolled hypertension.**
- **Surgery or trauma within the past 2 months.**
- **Aortic dissection**
- **Adverse effects: bleeding- immunogenic**
- **Antidote: antibirinolytic drugs**

Antibibrinolytic drugs

- **Mechanism of action:**
- **Competitive blocking of plasminogen activation by covering and protecting plasminogen.**
- **Aminocaproic acid (Oral and IV) and tranexamic acid (IV) : inhibit fibrinolysis.**

- **Indications:**
- **1- Stop bleeding induced by fibrinolytic drugs**
- **2- Prevent bleeding in tissues rich in plasminogen:**
- **After lung and prostate surgery**
- **Menorrhagia**
- **Ocular trauma**



DRUGS USED IN BLEEDING DISORDERS

1- Vitamin K1 (phytonadione) & Vitamin K2 (Menaquinone)

- Used in **warfarin toxicity** and also in **hemorrhagic disorders of neonates**. since its natural

2- Plasma fractions

- **Recombinant factor VIIa**.
- **Desmopressin acetate**: increase factor VII activity
- Cryoprecipitate

-They are used in bleeding particularly with **hemophilia**.

3- AMINOCAPROIC ACID

Therapeutic uses:

1- It is used to control bleeding caused by thrombolytic therapy.
2- Adjunctive therapy in hemophilia.
3- Prophylaxis for rebleeding from intracranial aneurysms.
4- Decrease postsurgical GIT bleeding and postprostatectomy bleeding.
5- Decrease bladder bleeding secondary to radiation or drug-induced cystitis.

Side effects:

- intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea and nasal stuffiness.

Contraindications:

- Disseminated intravascular coagulation
- upper genitourinary bleeding.