Antiplatelet drugs and thrombolytics

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Platelets and haemostasis

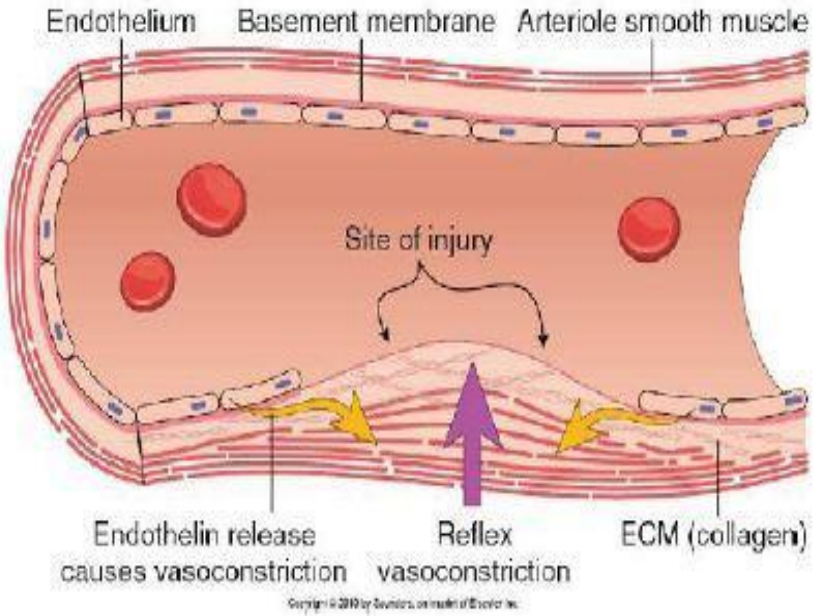
- Support in 3 ways

  Physical barrier-sticking to exposed collagen

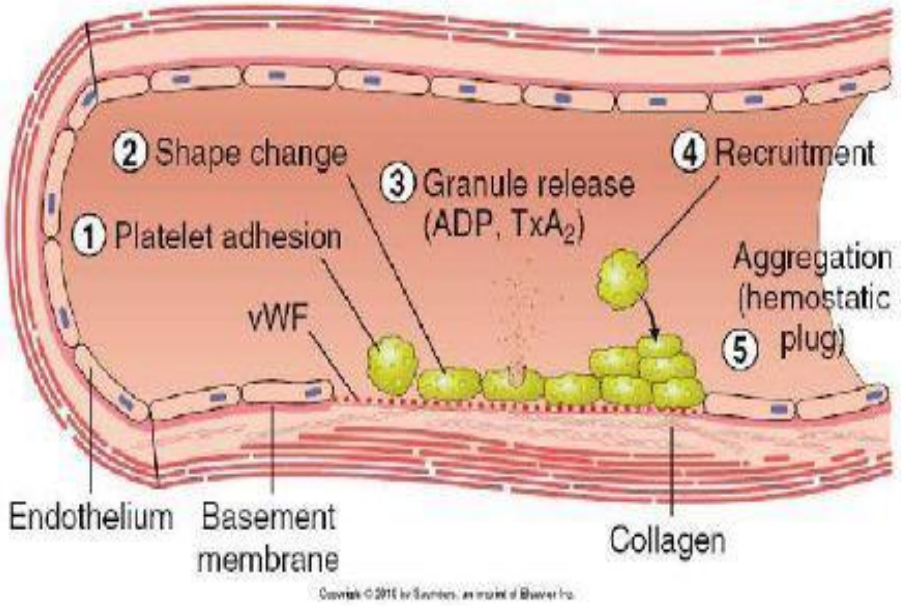
  Accelerates activation of coagulation proteins

  Vasoconstriction(release of storage granules)

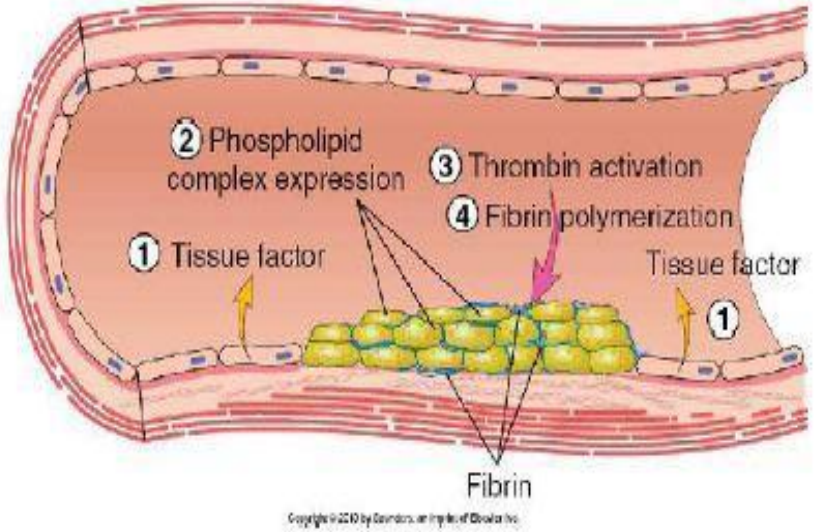
A. VASOCONSTRICTION



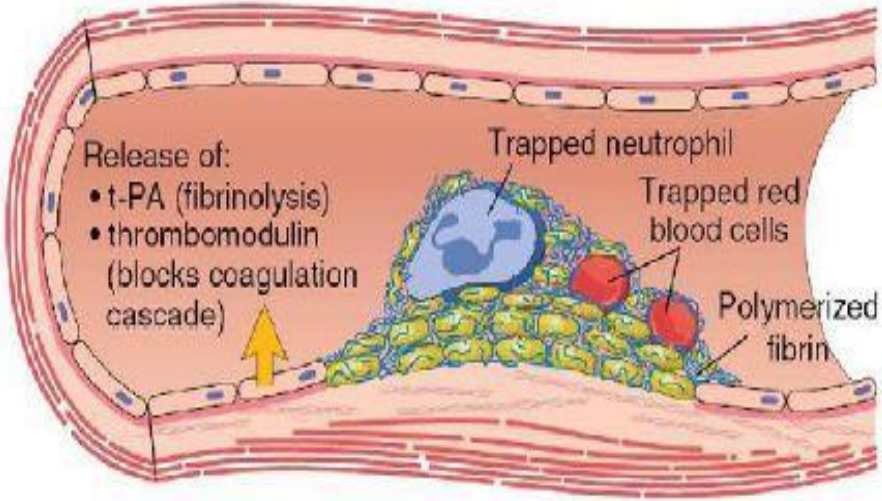
B. PRIMARY HEMOSTASIS



C. SECONDARY HEMOSTASIS



D. THROMBUS AND ANTITHROMBOTIC EVENTS



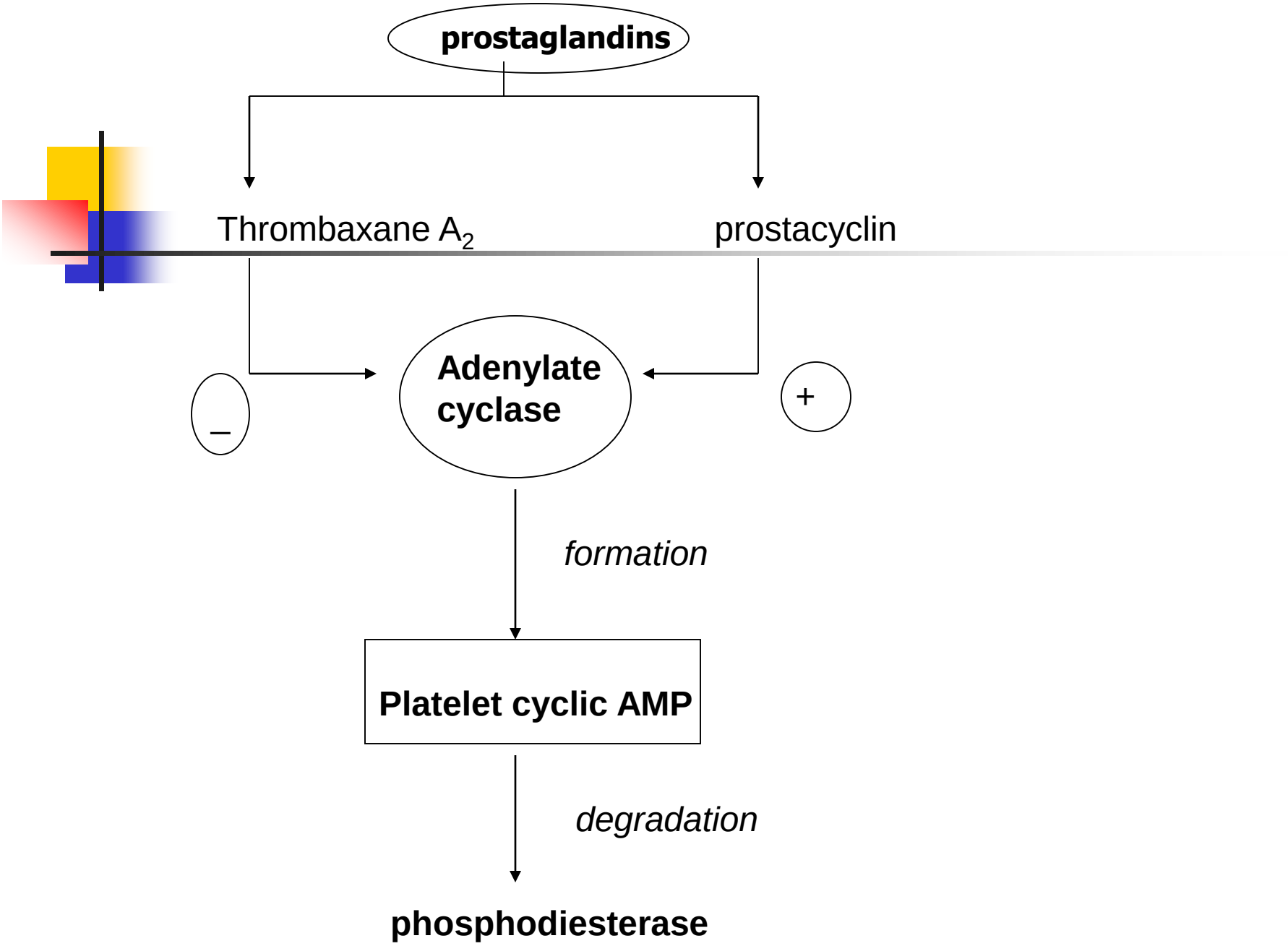
Platelet mechanisms

- Platelet aggregation does not occur
  - As long as the resting conformation of GPIIb/IIIa is maintained.
  - High concentrations of cyclic AMP is maintained within the platelet

Antiplatelet drugs

- Cyclooxygenase inhibitors
  - Aspirin
- ADP receptor inhibitors
  - Clopidogrel,ticlopidine
- Phosphodiesterase inhibitors
  - Cilostazol
- Glycoprotein II b/IIIa inhibitors
  - Abciximab,Tirofiban
- Adenosine reuptake inhibitors
  - Dipyridamole

- **Cyclooxygenase** (**COX**), officially known as **prostaglandin-endoperoxide synthase** (**PTGS**), is an enzyme that is responsible for formation of prostanoids, including prostaglandins such as prostacyclin and thromboxane.


prostaglandins
Thrombaxane A_2
prostacyclin
Adenylate cyclase
–
+
formation
Platelet cyclic AMP
degradation
phosphodiesterase

Aspirin

- Acetylates and thus inactivates COX
- Thus can prevent formation of TXA2 and PGI2
- These actions can be separated(abolish only the effect of TXA2) by using a ***low dose(75-100mg)/d***
- The acylation of COX is irreversible and lost for the life time of the platelet
- Even the low dose can cause increased risk of GI bleeds.

Dipyridamole

- Reversibly inhibits platelet phosphodiesterase →increase c.AMP levels in the platelet →platelet reactivity reduced
- T1/2 is 12 hrs

Ticlopidine

- Thienopyridine derivative
- Inhibits ADP dependent platelet aggregation
- T1/2 is 40 hrs
- More effective than aspirin in reducing strokes in patients with TIAs
- Reduces the risk of the combined out come of stroke,MI

Ticlopidine

- Neutropenia is the most serious side effect (risk 24%)

Clopidogrel

- Thienopyridine derivative
- More effective than aspirin in prevention of ischaemic stroke,MI or vascular death.
- More expensive than aspirin but cheaper than ticlopidine.

Glycoprotein II b/IIIa antagonists

- Glycoprotein II b/IIIa molecule mediates platelet aggregation via binding of adhesive proteins such as fibrinogen or Von Willibrands factor.
- Block a receptor on the platelet for fibrinogen or Von Willibrands factor.
- E.g.- abciximab,eptifibatide,tirofiban

Abciximab

- Human-murine chimeric monoclonal antibody
- The Fab fragment binds to the GP II b/IIIa complex with high affinity.
- It reduces the rate of death,MI,need for urgent CABG after percutaneous coronary angioplasty.
- Refractory unstable angina prior to percutaneous coronary intervention.

Side effects of abciximab

- Haemorrhage esp.high risk after failed fibrinolytic therapy(for acute MI).
- Platelet transfusion may be necessary.
- Thrombocytopenia may occur.

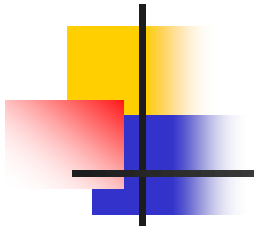
Other drugs

- Dextrans

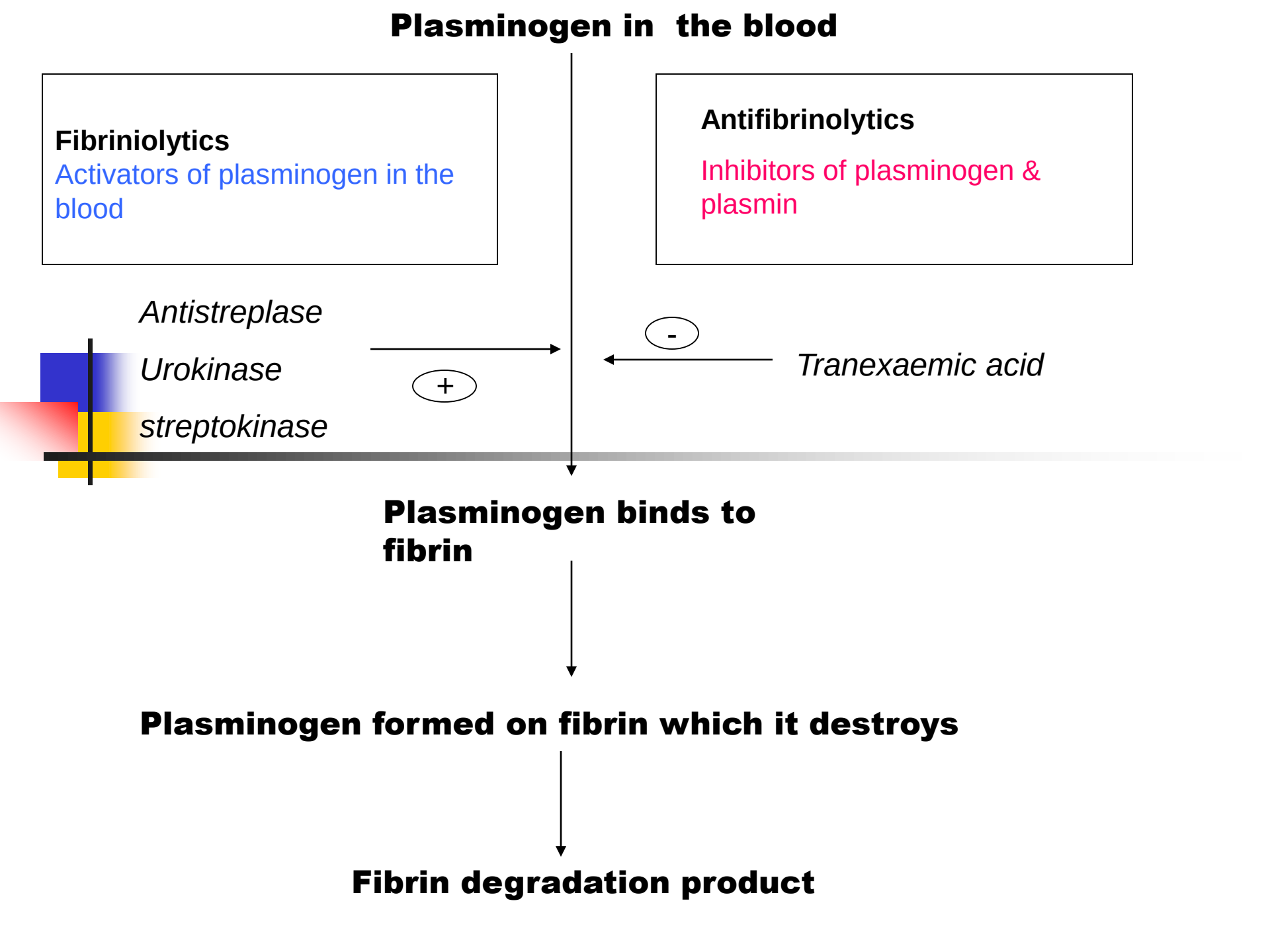
  Dextran 70 reduces post operative venous thromboembolism

Uses of antiplatelet drugs

- Non fatal MI and non fatal stroke reduced by one third.
- Death from any vascular cause reduced by one sixth.
- Aspirin+/-Dipyridamole reduce the risk of occlusion of vascular grafts.



Thrombolytic (fibrinolytic) drugs


Plasminogen in the blood
Fibriniolytics
Activators of plasminogen in the blood
Antifibrinolytics
Inhibitors of plasminogen & plasmin
Antistreplase
Urokinase
streptokinase
+
-
Tranexaemic acid
Plasminogen binds to fibrin
Plasminogen formed on fibrin which it destroys
Fibrin degradation product

The thrombolytic system

- Removal of products of coagulation is needed for the preservation of the intact vascular system.
- The system depends on formation of fibrinolytic enzyme plasmin from its precursor protein plasminogen.
- Fibrinolytics can remove established thrombi and emboli.

Drugs that promote fibrinolysis

- Important in dissolving thrombi in acute myocardial infarction. It limits necrosis of the ischaemic myocardium.Hence it can improve prognosis.
- The approach is to give a plasminogen activator intravenously so that ,the fibrinolytic enzyme plasmin is formed in increased amounts.

Fibrinolytics

- Non-fibrin selective-(Not well absorbed by fibrin thrombi)

1. streptokinase
2. Anistreplase
3. urokinase

- Fibrin selective(bind strongly to fibrin,can dissolve aging or resistant thrombi)

1. Recombinant prourokinase
2. Altiplase

Streptokinase

- Derived from beta-haemolytic streptococci.
- Converts plasminogen to plasmin.
- Rapid administration may cause a fall in blood pressure.

Anistreplase

- This is the plasminogen-streptokinase complex.
- Converts plasminogen to plasmin.
- Longer action than streptokinase.

Urokinase

- Made from human fetal kidney cells.
- Direct activator of plasminogen

Recombinant prourokinase

- Produced by recombinant DNA technology
- Binds to fibrin and converts to urokinase

Alteplase

- Produced by recombinant DNA technology

Uses of thrombolytic drugs

Coronary artery thrombolysis

- Reduce mortality with an acceptable frequency of adverse effects.
- Streptokinase &t-PA reduce mortality.This effect is better when combined with aspirin.

Adverse effects of coronary thrombolysis

- Bleeding-esp. at a vascular lesion
- Multiple micro emboli
- cardiac arrythmias (due to reperfusion)
- Allergy (avoid reuse within 5 to 12 months)

Non coronary thrombolysis

- Pulmonary thrombolysis

  Beneficial with evidence of haemodynamic decompression- Alteplase

- Deep vein thrombosis

  Esp. if affected vessels are proximal

- Distal arterial occlusion(Distal to the popletial)