2007a(10)/1999a(2): Explain the mechanisms that prevent blood clotting in intact blood vessels (do not draw the clotting cascade)

General: Haemostasis is the **physiological mechanism** where blood is **prevented from being lost** from damaged vessels whilst allowing blood to remain **fluid** in the circulation.

- **Involves a balance** between pro-coagulation system and anticoagulation system.
- **The coagulation system is a bioamplification system** → activation of a few substances triggers a cascade of precursor enzymes → ultimately converting soluble fibrinogen to insoluble fibrin → contributes to forming a haemostatic plug.

In vivo, the clotting mechanism is balanced by limiting coagulation reactions, preventing **platelet aggregation** → **prevent clots** from developing in uninjured vessels → maintain **blood in a fluid state**

**Virchow’s Triad for thrombus formation**
- Vessel wall
- Blood Flow
- Blood constituents

**Mechanisms involved:**

**Vessel Wall**

1. **Endothelium**
   - **Structure**
     - Blood vessels lined by **glycocalyx** → keeps the endothelium smooth
       - Repels platelets and clotting factors
       - Promotes non-turbulent flow of blood → maintains fluidity
     - Undamaged vessels → nil exposure of subendothelial contact factors (which stimulate platelet adhesion / coagulation cascade)
       - **Collagen** (intrinsic pathway, platelet adhesion)
       - **vWF** (component of factor VIII)
       - **TF** (extrinsic pathway)
   - **Substances produced by endothelial cells**
     - **Thrombomodulin** is expressed on surface of all vessels except cerebral microvasculature
       - Complexes with **thrombin** → activates **protein C** which inactivates of Va and VIIIa, stimulates fibrinolysis
     - **Prostacyclin** → Inhibits platelet aggregation via ↑cAMP / local vasodilatation

**Phospholipid → Phospholipase A₂ → Arachidonic Acid → COX → Prostacyclin**

- **NO** → inactivates platelet aggregation / local vasodilatation
- **Heparan sulphate** (natural heparin) → enhances **ATIII** activity (x1000) → Inhibits IIa, Xa
- **TPA** → converts inactive plasminogen to active plasmin → fibrinolytic

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Blood Flow
2. Blood Flow
- **Continuous laminar** (non-turbulent) blood flow
  o minimises contact time of platelets with endothelium (axial streaming)
  o Continually removes / dilutes clotting factors
    ▪ Eventually removed from circulation via RES
  o ‘Shear stress’ on vessels detaches weakly adhered platelets from surface

Blood Constituents
3. Coagulation factors
- Circulate as **inactive factors** → minimises spontaneous coagulation
4. Anticoagulants
- **ATIII**: Circulating protease inhibitor, blocks activity of activated clotting factors
  o Facilitated by heparin (see above)
  o Inactivates factors IIa, IXa, Xa, XIa, XIIa
  o ATIII/heparin responsible for 70% of capacity to limit coagulation
- **Protein C/S**: Protein C activated by thombin-thrombomodulin complex
  o Protein C adhered to platelet surface by Protein S
  o Protein C
    ▪ inactivates Va and VIIIa → ↓ coagulation
    ▪ inactivates inhibitors of TPA → ↑ fibrinolysis
- **α₂ macroglobulin**: Inhibits IIa and contact factors
- **α₂ antiplasmin / α₂ antitrypsin**: inhibit circulating serine proteases
5. Fibrinolytic System
- **APC** → inactivates inhibitors of TPA → ↑ TPA
  o TPA: converts inactive plasminogen → active plasmin
- **Plasmin**: cleaves fibrin and fibrinogen into **fibrin degradation products**
  o Lyses fibrin plug
  o FDP also inhibit IIa