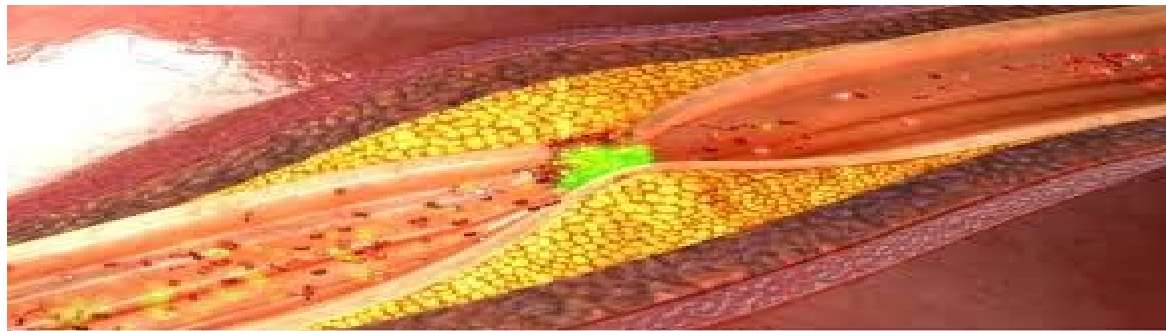


THROMBOLYTICS OR FIBRINOLYTICS

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Objectives

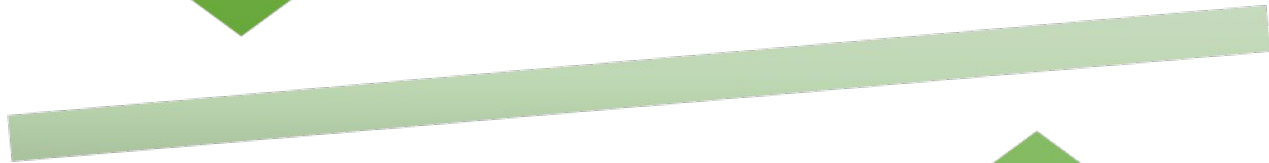
- At the end of the class 3rd yr students should be able to;
- Describe **mechanism of action** of Anti-plasmin (antifibrinolytic) drugs.
- Describe **clinical uses** and **adverse effects** of Anti-plasmin (antifibrinolytic) drugs

INTRODUCTION

- **Blood clots (thrombus/thrombi)**
 - **Vascular bed/Blood vessels**
 - **Coronary thrombi** cause myocardial infarctions
 - **Cerebrovascular thrombi** produce strokes
 - **Pulmonary thromboemboli**
 - Can lead to respiratory and cardiac failure
- **So it is important to rapidly diagnose and treat blood clots.**



Coagulation



Fibrinolysis



THROMBOLYSIS

PLASMINOGEN



← PLASMINOGEN
ACTIVATOR

PLASMIN



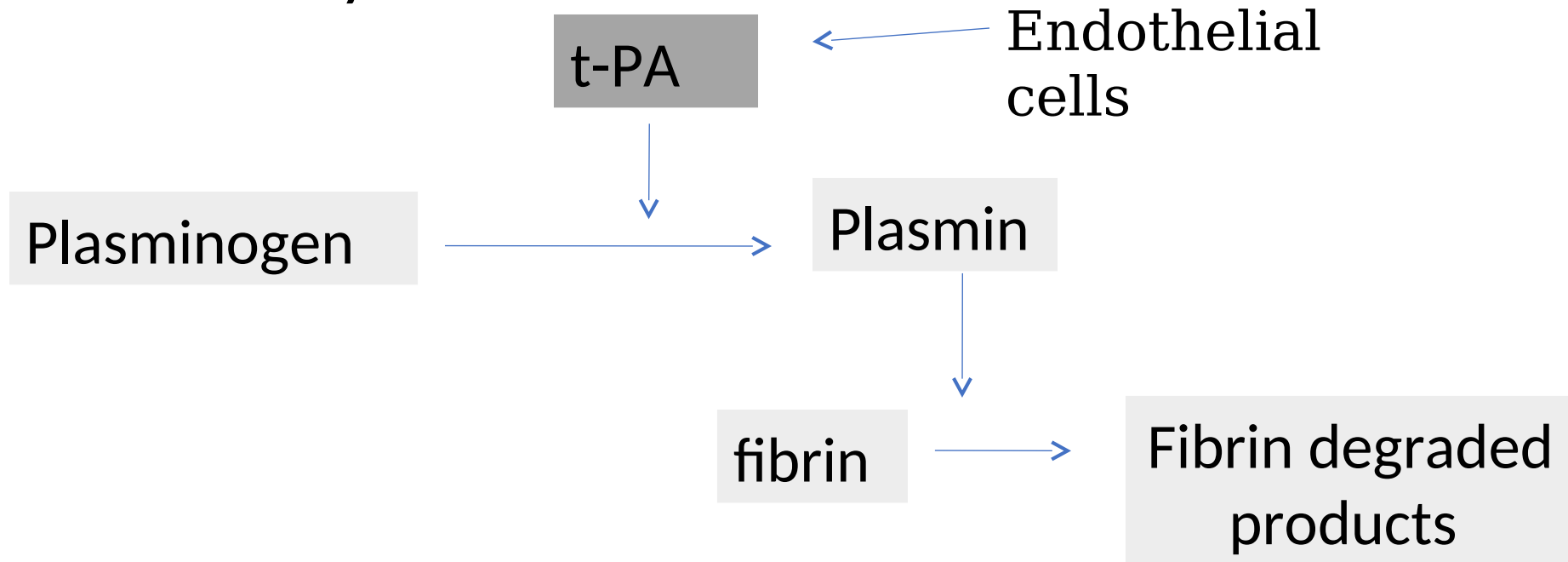
FIBRIN DEGRADATION PRODUCTS

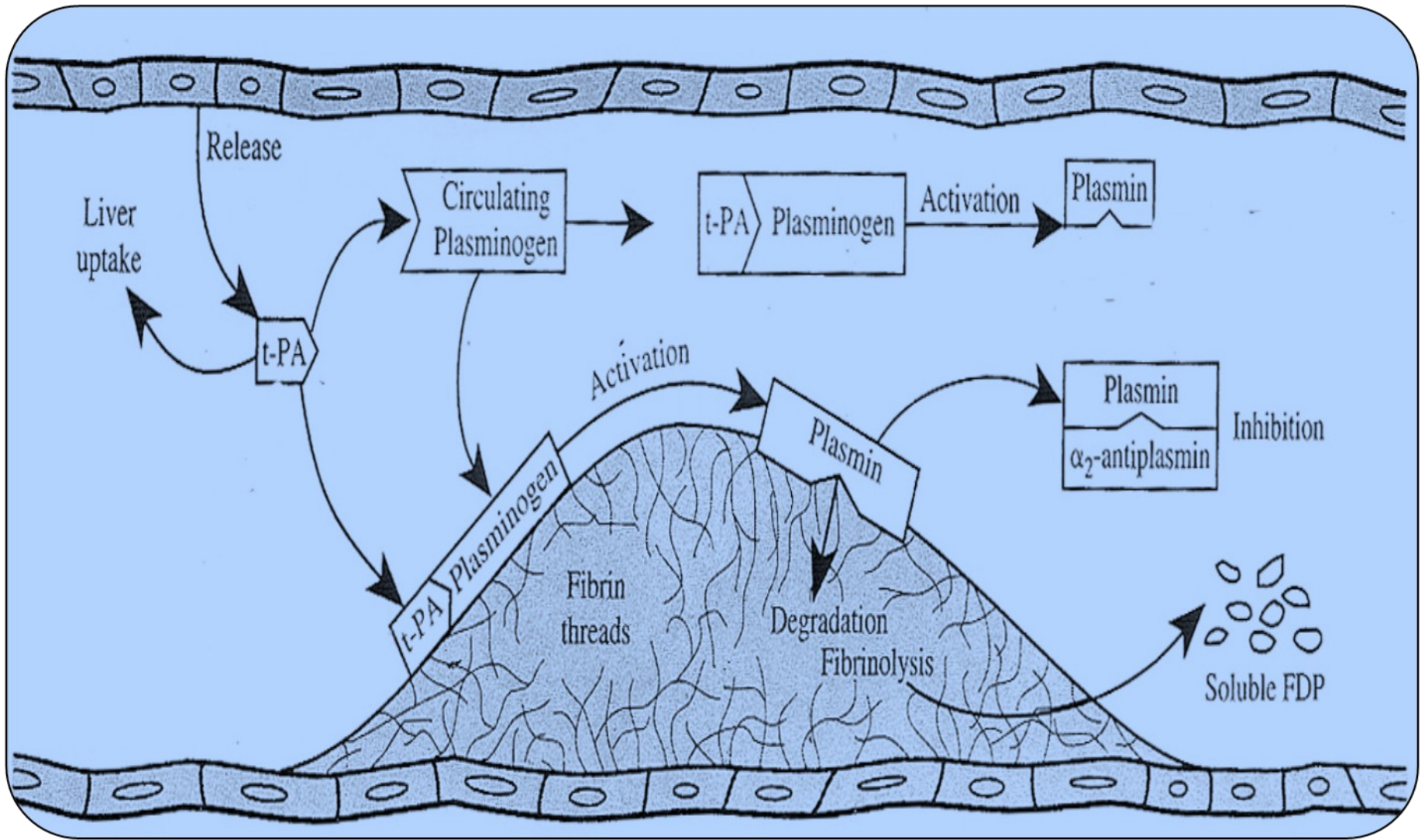


CLOT DISSOLUTION

FIBRINOLYTIC SYSTEM

- The process of dissolution of clot is called fibrinolysis





THROMBOLYTIC DRUGS

➤ **Thrombolytic drugs**

- Dissolve blood clots
- By activating plasminogen
- Which forms a cleaved product called plasmin.

➤ **Plasmin is**

- A proteolytic enzyme
- That is capable of breaking cross-links
- Between fibrin molecules.
- which provide the structural integrity of blood clots.

➤ Because of these actions, thrombolytic drugs are

- Also called "**plasminogen activators**" and "**fibrinolytic drugs.**"

MOA - THROMBOLYTICS

- **Fibrinolytic drugs**

- Catalyze the conversion of precursor plasminogen into active plasmin
- Rapidly lyse or break down thrombi

- **Plasmin is**

- An endogenous fibrinolytic enzyme
- That degrades clots by splitting fibrin into fragments

- **Plasmin itself can not be used**

- Because naturally occurring inhibitors in plasma prevent its effects.

- **Some drugs are more clot specific as**

- They only act on fibrin bound plasminogen.

THROMBOLYTIC DRUGS

- Streptokinase
- Urokinase
- Anistreplase
- Tissue Plasminogen Activators (t-PA)
 - Alteplase
 - Reteplase
 - Tenecteplase

STREPTOKINASI



SOURCE:

- A protein Produced by beta-hemolytic streptococci.

MOA:

- **It combines with**
 - Proactivator plasminogen to form a complex.
- **This complex catalyzes**
 - The conversion of plasminogen to active plasmin.
- So rapid lysis of the clot by plasmin.

PLASMA HALF LIFE:

(t_½) 40-80 minutes

ADVERSE EFFECTS:

- Not clot specific.
 - Hemorrhage --- most serious cerebral hemorrhage
 - Allergic reactions, rarely anaphylaxis and fever.

Clinical Uses

- ✓ Acute Myocardial Infarction
- ✓ Pulmonary Embolism (obstruction of an artery)
- ✓ Deep Vein Thrombosis
- ✓ Arterial Thrombosis (Blood **clot** that develops in an **artery**) or Embolism
- ✓ Occlusion of Arteriovenous Cannulae

UROKINASE

- A two chain serine protease
 - Containing 411 amino acid residues Isolated from cultured human kidney cells.
- An **enzyme** Produced by the **kidney** Found in the urine

MOA:

- Converts plasminogen to active plasmin.
- It is not clot specific:
 - Both **protective haemostatic thrombi** and **target thromboemboli**
 - Are broken down.



- Administered by intravenous infusion
- Rapidly cleared by the liver
- Half-life of 12-20 minutes

CLINICAL USES:

- **For the lyses of**
 - Acute massive pulmonary emboli.

ANISTREPLASE (APSAC)

- (APSAC- Anisolyted Plasminogen Streptokinase Activator Complex)
- A complex of purified human plasminogen & bacterial streptokinase that has been acylated
 - To protect the enzymes active site.
- On I/V administration,
 - The acyl group spontaneously hydrolyzes.
- Free activated streptokinase - proactivator complex produces
 - Lysis of clots also degrades fibrinogen.

ADVANTAGES:

- Rapid I/V injection may be given.
- Greater clot selectivity .
- More thrombolytic activity.

TISSUE PLASMINOGEN ACTIVATOR (T-PA) ALTEPLASE (RT.PA)

A tissue plasminogen activator (t.PA)

- Produced by recombinant DNA technology of 527 amino acids

MECHANISM:

- It is an enzyme
- Which has the **property of fibrin-enhanced conversion of plasminogen to plasmin**
- It **produces limited conversion of free plasminogen in the absence of fibrin**
- When introduced into the systemic circulation
- It binds to fibrin in a thrombus and
- Converts the entrapped plasminogen to plasmin
- Followed by activated local fibrinolysis with limited systemic proteolysis

PHARMACOKINETICS:

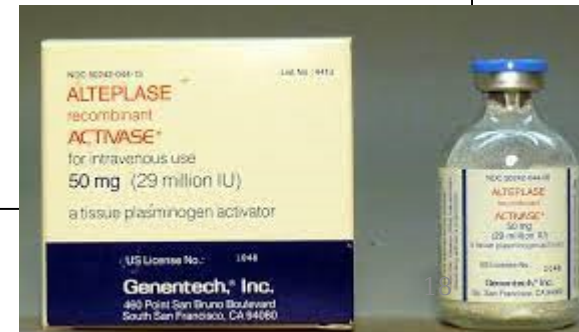
- Very short $t_{1/2}$ of 5 minutes

SIDE-EFFECTS:

- Bleeding including GIT & cerebral hemorrhage
- Allergic reactions,
 - Anaphylactoid reaction,
 - Laryngeal edema,
 - Rash, and urticaria

clinical uses of alteplase

- Acute Myocardial Infarction
- Acute Ischemic Stroke (Permanent brain injury secondary to disruption of blood flow.)
- Pulmonary Embolism



TISSUE PLASMINOGEN ACTIVATOR (T-PA)

Reteplase:

- Recombinant human t-PA.
 - From which several amino acid sequences have been deleted.
- Faster OOA & slighter longer DOA.
- Less expensive
- Less fibrin specific than t-PA.

Tenecteplase:

- Mutant form of t-PA
- With a longer DOA.
- Slightly more fibrin-specific than t-PA.



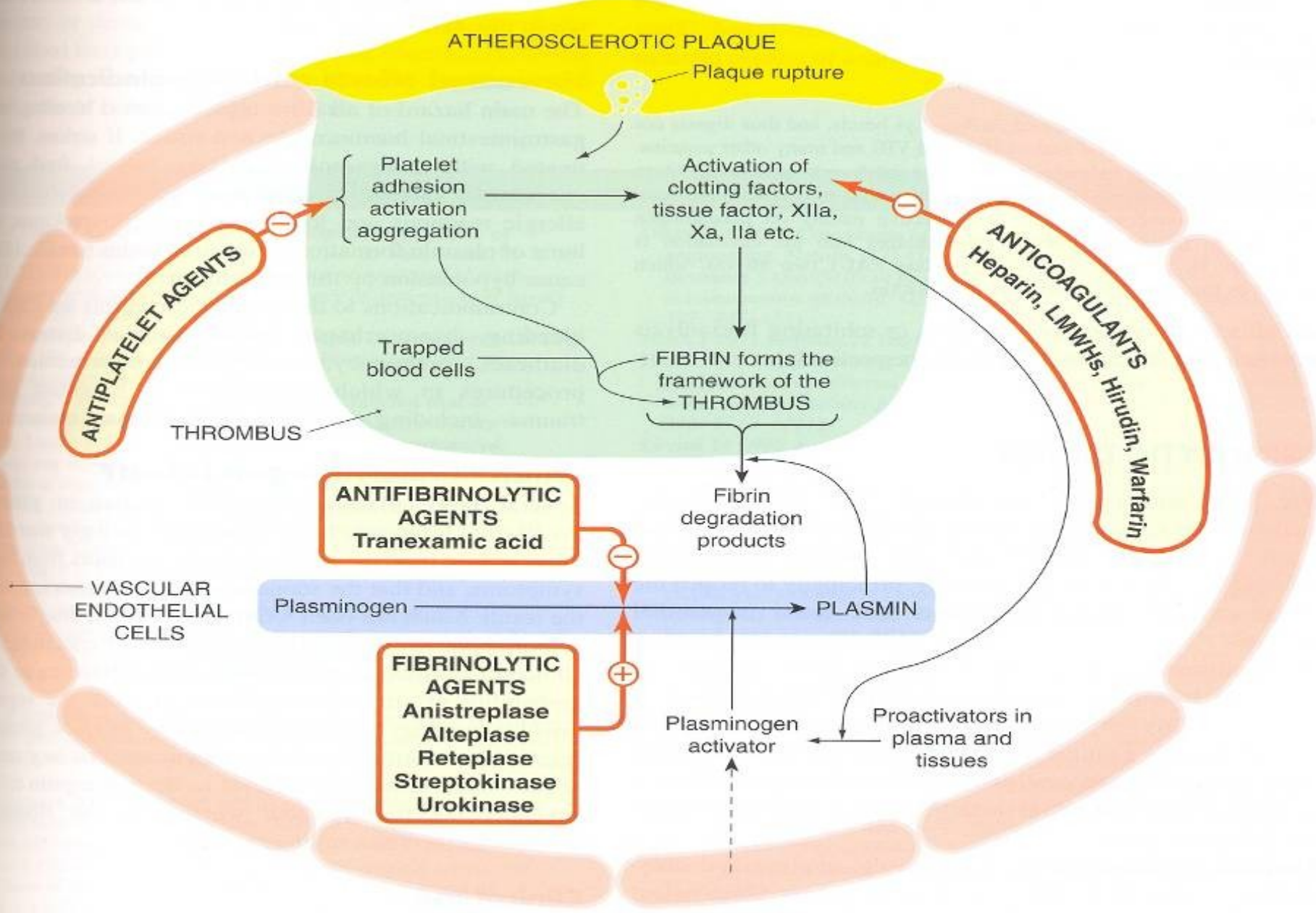


Fig. 20.10 Fibrinolytic system. The schematic shows interactions with coagulation and platelet pathways and sites of action of drugs that modify these systems. (LMHs, low-molecular-weight heparins.) For more details of platelet activation and the coagulation cascade refer to Figures 20.1, 20.2 and 20.7.

THANK YOU