
بسم الله الرحمن الرحيم

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

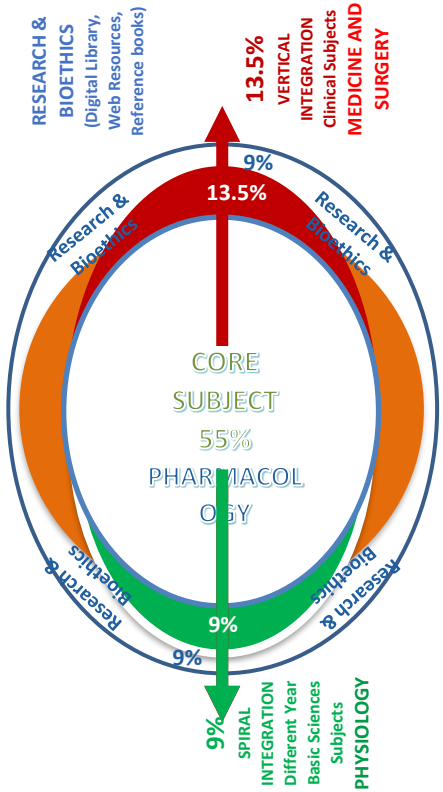
Drugs Used in Disorders of Coagulation

Learning objectives

At the end of the lecture, students should know about

- Mechanism of homeostasis and role of clotting factors in it
- Classification of anti-coagulant drugs
- Mechanism of action, indication, precautions, monitoring, dosing and adverse effects of different anti coagulants
- Comparison between oral and parenteral anti coagulants

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures

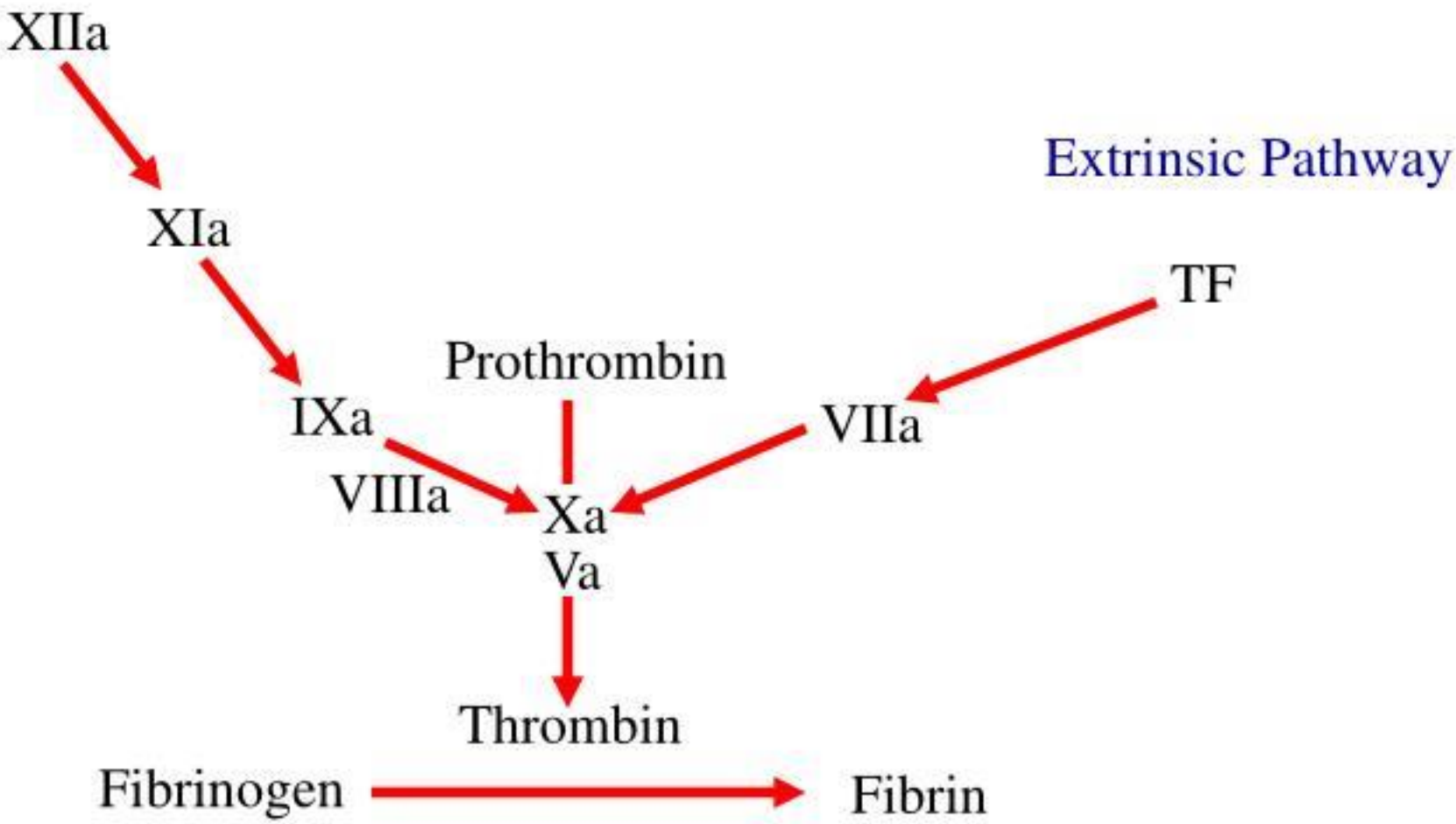


Model 3rd Year Pharmacology LGIS (71 slides)	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

➢ SPIRAL INTEGRATION

PHYSIOLOGY

Intrinsic pathway



Natural anticoagulants

- **Antithrombin(AT)** inactivates clotting factors IIa ,IXa ,Xa ,XIa , XIIa

- **Protein C and protein S** cause proteolysis of two cofactors Va and VIIIa

- Defects in natural anticoagulants result in an increased risk of venous thrombosis

Core Subject

Anticoagulant drugs

- **1. Indirect thrombin inhibitors**
  - **Unfractionated heparin (UFH)**
  - **Low molecular heparin (LMWH)**
  - **Fondaparinaux (Synthetic)**
- **2. Direct thrombin inhibitors**
- **Hirudin** **Dabigatran**
- **Bivalirudin**
- **Argatroban**
- **Melagatran**
- **3. ORAL Direct factor Xa inhibitors**
  - **Rivoroxaban**
  - **Apixaban**
- **4. Warfarin and other coumarin anticoagulants**

M .O.A

- **Heparin has anti coagulant effect that depends upon anti-thrombin III which is an endogenous anti-coagulant that inhibits activated clotting factors (IIa, IXa, Xa, XIa).**

- **This inhibition is slow but increased to 1000 folds in the presence of heparin**

PHARMACOKINETICS

- Given only parenterally (IV, SC) not IM (Hematoma)

MONITORING

- Activated partial thromboplastin time (aPTT)
- Whole blood clotting time

Parenteral Anticoagulants

FEATURE	HEPARIN	LMWH	FONDAPARINUX
Source	Biologic	Biologic	Synthetic
Molecular weight	15,000	5000	1728
Target	Xa and IIa	Xa and IIa	Xa
Bioavailability (%)	30	90	100
Half-life (hr)	1	4	17
Renal excretion	No	Yes	Yes
Antidote	Complete	Partial	No
HIT	<5%	<1%	Never

- **VERTICLE INTEGRATION**

MEDICINE/ SURGERY

CLINICAL USES of HEPARIN

- DVT (surgical, orthopedic, and medical patients)
- Treatment of VTE in pregnancy
- Acute MI
- Unstable angina
- Prevention of clotting in dialysis patients
- Thrombosis in prosthetic heart valves
- Thrombosis in pts with atrial fibrillation

Toxicity

1. Bleeding --- can be prevented by careful monitoring

2. Allergy reactions

3. Increase hair loss and reversible alopecia

4. Long term heparin therapy causes
    - Osteoporosis and spontaneous fracture
    - Mineralocorticoid deficiency with consequent hyperkalemia

Heparin induced thrombocytopenia

- **Very serious complication occurs in 1-4% pts treated with UFH for minimum 7 days .**
- **Cause is IgM or IgG antibodies against complexes of heparin and platelet factor 4 (platelet protein)**
- **Activates more platelets with release of platelet factor 4 causing aggregation and thrombocytopenia and DIC**

Reversal of Heparin action

- **Stop giving heparin and start Protamine sulfate**
- **Highly basic positively charged peptide binds with negatively charged heparin forming stable complex**

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Core subject – Pharmacology

Parenteral Direct thrombin inhibitors

- Hirudin
- **Specific irreversible thrombin inhibitor from leech saliva**
- Lepirudin, Desirudin and bivalirudin **-available in recombinant form**
- **Alternative to heparin in patients with HIT**

Oral Direct Thrombin Inhibitors

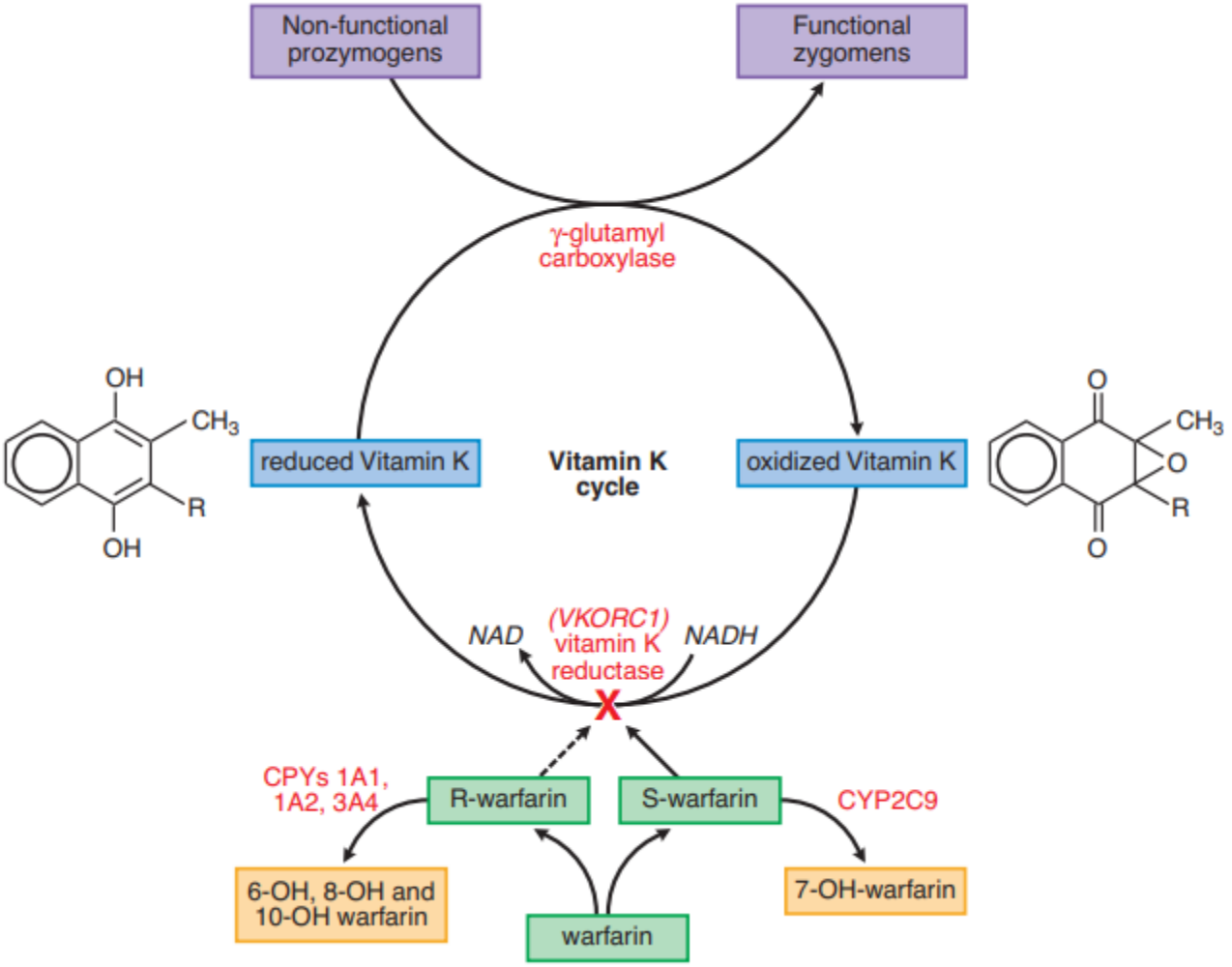
- **Dabigatran**
- **Predictable pharmacokinetics allow fixed dosing**
- **Renal functions should be assessed**
- **Increased risk of GIT bleeding compared to warfarin**
- **Antidote for dabigatran is Idarucizumab**

ORAL DIRECT FACTOR Xa INHIBITORS

- –RIVOROXABAN
- –APIXABAN
- –EDOXABAN

- **Dose adjustments for rivoroxaban and apixaban is required in renal impairment**
- **Adexanet alfa can be used as a reversal agent for rivaroxaban and apixaban in case of severe bleeding**

MOA WARFARIN



PHARMACOKINETICS

- Oral, I/V, Rectal
- Food in GIT decreases rate of absorption
- Highly protein bound
- Metabolized in liver through CYP2C9.
- Half life (25-60h) , duration of effect 2-5 days
- Narrow therapeutic index

- **VERTICLE INTEGRATION**

MEDICINE/ SURGERY

Clinical Uses

- **To prevent progression or recurrence of DVT or pulmonary embolism following an initial course of heparin.**
- **To prevent venous thromboembolism in patients undergoing orthopedic or gynecological surgery**
- **Acute MI**
- **Systemic embolization in patients with prosthetic heart valves or chronic atrial fibrillation.**

Toxicity

- **Bleeding**
- **BIRTH DEFECTS:**
  - **Warfarin crosses the placenta readily and can cause a hemorrhagic disorder in the foetus**
  - **foetal proteins in bone and blood may b affected**
  - **serious birth defect characterized by abnormal bone formation ,so should never be given in pregnancy**
- **Cutaneous necrosis with reduced activity of protein C during first weeks of therapy**
- **Infarction of breast, fatty tissues, intestine and extremities**

Reversal of Warfarin action

- **Stop giving the drug**
- **Give vitamin K, FFPs, prothrombin complex concentrates**
- **Titrate to appropriate INR**

RESEARCH ARTICLE RELATED TO ANTICOAGULANTS

- Low Molecular Weight Heparin (LMWH)
- https://www.statpearls.com/ArticleLibrary/viewarticle/24433

The Four Key Principles of Bioethics

Non-Maleficence

"Do no harm." Minimize any possible risks to the patient.

Autonomy

The patient family retains the right to make treatment decisions with all relevant information presented to them.

Beneficence

The overall needs of the individual must be taken into account with the benefits balanced against the risks.

Justice

Access to treatment and care should be fair and equitable.

How To Access Digital Library

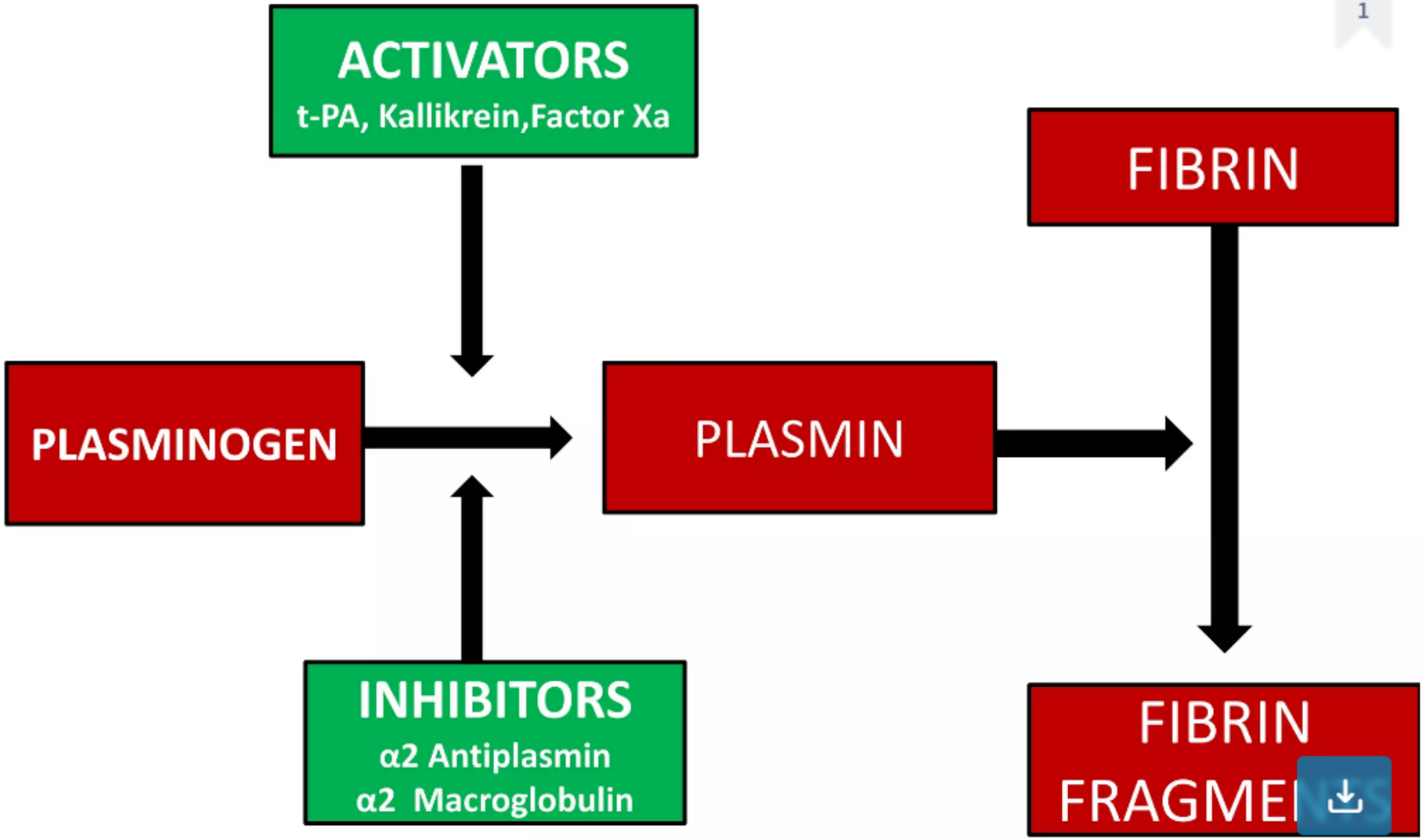
- **Steps to Access HEC Digital Library**

1. Go to the website of HEC National Digital Library.
2. On Home Page, click on the INSTITUTES.
3. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
4. Select your desired Institute.
5. A page will appear showing the resources of the institution
6. Journals and Researches will appear
7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

Thank you

FIBRINOLYTICS
&
ANTIFIBRINOLYTICS

NATURAL FIBRINOLYTIC SYSTEM


ACTIVATORS
t-PA, Kallikrein,Factor Xa
FIBRIN
PLASMINOGEN
PLASMIN
INHIBITORS
α2 Antiplasmin
α2 Macroglobulin
FIBRIN
FRAGME

Fibrinolysis

- Fibrinolysis refers to the process of fibrin digestion by the fibrin specific protease ,plasmin .plasmin circulates in an inactive form as plasminogen .in response to injury ,endothelial cells synthesize and release t-PA which converts plasminogen into plasmin .plasmin remodels thrombus and limits its extension by proteolytic digestion of fibrin

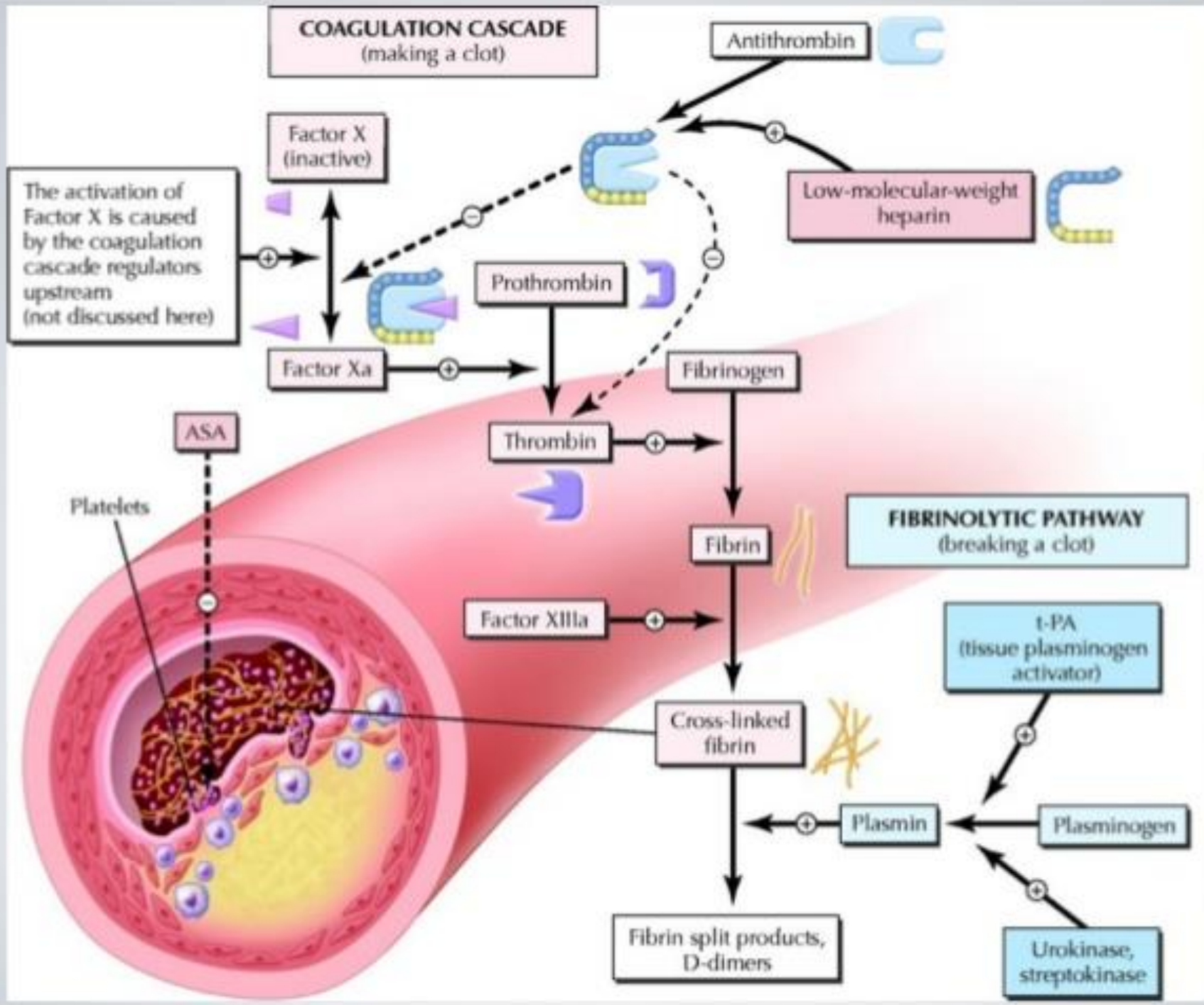
- Both plasminogen and plasmin have specialized protein domains(kringles) that bind to exposed lysines on the fibrin clot and impart clot specificity at physiological levels
- At pharmacological levels of t-PA used in thrombolytic therapy , clot specificity is lost, systemic lytic state is created, risk of bleeding

FIBRINOLYTICS

Drugs used to lyse thrombi to recanalize occluded blood vessels

Clinically important fibrinolytics are,

- Streptokinase
- Urokinase
- Alteplase (rt PA)
- Reteplase
- Tenecteplase


COAGULATION CASCADE
(making a clot)
Antithrombin
Factor X
(inactive)
Low-molecular-weight
heparin
The activation of
Factor X is caused
by the coagulation
cascade regulators
upstream
(not discussed here)
Prothrombin
Factor Xa
Fibrinogen
ASA
Thrombin
Platelets
FIBRINOLYTIC PATHWAY
(breaking a clot)
Fibrin
Factor XIIIa
t-PA
(tissue plasminogen
activator)
Cross-linked
fibrin
Plasmin
Plasminogen
Fibrin split products,
D-dimers
Urokinase,
streptokinase

streptokinase

- It is a protein synthesized by streptococci ,it combines with plasminogen ,catalyzing the conversion of inactive plasminogen into active plasmin ,
- Urokinase is human enzyme synthesized by kidney that directly converts plasminogen to active plasmin

- Plasmin itself cant b used b/c naturally occuring inhibitors in plasma prevent its effects
- No inhibitors for urokinase and streptokinase –proactivator complex permits their use clinically
- Plasmin formed inside a thrombus by these activators is protected from plasma antiplasmins ,lyse thrombin from within .

Unwanted effects and contraindications

- Main hazard is bleeding ,GIT haemorrhage and haemorrhagic stroke ,if serious treated with tranexamic acid ,FFPs,or coagulation factors
- Strptokinase can cause serious allergic reactions and low grade fever ,hypotension

Anistreplase

- It consists of a complex of purified human plasminogen and bacterial streptokinase that is acylated to protect the enzyme s active site
- When administered ,the acyl group spontaneously hydrolyzes ,freeing the activated streptokinase –proactivated complex
- It allows rapid i/v administration, greater clot selectivity, more selective on plasminogen

- associated with clots than free plasminogen in the blood and more thrombolytic activity

Alteplase ,Reteplase

Both are prepared by recombinant DNA technology ,are tissue plasminogen activators

They activate plasminogen that is bound to fibrin,to avoid systemic activation

Indications

Pulmonary embolism with hemodynamic instability

DVT (severe)

Peripheral vascular disease

Ascending thrombophlebitis of iliofemoral vein with severe lower extremity oedema

Acute MI

Dosage

- Streptokinase given i/v infusion of a loading dose of 250,000 units ,followed by 100,000 units /h for 24-72hrs

Contraindications

- Active internal bleeding ,
- haemorrhagic CVS disease,
- bleeding diathesis ,
- pregnancy ,
- uncontrolled hypertension ,
- invasive procedures requiring hemostasis ,
- and recent trauma

- Tissue Plasminogen Activator. t-PA is a serine protease of 527 amino acid residues. It is a poor plasminogen activator in the absence of fibrin, physiological t-PA concentrations of 5-10 ng/mL do not induce systemic plasmin generation

- During therapeutic infusions of t-PA, however, when concentrations rise to 300-3000 ng/mL, a systemic lytic state can occur.
- Clearance of t-PA primarily occurs by hepatic metabolism, and its t1/2 is ~5 min.
- t-PA is effective in lysing thrombi during treatment of acute myocardial infarction or acute ischemic stroke. t-PA (alteplase, ACTIVASE) is produced by recombinant DNA technology.

- Recombinant variants of t-PA now are available (reteplase, RETAVASE and tenecteplase, TNKASE).
- They differ from native t-PA by having longer plasma half-lives that allow convenient bolus dosing;
- Reteplase is administered in two bolus doses given 30 minutes apart, while tenecteplase requires only a single bolus.
- In contrast to t-PA and reteplase, tenecteplase is relatively resistant to inhibition by PAI-1.
- Despite these apparent advantages, these agents are similar to t-PA in efficacy and toxicity

ANTIFIBRINOLYTICS

Drugs which inhibit plasminogen activation & dissolution of clot

AMINOCAPROIC ACID (EACA)

- Synthetic analogue of lysine
- Competitively inhibits plasminogen activation
- Rapid oral absorption
- Cleared from kidney
- Dose 6-g four times daily
- Tranexamic acid is its analogue with same properties

USES

- Adjunct therapy in hemophilia
- Bleeding from thrombolytic therapy
- Prophylaxis for rebleeding from intracranial aneurysms
- Postsurgical GIT and postprostatectomy bleeding
- Bladder hemorrhage secondary to radiation and drug induced cystitis

Adverse Effects

- Intravascular thrombosis from inhibition of plasminogen activatior
- Hypotension
- Myopathy
- Abdominal discomfort
- Diarrhea
- Nasal stuffiness

contraindications

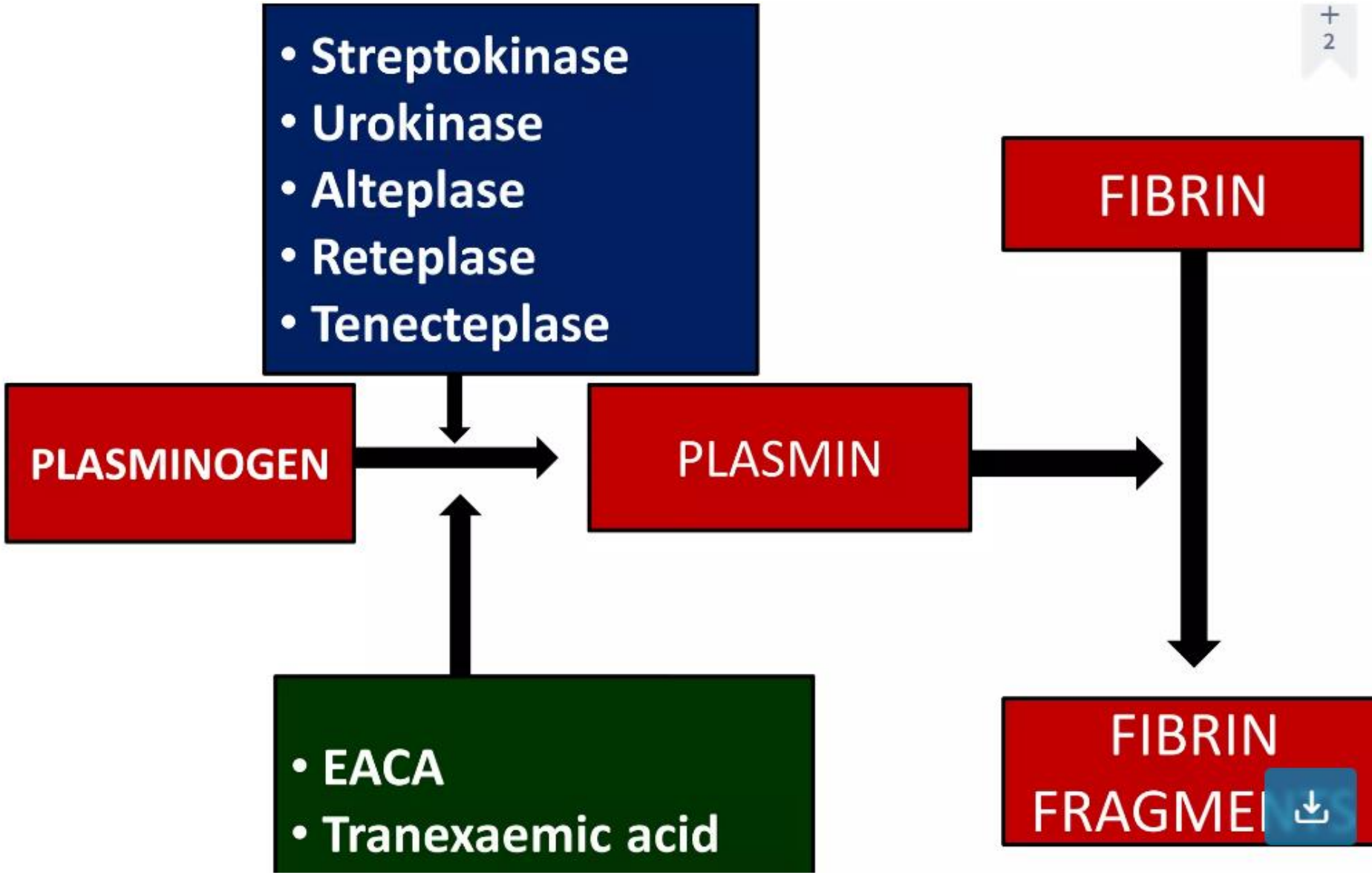
- DIC
- Genitourinary bleeding of the upper tract, e.g, kidney and ureters because of potential for excessive clotting

TRANEXAMIC ACID

- MOA-similar to EACA
- 7 times potent than EACA
- Preferred drug for bleeding due to
  - Fibrinolytic drugs
  - Cardiopulmonary bypass surgery
  - Tonsillectomy,prostatic surgery,tooth extraction in haemophiliacs
  - Menorrhagia
  - Recurrent epistaxis,hyphema due to ocular

Adverse Effects

- Nausea
- Diarrhoea
- Thromboembolic events
- Disturbed colour vision
- Allergic reactions
- Thrombophlebitis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FIBRIN
PLASMINOGEN
PLASMIN
• EACA
• Tranexaemic acid
FIBRIN
FRAGME

Thank You