Therapeutic products for the treatment of coagulation disorders

Factor	*Deficiency state*	*Concentration (%) relative to normal plasma required for hemostasis*	*Half-life (days) of infused factor*	*Therapeutic material*
I	Afibrinogenemia, defibrination syndrome	40	4	Plasma fibrinogen, cryoprecipitate
II	Prothrombin deficiency	40	3	Concentrate (factor IX-prothrombin complex)
V	Factor V deficiency	20	1	Fresh-frozen plasma
VII	Factor VII deficiency	Unknown	0.25	Concentrate (some preparations of factor IX)
VIII	Hemophilia A	25–35	0.5	Plasma cryoprecipitate (classic) and other factor VIII concentrate
	von Willebrand's disease	30	Unknown	
IX	Hemophilia B (Christmas disease)	25	1	Plasma, factor IX-prothrombin complex
X	Stuart-Prower defect	25	1.5	Plasma, concentrate (some preparations of factor IX)
XI	PTA deficiency	Unknown	3	Fresh-frozen plasma
XII	Hageman defect	Not required	Unknown	Treatment not needed
XIII	Fibrin-stabilizing factor deficiency	2	6	Fresh-frozen plasma
AT III	Antithrombin III deficiency	80	3	Concentrate (AT III-specific)

Uses of heparin (immediate anticoagulant)

1. **Prophylaxis in surgery, MI, CHF, pregnancy** (because it does not cross placenta unlike warfarin), chronic **DIC, warfarin failure.**
2. **Venous thromboembolism** and **pulmonary embolism.**

LMW heparin: MW 3000–7000, **different** anticoagulant profile.

Mech

1. Selectively inhibits factor **Xa** with little effect on **IIa.**
2. Induces **conformational** changes in **AT III** (smaller effect on **aPTT** and **whole blood CT** than unfractionated heparin—UFH).
3. Eno**Xa**prin acts on factor **Xa** only (so, monitor **Xa** rather than aPTT) .
4. Lesser **antiplatelet** action.
5. Not interact with platelet thus not cause thrombocytopenia.

ADR: Lower incidence of **thrombocytopenia** than heparin.

CI: Renal failure.

PK: Has more predictable **dose-response relationship** than heparin.

Bioavailability **70–90%** compared to **UFH (20–30%).** Eliminated by **kidney by first order kinetics.** LMWH and UFH are **equally** efficacious.

Better absorbed after **SC injection** than heparin.

Usual dose: 200 U/kg/day (SC). **Longer t½.**

U: 1. **Prophylaxis of DVT** and **pulmonary embolism.**
2. Treatment of **DVT.**
3. To maintain patency of **cannula** and **shunts** in dialysis.

Heparan sulfate: Heparin like **natural substance** found on cell surface and in intercellular matrix. **Physiological antithrombotic** at the surface of vascular endothelium. **Less potent anticoagulant** than heparin. **Semi-synthetic heparinoids (sulfated mucopolysaccharides)** are potent anticoagulant.

Dextran sulfate: It is **sulfated polymeric sugar 1/7th as potent as heparin** but **duration** of action is **twice.**

Ancrod: It is **enzyme of Malayan pit viper venom.**

Mech: Degrades **fibrinogen** into unstable form of **fibrin** which is taken up by **RE cells** → depleted fibrinogen (**heparin like effect**).

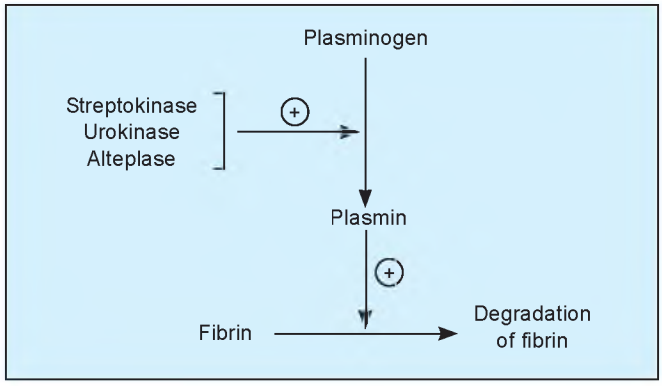
ADR: Bleeding, hypersensitivity, intravascular obstruction on IV injection.

U: 1. 2 U/kg 6 hourly in **DVT** (developing thrombocytopenia and hypersensitivity reaction to heparin).
2. Use of heparin → to initiate therapy.

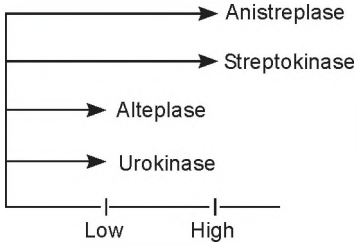
Protamine sulfate: It is **strongly basic LMW protein of sperm of fish.**

Mech

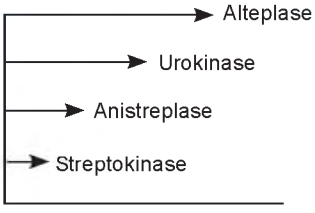
1. Causes **rapid reversal of heparinization** (positively charged molecule that acts by binding negatively charged heparin).
2. **Neutralises** heparin weight for weight (1 mg for every 100 U of heparin).
3. Acts as **weak anticoagulant** in the absence of heparin.



Antigenicity:



Fibrin specificity:



1. **Activators**
   (i) **Extrinsic (available in India)** — USA
   Alteplase (rt-PA), Urokinase, Streptokinase.
   (ii) **Intrinsic**: t-PA, Factor XIIa, kallikrein.

2. **Inhibitors**
   (i) **Extrinsic**: EACA, Aprotinin, Tranexamic acid. — TEA
   (ii) **Intrinsic**: α_2 antiplasmin, α_2 macroglobulin.

3. **Plasmin blocker:** Aminocaproic acid (antidote for fibrinolytics).

Newer fibrinolytics
1. **Anistreplase**
2. **Saruplase**: Recombinant human single chain urokinase type plasminogen activator, fibrin selective, non-pyrogenic, non-antigenic.
3. **Reteplase**: Non-glycosylated mutant of alteplase, 5 times more potent.

PK: Extensively metabolised by **liver. Renal** and **faecal** elimination.
ADR: Bleeding. **CLOPI**dogrel = **CLO**t (Platelet)/Oral Platelet Inhibitor.
IA: Interferes with metabolism of phenytoin, tolbutamide, warfarin, fluvastatin and tamoxifen if taken **concomitantly.**

Lepirudin: It is a **polypeptide** that is highly specific **thrombin blocker.** Produced by **recombinant DNA technology in yeast cells.** It is recombinant form of hirudin (polypeptide of salivary gland of leech) and inhibits thrombin used in heparin-induced thrombocytopenia.

Mech: **One molecule** of lepirudin binds to **one molecule of thrombin,** resulting in blockade of **thrombogenic** activity of thrombin.
Thrombin → IIa receptor
↑(–)
Lepirudin

PK: t½—**1 hr,** Undergoes **hydrolysis, renal** elimination.

ADR: Bleeding

U: HIT (IV)

HIT (heparin-induced thrombocytopenia) **Types I and II and HAT** (heparin-associated thrombocytopenia) are due to heparin use

HIT <
- Type I (nonimmunogenic)
- Type II (immunogenic, platelet count drops by **<50%,** life-threatening)

Antifibrinolytics inhibit plasminogen activation and clot dissolution.
EACA (epsilon aminocaproic acid): It is analogue of amino acid **lysine** and is specific **antidote** of fibrinolytic agents.

Mech: Combines with **lysine binding site of plasminogen** and **plasmin** → unable to bind to fibrin → lysis → **bleeding.**

ADR
1. Hypotension, bradycardia, arrhythmia
2. Myopathy (rarely)

U: Dose 5 gm oral/IV stat + 1 gm hourly **(maximum 30 gm/day)**
1. **Overdose** of fibrinolytic (urokinase/alteplase/streptokinase)
2. **Trauma** and surgical bleeding (prostatectomy in haemophilics)
3. **Menorrhagia,** PPH, abruptio placentae
4. **Recurrent** subarachnoid and GI bleeding
5. **Haematuria** (but causes ureteric obstruction by clots)

Tranexamic acid: 7 times more potent than EACA.

Mech: Binds to **lysine** binding site on plasminogen → inhibits its combination with fibrin.

ADR: 1. **Thrombophlebitis** of injected vein
2. Nausea, vomiting, giddiness
3. **Diarrhoea**