DRUGS AND COAGULATION

(a) ***To classify the anti-coagulants.***

(b) ***To describe the pharmacodynamics and pharmacokinetics of heparin and low molecular weight heparins including their side-effects.***

(c) ***To describe the mode of action and side-effects of protamine.***

(d) ***To describe the pharmacology of warfarin.***

(e) ***To classify and describe the pharmacology of anti-platelet drugs.***

(f) ***To describe the fibrinolytic pathway and outline the pharmacology of the thrombolytic agents.***

(g) ***To outline the pharmacology of antifibrinolytic agents such as epsilon aminocaproic acid, tranexamic acid and aprotinin.***

(A) **<u>Anti-Platelet Drugs</u>**:

> "Anti-platelet agent" → drug that interfere with normal platelet adhesion and aggregation, thus producing anti-thrombotic effect

<u>COX-1 inhibitor</u> (Eg. Aspirin)

Clinical uses	(i) Treat ACS (ii) Prevent CVA (iii) Prevent vascular stent/graft thrombosis
Mechanism of action	Irreversible inhibition of platelet COX-1 (via acetylation) → ↓ TXA2 synthesis → ↓ platelet aggregation and vasoconstriction
Duration of action	- Lasts 10-14 days b/c (i) platelet COX inhibition is irreversible and (ii) platelets cannot regenerate new COX enzyme (as it lacks nuclei), thus new platelets need to be generated - Should be withheld 7 days pre-operatively to ↓ risk of bleeding (but prolonged bleed time dissipates within 48 hrs of cessation)
Pharmacokinetics	- *Absorption* – Given PO → rapidly absorbed within GIT, esp small intestine > stomach - *Distribution* – ↑ protein-binding (85%), esp to albumin; ↓ V_D - *Metabolism* – Rapid hydrolysis by intestinal/hepatic esterases to salicylate (active metabolite), which is conjugated to glycine in liver → forms salicyluric acid - *Excretion* – Aspirin and its metabolites are excreted in urine (Nb. ↑ excretion with ↑ urine alkalinity 2° to "ion trapping") - Elimination t ½ = 15 mins (2-3 hrs for salicylate metabolite)
Side-effects	(1) GI toxicity (gastritis, ulcers, bleeding, anaemia) (2) Prolonged bleeding time → epistaxis, GI bleeding, Etc. (3) Aspirin-induced asthma (4) Hepatic dysfunction (5) Renal dysfunction (6) Reye's syndrome (mainly in children)

<u>Platelet phosphodiesterase inhibitor</u> (Eg. Dipyridamole)

Clinical uses	(i) Dipyridamole + aspirin → used to prevent CVA (ii) Dipyridamole + warfarin → used to prevent prosthetic valve thrombus formation
Mechanism of action	- (i) Inhibits platelet adenosine uptake → ↓ platelet adhesion to vessel walls - (ii) Potentiates endothelial PGI-2 → ↑ vasodilation (incl coronary artery) - (iii) Inhibits platelet phosphodiesterase (at high doses) → ↑ IC cAMP and ↓ Ca^{2+} → ↓ TXA2 → ↓ platelet aggregation > It inhibits platelet adhesion to vessel walls >>> platelet aggregation
Duration of action	Short duration of action → should be ceased 24 hrs pre-operatively to ↓ risk of bleeding
Pharmacokinetics	- Given PO → rapidly absorbed within GIT - Metabolised by liver (via glucuronidation) → excreted via bile - Elimination t ½ = 40 mins
Side-effects	Hypotension (2° to vasodilation)

<u>ADP receptor inhibitor</u> (Eg. clopidogrel, ticlodipine)

Clinical uses	(i) Clopidogrel → used with aspirin to prevent stent thrombosis, and ↓ risk of ACS/CVA in those with vascular disease (ii) Ticlodipine → used to prevent stent thrombosis and ↓ CVA risk in patients where aspirin is ineffective (not used 1st line due to side-effects)
Mechanism of action	- Clopidogrel and ticlodipine (thienopyridine derivatives) are "prodrugs" → need to be metabolised in liver to "active metabolite" - They irreversibly inhibit ADP binding to ADP receptor on platelet surface → prevents activation of GP IIb/IIIa → ↓ platelet activation, aggregation and degranulation
Duration of action	- Lasts 10-14 days b/c (i) platelet ADP receptor inhibition is irreversible and (ii) platelets cannot regenerate new receptors (as it lacks nuclei), thus new platelets need to be regenerated - Should be withheld 7 days (for clopidogrel) or 4 days (for ticlodipine) pre-operatively to ↓ risk of bleeding
Pharmacokinetics	- Given PO → rapidly absorbed in GIT - Both clopidogrel and ticlodipine are "prodrugs" → metabolised by liver to "active" metabolites - These metabolites are then metabolised by liver → form carboxylic acid and glucuronide metabolites that are excreted in urine - Elimination t ½ = 7 days (clopidogrel) and 4 days (ticlodipine)
Side-effects	(1) Prolonged bleeding time → GI bleed, intracranial bleed (2) Neutropaenia (esp with ticlodipine (2%) vs clopidogrel (0.02%) (3) Thrombotic thrombocytopaenic purpura (4) Hepatic dysfunction

Glycoprotein IIb/IIIa receptor antagonists (Eg. Abciximab, tirofiban)

Clinical uses	(i) Treat ACS (in conjunction with heparin therapy) (ii) Used during arterial stenting procedure
Mechanism of action	- Abciximab (monoclonal Ab) has high affinity for the GP IIb/IIIa receptor, while Tirofiban (non-peptide) has moderate affinity for it - They both inhibit platelet GP IIb/IIIa receptor → block final common pathway of platelet aggregation - Note – It does NOT block platelet adhesion or release reaction
Duration of action	- Abciximab → ceased 72 hrs pre-operatively - Tirofiban → ceased 24-72 hrs pre-operatively
Pharmacokinetics	- Given IV only - Abciximab → metabolised by plasma proteases → elimination t ½ 12-24 hrs (although remain bound in circulation for up to 15 days with residual activity) - Tirofiban → cleared renally (65%) and by bile (25%) → elimination t ½ 2-4 hrs
Side-effects	(1) Prolonged bleed time (2) Thrombocytopaenia (3) Allergic reaction

Dextran 40 and Dextran 70:

- Polysaccharides chains containing glucose produced by fermentation of sucrose by bacteria
- Clinical use – Mainly as plasma volume expanders, but also as prophylaxis against peri-operative VTE
- Mechanism of action – (i) ↓ platelet adhesiveness, (ii) inhibition of vWF, (iii) ↓ RBC aggregation (by coating RBC/vascular endothelium), (iv) diluting CFs
- Side-effects – Fluid overload, allergic reactions (incl anaphylaxis), impair cross-matching (due to rouleaux formation), renal failure

Epoprostenol (PGI2):

- Naturally occurring prostaglandin
- Clinical use – Facilitate haemofiltraiton by continuous infusion into extracorporeal circuit
- Mechanism of action – (i) Stimulates adenylyl cyclase → ↑ IC cAMP and ↓ Ca^{2+} → ↓ TXA2 → ↓ platelet adhesion and aggregation; (ii) Fibrinolytic effect also
- Side-effects – Systemic vasodilation (hypotension, tachycardia, facial flushing, headache)

(B) **Anti-Coagulants Drugs**:

> "Anti-coagulant agent" → drug that delays or prevents clotting of blood by direct or indirect actions on coagulation system

(I) Heparins:

(1) Unfractionated heparin:

Overview: Heterogenous mixture of anionic and highly sulphated glycosaminoglycans (variable MWT b/t 3-30 kDa) derived from bovine lung or bovine/porcine GI mucosa

> Note – Heparin is synthesised in the body → found in liver, basophils and mast cells

Clinical uses: (1) Given as IV infusion to treat arterial and venous thromboembolic disease (Eg. PE, DVT, ACS and peripheral arterial occlusion) and DIC
(2) Given S/C to prevent venous thromboembolism
(3) Prime extracorporeal circuits (Eg. HDx, CPB)

> Important to note – Potency of heparin dose is standardised by the "unit" → 1 unit = volume of heparin-containing solution that prevents 1 mL of citrated sheep blood from clotting for 1 hr after addition of 0.2 mL of 1:100 $CaCl_2$

Mechanism of action:

- (1) Binds to antithrombin III (ATIII) and ↑ its inactivation of CF II (thrombin), IX, X, XI and XII by 1000x → it promotes inactivation of CF II (thrombin) and CF X at low doses (on 1:1 ratio), but at higher doses it also inactivates CF IX, XI and XII
- (2) Inhibits thrombin-induced activation of CF V and VII
- (3) Inhibits platelet aggregation

Pharmacokinetics:

Absorption	- Can only be given S/V or IV - Cannot be given PO (due to its ↑ MWT and ↓ lipid solubility) or IM (due to haematoma formation)
Distribution	- Bound to several plasma proteins (Ie. ATIII, albumin, proteases, fibrinogen) due to its –ve charge - It does NOT cross placenta (cf. warfarin) due to its ↑ MWT and ↓ lipid solubility → nil toxic foetal effects
Metabolism and Excretion	- Metabolised by hepatic heparinases → produces depolymerised and less sulphated metabolites with 50% activity → metabolites excreted in urine - Note – Heparin clearance is ↓ with hypothermia (Eg. CPB) and hepatic/renal dysfunction

Monitoring heparin therapy:

- (1) Activated partial thromboplastin time (APTT) → normally 30-35 secs
  - Measures intrinsic system (CF VII, IX, XI, XII) and factors common to both systems
  - Requires phospholipid, surface activator (kaolin) and Ca^{2+} added to citrated blood

  > Important to note → Heparin therapy is aimed at 1.5-2.5x baseline APTT values

- (2) Activated coagulation time (ACT) → normally 90-120 secs
  - Used to monitor heparin and antagonism by protamine (Ie. for CPB)

- Requires mixing whole blood with an activation substance with a large SA (kaolin or celite) → induces clotting cascade → machine measures onset of clot formation

> Important to note – When titrating heparin for CPB → ACT aimed > 300 secs:
> - ACT measures are done (i) pre IV heparin, (ii) 3 mins post-IV heparin, (iii) 30 minutely
> - Dose-response curve (heparin dose on y-axis and ACT on x-axis) can be used to determine heparin doses required for a certain ACT → straight line using "pre IV heparin" and "3 mins post-IV heparin" data points used to extrapolate further heparin dosing for desired ACT
> - There are several factors that impact ACT value → (i) hypothermia, (ii) thrombocytopaenia, (iii) CF deficiencies (esp CF VII, XII and fibrinogen) and (iv) presence of contact activation inhibitors (esp aprotinin)

Adverse effects and issues:

- (1) Haemorrhage (most common)
  - Risk varies with – (i) intensity of anticoagulation needed (Ie. prophylaxis vs therapeutic), (ii) preexisting coagulation defects or comorbid disease (Eg. hepatic and renal disease), (iii) concurrent use of drugs that impact coagulation (Eg. aspirin)
  - Risk minimised by controlling heparin dose based on lab monitoring (APTT or ACT) → Nb. this is easier to do cf. warfarin as heparin onset of effects is faster and its elimination t ½ is shorter
  - Heparin antagonist (Eg. protamine) can be used to promptly reverse heparin
- (2) Heparin-induced thromobocytopaenia (HIT)
  - (i) Type I (non-immune based)
    - Common (30-40%) → mild TCP (platelet count < 100,000 cells/mm^3) occurs within 4 days post-exposure
    - Due to drug-induced platelet aggregation
    - Minimal clinical significance → platelet count normalises within 4 days of ceasing heparin (or even without cessation of heparin)
  - (ii) Type II (immune-mediated)
    - Rare (< 5%) → severe TCP (count < 50,000 cells/mm^3), arterio-venous thrombosis (Eg. PE, CVA) and heparin resistance occur within 4-14 days post-exposure
    - Due to formation of heparin-dependent anti-platelet Ab's (IgG) → trigger platelet aggregation and thrombosis

> Important to note → all patients on heparin should have platelets monitored routinely!

- (3) Allergic reactions
- (4) Hypotension (esp with rapid IV bolus of large doses, such as pre-CPB) → due to ↓ SVR (as heparin causes SM relaxation and vasodilation)
- (5) Others:
  - (i) Displaces alkaline drugs (Eg. propranolol, diazepam) from protein
  - (ii) Alters cell morphology (RBC and WBC)
  - (iii) Prothrombotic tendency (↓ ATIII levels by 66%) with long-term therapy
  - (iv) Osteoporosis
  - (v) Alopecia
  - (vi) ↑ K^+ (due to inhibition of aldosterone secretion, esp in CRF/DM patients and long-term therapy)

(2) <u>Fractionated (LMWT) heparin</u> (Eg. Enoxaparin, dalteparin):

Overview:

- Derived from chemical or enzymatic depolymerisation of unfractionated heparin → produce heterogenous heparin fragments ~ 1/3rd in size (4-8 kDa)

Mechanism of action:
- (1) Binds to antithrombin III (ATIII) but is more effective at inactivating CF X than CF II (thrombin) → 2:1 to 4:1 ratio (cf. 1:1 ratio with unfractionated heparin)
- (2) Less inhibitory effect on platelets (cf. unfractionated heparin)

Differences in clinical effect (cf. unfractionated heparin):
- (1) Superior bioavailability at low doses and more predictable anticoagulant response → due to ↓ protein binding
- (2) Daily dosing → due to longer t ½ β (4-5 hrs)
- (3) No monitoring of effect → does NOT affect PT/APTT results as it works almost entirely on CF X (not measured by either tests)
- (4) ↓ incidence of HIT syndrome
- (5) Similar risks of bleeding → need to cease 12 hrs pre-operatively
- (6) Effects not fully reversed by protamine (only reversal of 65% of effect)

(3) Fondaparinux:

Overview	Synthetic anticoagulant → penta-saccharide unit that make up active site of heparin that binds ATIII
Clinical uses	Used to prevent/treat DVT/PE → low HITS risk
Mechanism of action	Forms complex with ATIII → inactivates CFXa only (and has no direct activity against thrombin)
Pharmacokinetics	Given S/C → 100% renally excreted unchanged (t ½ β 15 hrs)

(4) Danaproid:

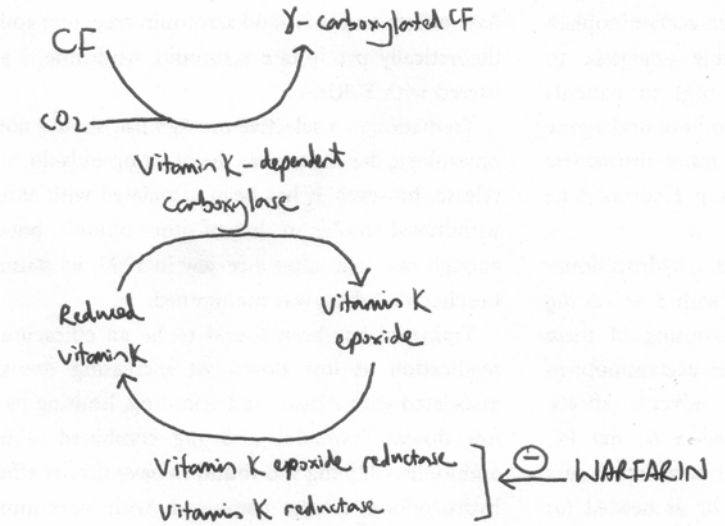
Overview	GAGs derived from porcine intestinal mucosa → mixture of heparin, dermatan and chondroitin sulphate
Clinical uses	Used to prevent/treat DVT/PE → low HITS risk
Mechanism of action	LMWT heparinoid compound binds ATIII → ↓ fibrin formation
Pharmacokinetics	100% renally excreted

(II) Oral anticoagulants (Warfarin):

Chemical structure: Coumarin derivative → 4-hydroxycoumarin nucleus with carbon group substitution at 3-position

Clinical uses: (1) Prophylaxis and treatment of venous thromboembolism
(2) Prophylaxis of systemic thromboembolism with AF, prosthetic heart valves, rheumatic heart disease

Mechanism of action:
- Vitamin K-dependent CFs (CF II, VII, IX, X and protein C/S) are synthesised in the liver and activated by γ-carboxylation of their glutamatic acid residues → the activation process is linked to (and dependent on) the oxidation of "reduced vitamin K" to "vitamin K epoxide"
- Warfarin competitively inhibits two enzymes – (i) Vitamin K epoxide reductase and (ii) Vitamin K reductase → blocks reduction of "vitamin K epoxide" to "reduced vitamin K", which prevents vitamin K-dependent CFs from being γ-carboxylated → thus, warfarin ↓ synthesis of functional vitamin K-dependent CFs → anti-coagulant effect



Important to note → delayed onset of effects of warfarin (effect peaks at 36-72 hrs) reflects (i) onset of inhibition of vitamin K-dependent CFs, (ii) elimination t ½ of preformed CFs, and (iii) "procoagulant" phase produced by faster inhibition of protein C/S (cf. other CFs)

Pharmacokinetics:

Absorption	Oral only → rapid and complete absorption from GIT (↑ bioavailability)
Distribution	- ↑ protein binding (95%), esp to albumin - Crosses placenta readily (causes foetal adverse effects), BUT does NOT cross into breast milk
Metabolism and Excretion	- Completely metabolised in the liver (by [O] and reduction) into inactive metabolites, which are conjugated with glucuronic acid and excreted in bile and urine - Almost nil unchanged drug excreted in bile or urine - Elimination t ½ 24-36 hrs

Monitoring warfarin therapy:

- (i) Prothrombin time (PT) → normally 10-14 secs
  - Measures extrinsic system (CF VII) and factors common to both systems → sensitive to 75% of vitamin K-dependent CFs (II, VII and X only)
  - Requires tissue thromboplastin (brain extract) and Ca^{2+} added to citrated plasma
- (ii) International normalised ratio (INR) → normally 1-1.5
  - INR is the ratio of "sample PT" to "control international standard PT"
  - INR is used to standardise PT values b/ different labs → this is b/c commercial PT reagents at different labs vary in responsiveness to warfarin-induced ↓ in CFs

Important to note → warfarin therapy is aimed at INR 2.0-3.5 (depending on clinical situations)

Important to note → managing warfarin therapy preoperatively:

- (i) With major surgery, warfarin should be discontinued 1-3 days preoperatively to allow PT and INR to ↓ to 20% of normal range (Nb. warfarin may be continued with minor surgery). Should anticoagulation be continued for clinical reasons, a transition to short-acting IV heparin can be made
- (ii) INR/PT should be checked pre-operatively to ensure they are at acceptable levels
- (iii) Warfarin reversal can be expedited with IV 1-5 mg vitamin K, 1-2 units FFP, recombinant CF VIIa or prothrombin complex concentrate
- (iv) Warfarin should be recommenced 1-7 days post-operatively

Adverse effects and issues:

- (1) Haemorrhage → risk dependent on (i) intensity of anticoagulant (esp if INR > 3), (ii) underlying disorders (Ie. PUD, CVA), (iii) concurrent use of antiplatelet agents (Eg. aspirin)
- (2) Initial pro-coagulant phase (due to initial inhibition of protein C/S) → need to cover this period with supplemental anti-coagulation with heparin
- (3) Foetal toxicity → warfarin easily crosses the placenta and cause (i) teratogenicity (esp in 1st TM), (ii) CNS damage (any TM), (iii) foetal haemorrhage (any TM)

> Note – Warfarin is NOT excreted in breast milk → thus safe with breast feeding!

- (4) Titration of warfarin therapy
  - INR fluctuates due to several factors → (i) dietary changes (Ie. leafy green vegetables are rich in vitamin K; sick patients lack vitamin K intake), (ii) comorbidities (Eg. liver disease, elderly), (iii) poor medication compliance, (iv) drug interactions (see below)
  - There is a delay in titrating warfarin dose on INR → ↑ INR is not rapidly corrected with ↓ dose due to long t ½ β of warfarin; ↓ INR is not rapidly corrected with ↑ dose due to delayed onset of therapeutic effect
- (5) Skin necrosis (due to extensive venous thrombosis in subcutaneous fat)
- (6) Several drug interactions:
  - Drugs ↑ bleeding with warfarin due to:
    - (i) Impaired coagulation/platelet aggregation (Eg. NSAIDs, aspirin)
    - (ii) Displaced warfarin plasma protein binding (Eg. NSAID, phenytoin)
    - (iii) Inhibition of warfarin metabolism (Eg. cimetidine, amiodarone, phenylbutazone, EtOH, omeprazole)
  - Drugs ↓ bleeding with warfarin due to:
    - (i) Induction of warfarin metabolism (Eg. barbiturates, rifampicin, carbamezapine)
    - (ii) Impaired warfarin absorption (Eg. cholestyramine)
    - (iii) Replacement of CFs (Eg. FFP, vitamin K, recombinant CF VII)

(III) <u>Direct thrombin inhibitors</u>:

Mechanism of action: Direct inhibition of thrombin (free and clot-bound)

Clinical uses:
* Used as an anticoagulant in patients with heparin resistance or HITS
* Unlike heparin, they are not associated with HITS, have similar or lower bleeding risks, and do not require monitoring/dose adjustments

Types of agents:

(1) <u>Recombinant hiuridin</u> (Eg. lepirudin, bivalirudin)
- Synthetic peptide agent (65 a.a) → available IV only
- Renally excreted (100%)
- Needs to be ceased 8 hrs pre-operatively

(2) <u>Ximelagatran</u>
- Oral agent given as a "prodrug" → converted by liver to melagatran
- Renally excreted (100%) with t ½ β 3-5 hrs
- Needs to be ceased 24 hrs pre-operatively

(3) <u>Argatroban</u>
- Arginine derivative → available IV only
- Extensive hepatic clearance
- Needs to be ceased 4-6 hrs pre-operatively

> Important to note – No antidote exists for these agents → excess bleeding or reversal of effect can be achieved by use of FFP, recombinant CFVIIa, or prothrombin complex concentrates (or use of HDx for recombinant hirudin only)

(C) **Protamine**:

Overview:	Strongly alkaline (contains 66% Arg), polycationic and LMWT protein found in salmon fish sperm
Clinical uses:	(1) Specific antagonist of heparin's anticoagulant effect (2) Formulated with insulin to prolongs its effects
Preparation:	Clear colourless solution (10 mg/ml) of protamine sulphate for IVI
Dosing:	Determined by (i) amount of circulating heparin to be neutralised (generally 1 mg for every 100 U heparin still circulating), (ii) time elapsed since heparin given, and (iii) ACT → maximum 50 mg given in any 10 min period to minimise adverse effects
Mechanism of action:	Protamine (+ve charged alkaline protein) combines with heparin (–vely charged acidic protein) to form a stable and inactive complex devoid of anticoagulant activity → this complex is rapidly cleared by the reticulo-endothelial system (within 20 mins)

Adverse effects:

(1) Cardiovascular effects:
- Triggered by histamine release causing peripheral vasodilation → (i) facial flushing, (ii) hypotension (2° to ↓ SVR), (iii) reflex tachycardia and ↑ C.O. (2° to ↓ BP). It may also have direct –ve cardiac inotropic effects (?debatable)
- This tends to occur with (i) rapid IVI (< 5 mins) and (ii) direct injection into RA (as protamine given peripherally or into LA becomes diluted in peripheral blood before reaching the lungs, where protamine is thought to induce histamine release)

(2) Pulmonary effects:
- Protamine-heparin complex triggers (i) complement activation, and (ii) secretion of TXA-2 and 5-HT → causes pulmonary vasoconstriction (pulmonary HTN, RVF and pulmonary oedema) and bronchoconstriction → V/Q mismatching/hypoxaemia
- This may be blunted by aspirin or NSAID (Eg. indomethacin)

(3) Allergic reactions (including anaphylaxis and anaphylactoid reactions):
- Risk factors include patients with – (i) chronic use of protamine-containing insulin preparations and (ii) previous fish allergies (Nb. vascectomised or infertile male with antisperm Ab are generally not at risk)

> Important to note – Patients with known protamine allergy and require reversal of heparin-induced anticoagulation → consider:
> - (i) Pre-treating with H1RB/H2RB and slowly infusing protamine
> - (ii) Complete avoidance of protamine → await spontaneous dissipation of heparin
> - (iii) Administer an alternate heparin antagonist (if available)

(4) Anticoagulation
- Protamine has an "intrinsic" anticoagulant effect due to its interactions with platelets and fibrinogen → this tends to occur when high doses of protamine given (Ie. levels in excess of heparin present in plasma) or when protamine is given alone

(D) **Thrombolytic Agents**:

> "Thrombolytic agent" → drug that enhance body's fibrinolytic system by acting on plasminogen activators, which ↑ conversion of plasminogen into plasmin

Streptokinase:

Overview: Enzyme produced by group C β-haemolytic streptococci

Clinical uses: Restore circulation through occluded arterial vessel → treat acute AMI, ischaemic CVA, PE, or acute peripheral arterial occlusion

Mechanism of action: * Binds non-covalently to plasminogen to form a "streptokinase-plasminogen activator complex" → ↑ conversion of plasminogen to plasmin → ↑ fibrinolysis
* It is NOT fibrin-specific → causes systemic fibrinolysis

Pharmacokinetics: Given IV → hepatic clearance of streptokinase-plasminogen complex (t ½ β = 20 mins)

Adverse effects and issues:

- (1) Severe haemorrhage (esp spontaneous ICH)

> Important to note → contraindications to fibrinolysis include active internal bleeding, trauma/surgery in last 2/52, recent head injury or intracerebral aneurysm, haemorrhage CVA, uncontrolled HTN, Etc.)

> Important to note → bleeding 2° to thrombolytic agents are treated with FFP, cryoprecipitates, platelets and antifibrinolytic agents (see below)

- (2) Reperfusion hypotension and arrhythmias (only during AMI therapy)
- (3) Immunological issues
  - (i) Allergic reactions (fever, anaphylaxis) due to reaction with anti-streptococcal Ab's from previous streptococcal infections
  - (ii) Loading dose needs to be given to neutralise any anti-streptococcal Ab's from previous streptococcal infections
  - (iii) Streptokinase is very antigenc → produces ↑ Ab titres up to 1 year post-exposure, thus streptokinase CANNOT be reused (need to consider other agent)

Urokinase:

- Previously extracted from human urine but now made form renal cell cultures
- Clinical uses, mechanism of action and pharmacokinetics similar to streptokinase
- Similar adverse effects/issues as streptokinase, EXCEPT it is NOT antigenic

Alteplase (rt-PA):

Overview: Recombinant DNA-derived version of naturally occurring glycoprotein

Clinical uses: Same as streptokinase/urokinase

Mechanism of action: * Glycoprotein that is activated when bound to fibrin (clot) only → then selectively converts fibrin-bound plasminogen to plasmin to cause fibrinolysis
* It is fibrin-specific → causes less systemic fibrinolysis (cf. streptokinase)

Pharmacokinetics: Given IV → hepatic metabolism (t ½ β < 5 mins)

Adverse effects and issues:

- (1) Severe haemorrhage (as streptokinase)
- (2) Minimal hypotensive/arrhythmic effects with AMI therapy
- (3) Minimal allergic/immunological issues

(E) **Antifibrinolytic Drugs**:

Aprotinin:

Class	Naturally-occurring anti-fibrinolytic → single chain polypeptide (58 a.a.) derived from bovine lung tissue
Clinical uses	- (i) Treat bleeding 2° to hyperplasminaemia - (ii) Minimise operative bleeding (esp with cardiopulmonary bypass, TURP, liver transplantation)
Mechanism of action	Proteolytic enzyme inhibitor that acts on trypsin, plasmin and tissue kallikrein → forms reversible enzyme-inhibitor complex that inactivates free plasmin → ↓ clot lysis
Pharmacokinetics	- Given IV only - Highly protein-bound (to A1AGP) - Renal metabolism to peptides/a.a.'s → excreted - Elimination t ½ 1-2 hrs
Adverse effects	(1) Allergic reactions (incl anaphylaxis) (2) Prothrombotic (3) Prolongs paralysis due to SCh

Tranexamic acid:

Class	Synthetic anti-fibrinolytic → lysine derivative
Clinical uses	↓ bleeding 2° to excess fibrinolysis (esp cardiopulmonary bypass, prostatectomy, DIC, thrombolysis toxicity, haemophiliacs)
Mechanism of action	Competitive inhibition of plasminogen conversion to active plasmin → ↓ fibrin (clot) lysis
Pharmacokinetics	- Given PO (35% bioavailability) or IV - Minimal metabolism → 95% renal excretion unchanged - Elimination t ½ 1-2 hrs
Adverse effects	(1) Prothrombotic (2) GI side-effects

Aminocaproic acid:

Class	Synthetic anti-fibrinolytic → lysine derivative
Clinical uses	- (i) Treat excessive operatively bleeding (esp cardiac surgery) - (ii) Treat thrombolysis toxicity
Mechanism of action	Forms reversible complex with plasminogen → ↓ conversion to active plasmin → ↓ fibrin (clot) lysis
Pharmacokinetics	- Given PO or IV - Renal metabolism - Elimination t ½ 2 hrs
Adverse effects	(1) Prothrombotic (2) Organ inflammation (esp hepatitis, appendicitis) (3) Fevers