Pharmacology

CHAPTERWISE NOTES

Drugs Affecting Blood and Blood Formation

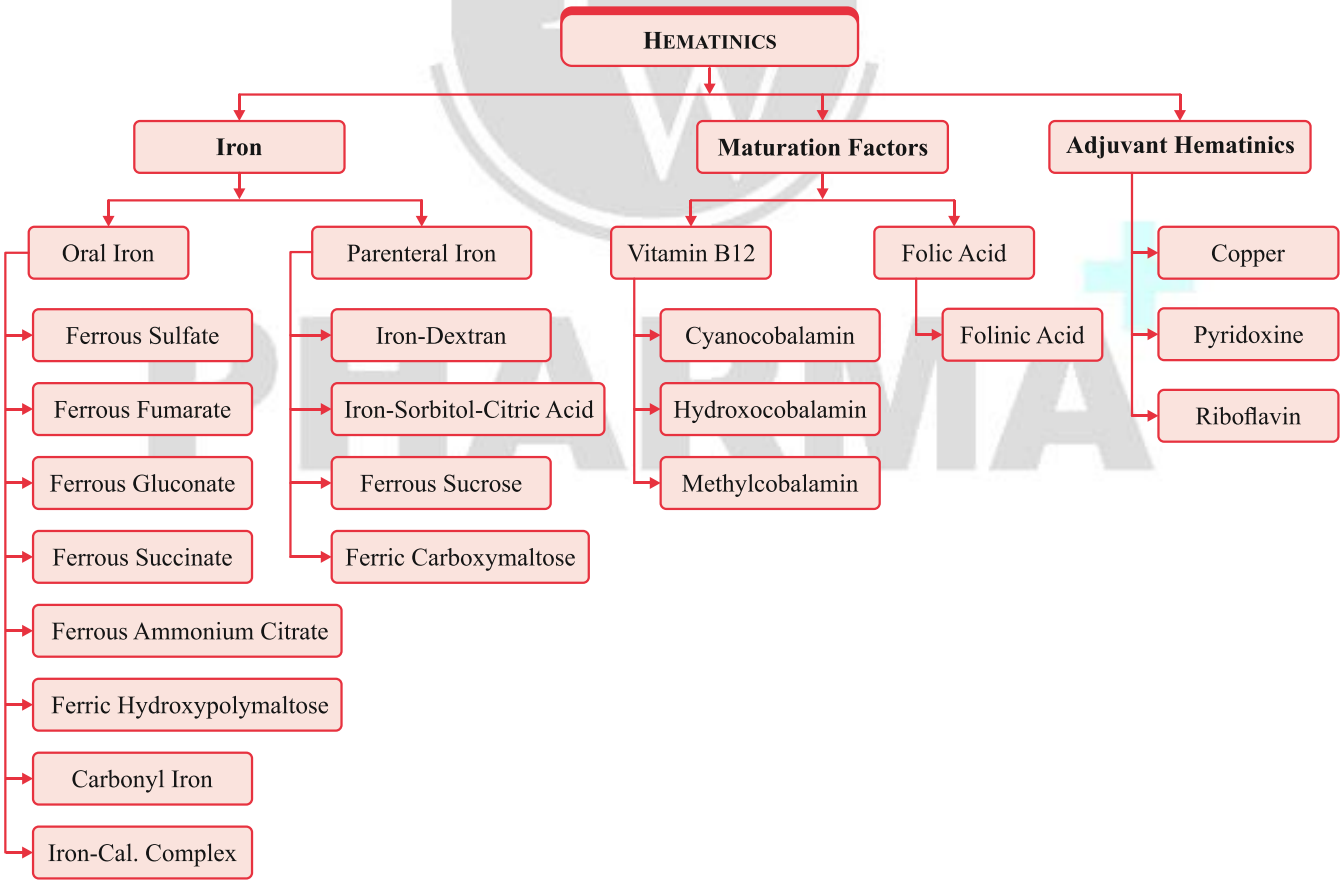
PHARMA

PHARMACOLOGY

Drugs Affecting Blood & Blood Formation

HAEMATINICS AND ERYTHROPOIETIN

- **Haematinics** are substances essential for the **formation of blood**, primarily used for the treatment of **anaemias**.
- **Causes of Anaemia:**
  - Anaemia results from an imbalance between **red blood cell (RBC) production and destruction**, caused by:
    - **Blood loss** – either **acute or chronic**.
    - **Impaired red cell formation due to:**
      - **Deficiency of essential factors** like **iron, vitamin B12, folic acid.**
      - **Bone marrow depression** (hypoplastic anaemia) or **erythropoietin deficiency**.
    - **Increased destruction of RBCs** – seen in **haemolytic anaemia**.

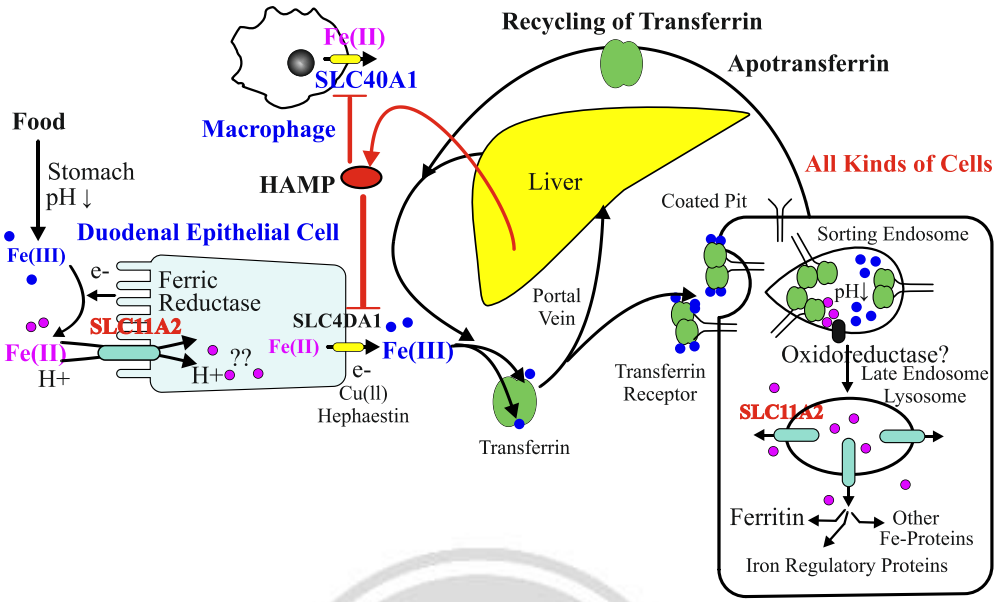


➤ Iron

- ✷ **Essential element** for haemoglobin synthesis and cellular functions.
- ✷ **Total body iron: 2.5-5 g**, with **62% in haemoglobin, 25% stored as ferritin/haemosiderin, 7% in myoglobin**, and **6% in enzymes (cytochromes, catalases, etc.)**.
- ✷ More iron in men (50 mg/kg) than women (38 mg/kg).
- ✷ **Daily Requirement:**
  - **Adult male:** 0.5–1 mg/day.
  - **Adult female (menstruating):** 1–2 mg/day.
  - **Pregnancy (last 2 trimesters):** 3–5 mg/day.
  - **Infants:** 60 µg/kg/day.
  - **Children:** 25 µg/kg/day.
- ✷ **Dietary Sources:**
  - **Rich sources :** Liver, Egg yolk, Dry beans, Wheat germ, Oyster, Yeast.
  - **Moderate sources :** Meat, Fish, Spinach, Banana, Apple.
  - **Poor sources :** Milk and root vegetables.

Drug/Form	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Ferrous Sulfate	20–32% elemental iron; absorbed in upper intestine; better on empty stomach	Dissociates in stomach, ferrousion absorbed via DMT1 in mucosal cells	Iron deficiency anemia, prophylaxis in pregnancy/ infancy	Gastric irritation, metallic taste, constipation, nausea, bloating	Antacids, tetracyclines, food may reduce absorption
Ferrous Gluconate	12% elemental iron, lower iron content, oral absorption like sulfate			Generally milder GI side effects	
Ferrous Fumarate	33% elemental iron, tasteless, less water soluble			Similar to ferrous sulfate	
Colloidal Ferric Hydroxide	50% elemental iron, oral drops	Ferric form converted to ferrous before absorption	Pediatric iron supplementation	Stains teeth, GI effects	Absorption reduced by antacids, phosphates

Carbonyl Iron	~75% bioavailability of ferrous sulfate; slow release from intestines	Metallic iron slowly absorbed in intestine	Iron deficiency anemia	Better gastric tolerance, mild GI effects	Fewer due to slow release
Ferric Carboxymaltose (IV)	High dose (up to 1000 mg); slow release; taken up by RES	Iron released from complex, used for Hb synthesis	CKD, iron deficiency, postpartum anemia	Mild: nausea, pain, rash; Rare: anaphylaxis, hypotension	Do not co-administer oral iron within 5 days
Iron Isomaltoside-1000 (IV)	High single dose (up to 2g); t½: 20–32 hrs; slow release	Taken up by RES, iron released gradually	CKD, IBD, heart failure, rapid replenishment	Mild GI symptoms, very low hypersensitivity	Not established; minimal interaction risk
Ferrous Sucrose (IV)	100–200 mg/day; not suitable for total dose infusion; safe profile	Utilized via RE uptake and release	CKD-related anemia, when oral iron not tolerated	Low hypersensitivity, headache, mild GI upset	No oral iron 5 days before/after
Iron Dextran (IV/IM)	50 mg/ml; long-acting, IM/IV; needs dose calculation	Taken up by RE cells, iron slowly released	Severe iron deficiency, noncompliance to oral iron	Anaphylaxis, local pain, skin pigmentation, sterile abscess	Risk with other IV drugs; requires emergency setup
Oral Complexes (e.g. iron aminoate, ferric polymaltose)	Variable iron content, generally better tolerated due to low content	Similar to ferrous salts	Anemia, prophylactic use	Milder GI side effects	Lower interaction profile due to lower iron levels



- **Absorption is better on an empty stomach** but causes more side effects.
- **Vitamin C enhances** iron absorption by reducing ferric to ferrous.
- **Food, antacids, phosphates, phytates, and tetracyclines** impair iron absorption.
- **Parenteral iron** is reserved for intolerance, malabsorption, or severe deficiency.
- **Ferric carboxymaltose and iron isomaltoside** are currently preferred for parenteral therapy due to safety and convenience.
- **Total body iron regulation** includes mucosal block, ferritin storage, and transferrin recycling.
- **Acute Iron Poisoning:**

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Desferrioxamine	Poor oral absorption; given IM or IV; dose: 0.5–1 g IM or 10–15 mg/kg/h IV; max 75 mg/kg/day	Chelates free iron forming ferrioxamine, which is excreted in urine	Acute iron poisoning	Hypotension, allergic reactions, flushing, pulmonary complications	Avoid with nephrotoxic drugs; iron chelate may enhance bacterial infections
DTPA	Administered IV; rapid clearance via kidneys	Chelates metal ions including iron	Alternative chelator of desferrioxamine is unavailable	Renal toxicity, electrolyte imbalance	May chelate other essential metals (e.g., zinc, calcium)
Calcium Edetate	Given IV/IM; excreted	Binds divalent and trivalent	Used as an alternative	Nephrotoxicity, hypocalcemia	Avoid concurrent use

	unchanged in urine	metals to form stable, non-toxic complexes excreted renally	chelator in iron poisoning		with nephrotoxic agents
BAL (British Anti-Lewisite)	Given IM; distributed widely, metabolized in liver, excreted in urine	Forms toxic complexes with iron	Contraindicated in iron poisoning due to toxicity of iron-BAL complex	Hypertension, tachycardia, nausea, neurotoxicity	Not to be used with iron or in G6PD deficiency
Diazepam	Oral/IV; hepatic metabolism via CYP450; long half-life	Enhances GABAergic activity at GABA-A receptors	Control convulsions in iron poisoning	Sedation, respiratory depression, hypotension	Additive CNS depression with alcohol, opioids, or other sedatives
Copper Sulphate	Oral; absorbed in small amounts; excess excreted in bile	Acts as a cofactor in haeme synthesis	Used only if copper deficiency is documented	GI irritation in excess, metallic taste	Antagonized by high zinc intake
Pyridoxine (Vitamin B6)	Oral/IV; converted to active form (PLP) in liver	Cofactor in haeme synthesis; restores function impaired by isoniazid/ pyrazinamide	Sideroblastic anemia (esp. drug-induced)	Neuropathy in large doses (>200 mg/day chronically)	Isoniazid and hydralazine interfere with pyridoxine metabolism

VITAMIN B12

- **Vitamin B12** (cyanocobalamin and hydroxocobalamin) are cobalt-containing compounds essential for blood formation.
- **Discovered through the study of pernicious anaemia**, where gastric mucosal atrophy led to B12 malabsorption.
- Only **microorganisms** synthesize B12; plants and animals acquire it from them.
- **Dietary Sources:**

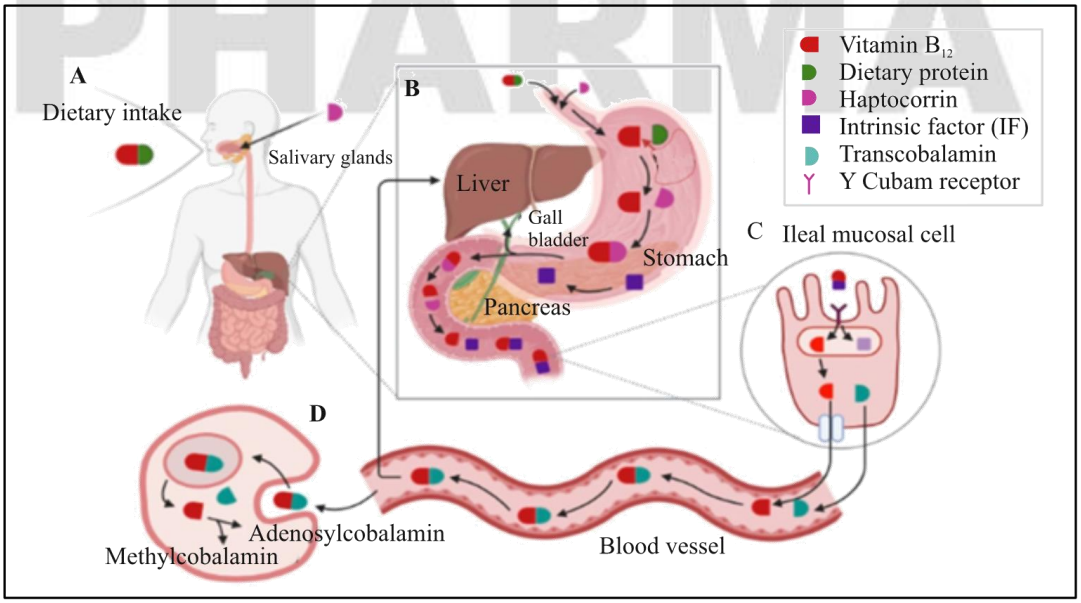
- **Animal sources:** Liver, kidney, fish, egg yolk, meat, cheese.
- **Vegetable source:** Legumes (pulses), through bacteria in root nodules.
- **Human colonic bacteria** produce B12, but it is **not absorbed from the colon**.

✶ **Daily Requirement:**

- Adults: **1-3 µg/day**.
- Pregnancy & lactation: **3-5 µg/day**.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Cyanocobalamin	Water-soluble; poorly retained; less protein binding; absorbed via intrinsic factor-dependent active transport; excreted in bile with enterohepatic circulation	Converts homocysteine to methionine (via methyl-B12); essential for DNA synthesis, methylation reactions, and normal myelin synthesis	Treatment and prevention of B12 deficiency-Megaloblastic anaemia-Supportive therapy in neuropathy	Very safe; rare allergic reactions; IV use can cause anaphylactoid reactions (due to sulfites)	Absorption reduced by neomycin, colchicine, metformin, alcohol, and PPIs
Hydroxocobalamin	More protein-bound than cyanocobalamin; better retained; slowly excreted; preferred for parenteral use	Same as cyanocobalamin; also binds cyanide forming cyanocobalamin — used in cyanide detox	Preferred for parenteral treatment of B12 deficiency-Tobacco amblyopia-Cyanide poisoning (massive doses)-Maintenance after IM loading	Similar to cyanocobalamin; rare allergic or anaphylactoid reactions	Same as cyanocobalamin
Methylcobalamin	Active coenzyme form; given orally or IM;	Directly involved in methionine synthesis and myelin formation	Used in peripheral neuropathies (diabetic,	Very safe; adverse effects are rare	None significant

	good bioavailability; 0.5–1.5 mg/day dose commonly used	(via S-adenosylmethion i ne synthesis); bypasses metabolic activation steps	alcoholic)- Neurological symptoms of B12 deficiency- General nutritional supplementatio n		when used as monotherapy
Folic Acid (added adjunctively)	Oral; well absorbed from small intestine	Works with B12 in DNA synthesis and one-carbon metabolism	- Added to correct coexisting folate deficiency- Improves megaloblastic changes	High doses may mask B12 deficiency, allowing neurologic damage to progress	Phenytoin, sulfasalazine, methotrexate may antagonize folate effect
Iron (added adjunctively)	Oral or parenteral; absorbed from duodenum; stored as ferritin	Required for haemoglobin synthesis	To correct concurrent iron deficiency anaemia	GI irritation, constipation, nausea with oral use; hypersensitivit y with parenteral forms	Antacids, tetracyclines, and certain foods reduce absorption

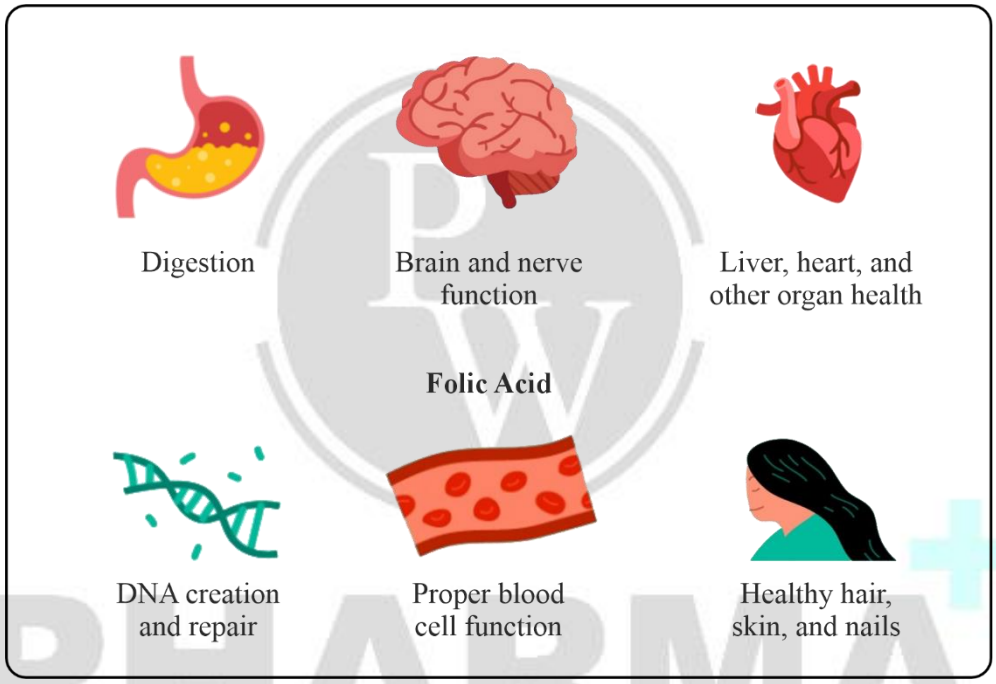


➤ FOLIC ACID

- **Folic acid** (Pteroyl Glutamic Acid) is a yellow crystalline compound, insoluble in water, but its sodium salt is water-soluble.
- In **vitamin B12 deficiency**, folic acid must **never be used alone**.
- Folate deficiency manifests faster than B12 deficiency due to smaller body stores.
- Routine **pregnancy supplementation** with folic acid prevents **neural tube defects**.
- **Sources:**
  - **Dietary sources:**
    - Liver, green leafy vegetables (spinach), eggs, meat, yeast.
- **Daily Requirement:**
  - **Adult requirement:** <0.1 mg/day.
  - **Recommended dietary allowance:** 0.2 mg/day.
  - During **pregnancy, lactation,** or high metabolic states, the requirement rises to **0.8 mg/day**.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Folic Acid	Poorly water-soluble (acid form); sodium salt is water-soluble- Absorbed in upper small intestine after deconjugation- Stored in liver (5–10 mg body stores)- Undergoes enterohepatic circulation- Excess excreted in urine	Inactive as such; reduced to DHFA and THFA- THFA acts as a coenzyme in one-carbon transfers (e.g., thymidylate, methionine, purine synthesis)- Critical for DNA synthesis and cell division	1. Megaloblastic anaemia due to: • Nutritional deficiency • Pregnancy/ lactation • Malabsorption syndromes • Hemolytic anaemia 2. Folate deficiency during antiepileptic therapy 3. Prophylaxis in pregnancy to prevent neural tube defects	Oral use is nontoxicRare sensitivity reactions with injection	Large doses may reduce efficacy of phenytoin and other anticonvulsants- Should not be given alone in B12 deficiency—may worsen neurological symptoms due to masking effect
Folinic Acid (Leucovorin, 5-formyl THFA)	Active form; bypasses need for DHFR enzyme- Given	Directly participates in one-carbon transfer	1. Methotrexate toxicity (rescue therapy)2. Citrovorum factor	Rare sensitivity or allergic reactions when	Antagonizes methotrexate toxicity- Enhances 5-FU

	parenterally- Good tissue penetration	reactions- Bypasses dihydrofolate reductase inhibition- Enhances inhibition of thymidylate synthase when used with 5-FU	rescue in high-dose methotrexate therapy3. Enhances efficacy of 5-fluorouracil (5-FU) in cancer therapy4. Not used for routine folate deficiency (too costly)	given by injection	efficacy- No significant adverse interaction with other drugs when used as prescribed

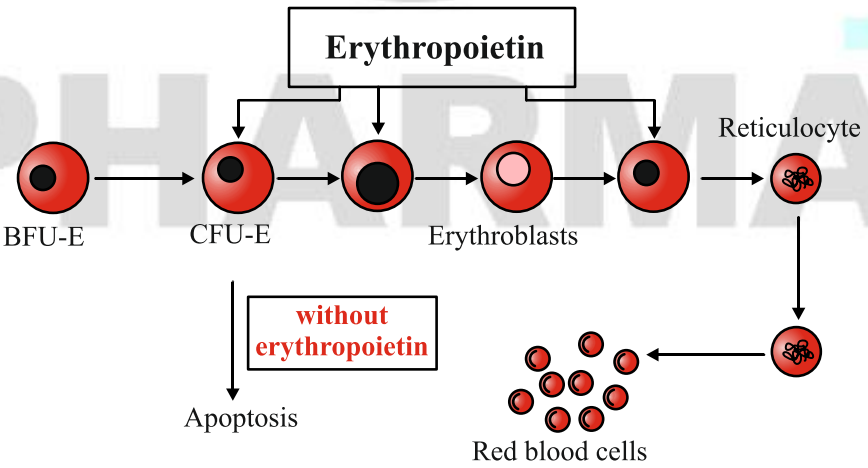


ERYTHROPOIETIN

- **Erythropoietin (EPO)** is a **sialoglycoprotein hormone** with a molecular weight of 34,000.
- It is produced by **peritubular cells in the kidney**.
- EPO is essential for normal **erythropoiesis** (red blood cell formation).
- **Anaemia** and **hypoxia** stimulate EPO secretion.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Epoetin α / β (Recombinant	IV or SC route- Plasma t½: 6–10	Binds to EPO receptors (JAK-STAT	1. Anaemia of chronic renal failure	- Hypertension or hypertensive crises	- Iron therapy must be co-administered

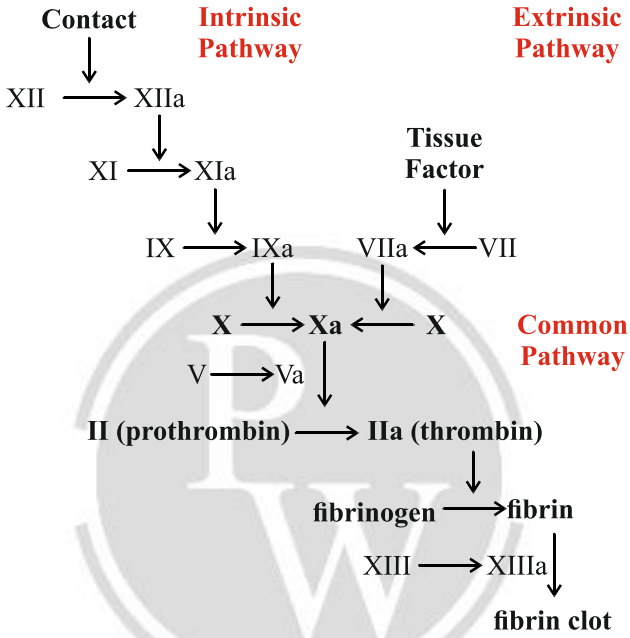
Human Erythropoietin)	hours- Action lasts several days- SC more efficient (30% dose reduction possible)- Requires iron supplementation	pathway) on erythroid progenitor cells → stimulates proliferation, Hb synthesis, maturation, and reticulocyte release	2. Chemotherapy-indu ced anaemia 3. Anaemia in AIDS (on zidovudine) 4. Preoperative blood building (autologous transfusion)	- Thromboembolism (AV shunts) - Seizures (rare) - Flu-like symptoms (2–4 hrs) - Overcorrection increases mortality risk	(oral or IV)- Poor response in nutritional or marrow-related anaemias- Use with caution in uncontrolled hypertension
Darbepoetin α	- Hyperglycosylated analogue of epoetin- SC or IV- t½: 24–36 hours (longer-acting)- Once weekly dosing	Same as epoetin: Binds to EPO receptor, activates JAK-STAT → stimulates erythropoiesis in dose-dependent manner	Same indications as epoetin: 1. Chronic renal failure anaemia 2. Chemotherapy-indu ced anaemia 3. Others as above	Same as epoetin: dose-related increase in blood viscosity, thrombotic risk, flu-like syndrome, hypertension	- Same as epoetin- Careful titration required to avoid Hb overshoot (target 10–11 g/dL, not normal Hb)



BFU-E: Burst-Forming Unit-Erythroid
CFU-E: Colony-Forming Unit-Erythroid

DRUGS AFFECTING COAGULATION, BLEEDING AND THROMBOSIS

- **Haemostasis** refers to the arrest of blood loss, involving interactions between:
  - Injured vessel wall
  - Platelets
  - Coagulation factors
- **Coagulation Cascade:**



- **Laboratory Tests**
  - **aPTT (Activated Partial Thromboplastin Time):**
    - Assesses intrinsic and common pathways.
  - **PT (Prothrombin Time):**
    - Assesses extrinsic and common pathways.

Pathway	PT	aPTT
Intrinsic	Normal (12-14S)	Prolonged
Extrinsic	Prolonged	Normal (26-32S)
Common	Prolonged	Prolonged

- **Key Factors:**
  - Most clotting factors circulate as **inactive zymogens**.
  - They are activated by **proteolysis**, triggering the next factor in the cascade.
- **Role of Thrombin:**
  - **Thrombin** plays a central role by:
    - Cleaving fibrinogen to **fibrin**.

- ➢ Activating upstream factors (Factors XI, VIII, V), amplifying the cascade.
- ➢ Activating **platelets**, enhancing clot formation.

✶ **Anti-coagulation Mechanisms:**

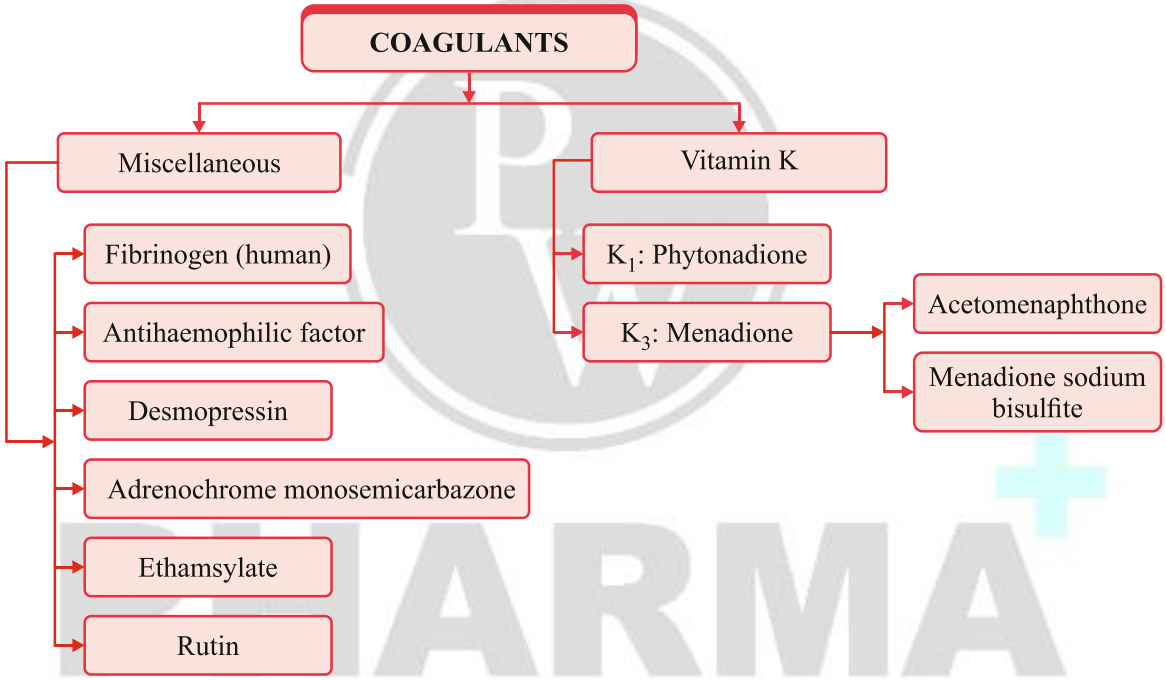
- ○ **Antithrombin, Protein C, Protein S, Antithromboplastin,** and the **Fibrinolysin System**:
  - ➢ Oppose excessive clotting.
  - ➢ Maintain blood flow while allowing local haemostasis at injury sites.

➢ COAGULANTS

✶ **Coagulants** are substances that promote blood coagulation, primarily used in **haemorrhagic states**.

✶ In addition to blood products, certain drugs can also restore haemostasis.

✶ These include agents that supply specific **clotting factors** or influence **platelet function, fibrin formation**, or **capillary integrity**.



Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Vitamin K₁ (Phytonadione)	Fat-soluble; absorbed in jejunum (active transport); requires bile salts; metabolized	Cofactor for γ-carboxylation of glutamate residues in clotting factors II, VII, IX, X	- Vit K deficiency (dietary, malabsorption, obstructive jaundice) - Prolonged antibiotic use -	Rare allergy (oral/i.m.); anaphylactoid reaction (i.v.)	High doses reduce warfarin response for 7–10 days

	in liver; excreted in bile & urine	(→ Ca^{2+} binding & coagulation cascade)	Newborn prophylaxis - Reversal of oral anticoagulant overdose		
Vitamin K_3 (Menadione)	Water-soluble; absorbed by passive diffusion; not stored; metabolized in liver		Rarely used due to toxicity	Dose-dependent hemolysis (esp. in G6PD deficiency & neonates) - Kernicterus risk	Contraindicated in neonates; not effective in warfarin reversal
Acetomenaphthone	Orally active; used in vitamin K deficiency		Bleeding disorders	Minimal (specific data limited)	Not specified
Menadione Sodium Bisulfite	Water-soluble; oral		Vitamin K deficiency (older formulations)	Haemolysis, kernicterus (similar to K_3)	Avoid in neonates and G6PD deficiency
Fibrinogen (FIBRINAL)	I.V. use; 0.5 g/bottle	Replaces fibrinogen to aid clot formation	Hemophilia, AHG deficiency, afibrinogenemia	Risk of thrombosis, allergic reaction	Blood product precautions (cross-matching, viral transmission)
Antihaemophilic Factor (Factor VIII)	I.V. use; short half-life (1–2 days)	Replaces deficient Factor VIII	Hemophilia A	Allergic reaction, inhibitor formation	Antibodies to factor VIII may develop
Desmopressin	I.V. or nasal; synthetic vasopressin analog	Releases Factor VIII & vWF from endothelium	Mild hemophilia A, von Willebrand disease	Water retention, hyponatremia	Caution with SSRIs, NSAIDs (SIADH risk)

Adrenochrome Monosemicarbazone	Oral/i.m.; 1–5 mg	Reduces capillary fragility; unclear MOA	Epistaxis, haematuria, wound bleeding	Limited data	Efficacy and interactions uncertain
Rutin	Oral; 60 mg BD–TDS	Plant glycoside; may reduce capillary bleeding	Capillary fragility-related bleeding	Uncertain	Taken with vitamin C to enhance effect
Ethamsylate	Oral/i.v.; 250–500 mg	Improves platelet adhesion; reduces capillary bleeding	Menorrhagia, epistaxis, hematuria (unproven)	Nausea, rash, headache, hypotension (i.v.)	Not antifibrinolytic; avoid with anticoagulants without supervision

➤ LOCAL HAEMOSTATICS (STYPTICS)

✶ **Local haemostatics (styptics)** are substances applied directly to a bleeding site to stop bleeding, particularly useful on **oozing surfaces** such as:

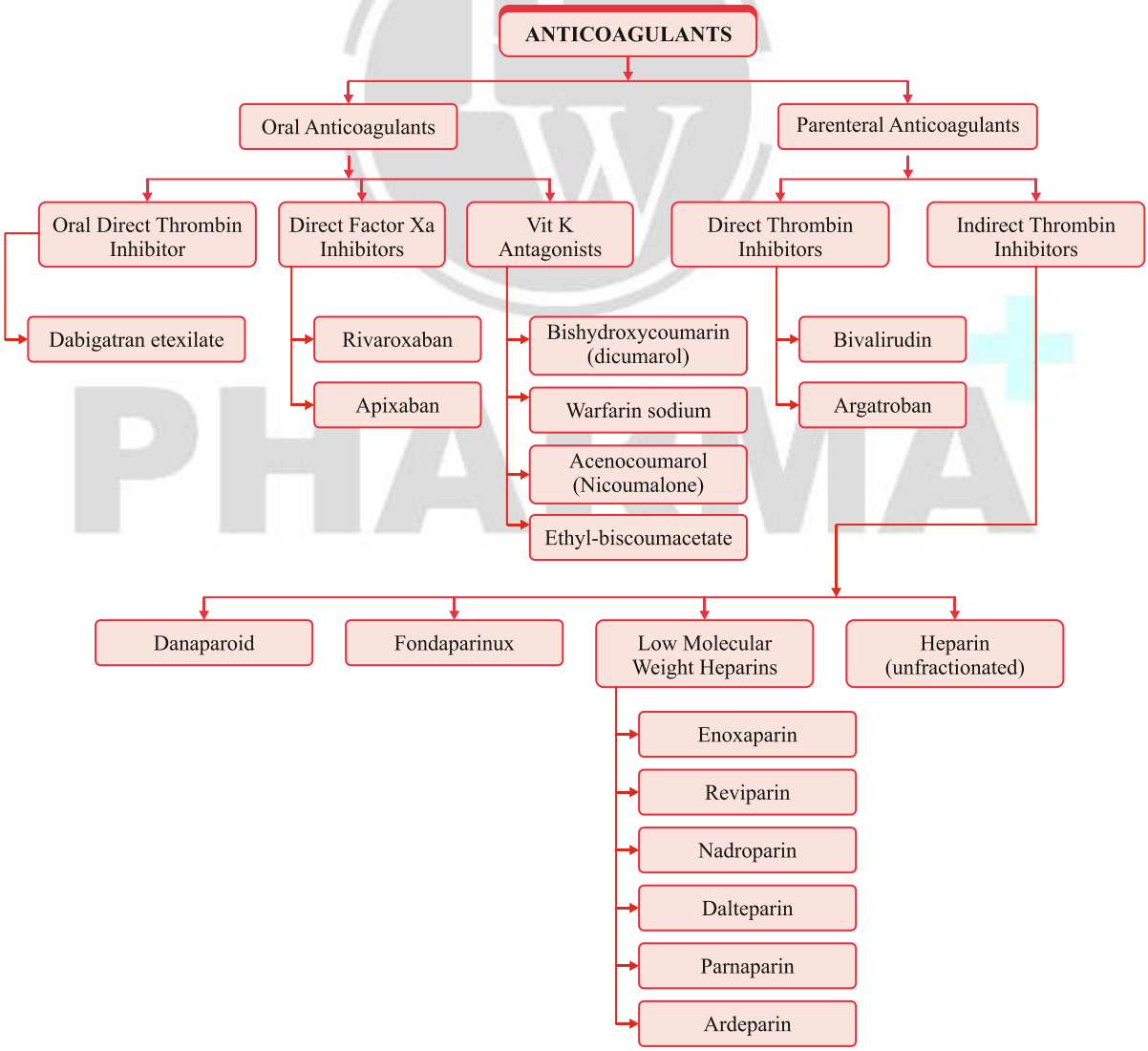
- Tooth sockets
- Abrasions

Drug/Agent	Drug/Agent	Mechanism of Action	Therapeutic Uses	Side Effects
Fibrin (sheet or foam)	Absorbed in 1–4 weeks when left in situ; no significant systemic absorption	Provides meshwork that activates clotting mechanism	Control of bleeding from oozing surfaces, abrasions, tooth sockets	Minimal; no foreign body reaction when absorbed
Gelatin foam	Absorbed in 1–4 weeks	Mechanical support for clot formation	Local bleeding control in surgical wounds or abrasions	Minimal; rare foreign body reaction
Oxidized cellulose	Absorbed in 1–2 weeks	Provides surface for platelet adhesion and clot formation	Used in surgical wounds, abrasions	May delay wound healing if not absorbed properly
Thrombin (bovine origin)	Topical application only; not absorbed systemically	Converts fibrinogen to fibrin locally	Bleeding control in haemophiliacs, surgical sites	Risk of hypersensitivity (from animal source)

Adrenaline (0.1% sol.)	Rapid onset; short duration when applied locally; minimal systemic absorption	Vasoconstriction via α1 receptors	Local bleeding (e.g., tooth socket, epistaxis)	Local irritation, systemic effects if absorbed (↑BP, tachycardia)
Tannic acid	Topical use; negligible systemic absorption	Astringent; precipitates proteins and contracts tissues	Minor bleeding: bleeding gums, piles	Local irritation, tissue damage on prolonged use
Metallic salts (e.g., alum)	Topical use; minimal systemic absorption	Astringent; protein precipitation leading to vasoconstriction and haemostasis	Bleeding gums, minor abrasions	Local irritation, allergic reactions

ANTICOAGULANTS

✶ These are drugs used to reduce the coagulability of blood.



PHARMA

Heparin

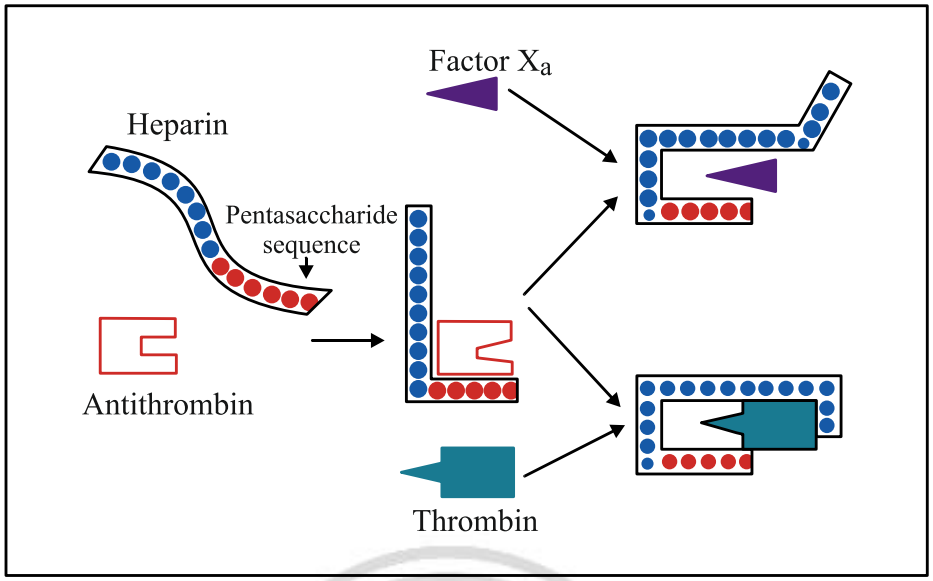
- Heparin is a mixture of mucopolysaccharides with a molecular weight of 10,000-20,000.
- It is strongly acidic and found in mast cells, particularly in the lung, liver, and intestine.
- Commercially sourced from ox lung and pig intestinal mucosa.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Heparin (Unfractionated)	Not absorbed orally (due to high ionization)- Given IV (immediate effect) or SC (effect in ~60 min)- Variable SC bioavailability- Does not cross BBB or placenta- Metabolized in liver by heparinase- t½: ~1 hr (dose-dependent; prolonged in cirrhosis, renal failure; shorter in PE)- Excreted in urine	Activates antithrombin III (AT-III), which inhibits clotting factors IIa (thrombin), Xa, IXa, XIa, XIIa, XIIIa- Requires heparin's long chain (scaffold) and specific pentasaccharide sequence for action- Low doses: mainly inhibit Xa- High doses: inhibit Xa + IIa- Also releases lipoprotein lipase → clears plasma lipids- High doses inhibit platelet aggregation	Prevention and treatment of DVT, PE- Anticoagulation during cardiac surgeries, dialysis- Acute coronary syndromes- Anticoagulant of choice in pregnancy- Low-dose SC heparin: for postoperative DVT prophylaxis (except neurosurgery)- Topical use in superficial thrombophlebitis (QPS)	**1. Bleeding** (dose-dependent; more common from deep sites) **2. Heparin-induced thrombocytopenia (HIT)** – mild to severe (immune-mediated form can cause thrombosis) **3. Alopecia** (reversible) **4. Osteoporosis** (with prolonged high doses) **5. Hypersensitivity** – urticaria, fever, rigor, anaphylaxis **6. Elevated liver enzymes**	Aspirin/Antiplatelets: ↑ bleeding risk- Oral anticoagulants: additive effect- Do not mix with penicillin, tetracyclines, hydrocortisone, noradrenaline in same syringe/infusion- Incompatible with blood counts, complement fixation tests (alters RBC/WBC shapes)- Avoid in patients with history of HIT, bleeding disorders, severe HTN, neurosurgery, GI ulcers, etc.

- **Low Molecular Weight Heparins (LMWH):**
  - LMWH are derived by fractionating standard heparin into smaller molecules (MW 3000-7000).
  - They exhibit a different anticoagulant profile, mainly inhibiting **Factor Xa** rather than **Factor IIa (thrombin)**.

Drug (Example)	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Enoxaparin (Clexane)	- MW: 3,000–7,000- SC bioavailability: 70–90%- t½: 4–6 hours (monoexponential)- Once daily SC dose possible- Primarily renal excretion- Not affected by aPTT- Dosing: 20–40 mg SC OD	- Binds to antithrombin III- Inhibits factor Xa (more selectively than IIa)- Does not form scaffold for thrombin inhibition- Minimal effect on aPTT	- DVT/PE prophylaxis and treatment- Unstable angina, MI- Patency of cannula/shunts in dialysis- Pre- and postoperative thromboprophylaxis	- Lower risk of bleeding than UFH- Thrombocytopenia (less common)- Rare allergic reactions- Less risk of osteoporosis	- Antiplatelet drugs (e.g., aspirin, clopidogrel) → ↑ bleeding risk- NSAIDs → ↑ bleeding- Effects not fully reversed by protamine- Avoid in renal failure
Reviparin (Clivarine)	- Prefilled syringe: 13.8 mg/0.25 ml- Once daily SC for 5–10 days- Similar PK to enoxaparin				
Nadroparin (Fraxiparine, Cardioparin)	- SC administration- Multiple strengths available- Dose: individualized based on indication				
Dalteparin (Fragmin)	- t½: ~4–6 hours- Dose: 2500 IU OD (prophylaxis)100 IU/kg 12 hr or 200 IU/kg OD (treatment)		- DVT prophylaxis & treatment- ACS (UA, MI)		
Parnaparin (Fluxum)	- SC dose: 0.6 ml OD- Pre-filled syringes: 3200–6400 IU		- DVT prophylaxis & treatment- ACS (UA, MI)		
Ardeparin (Indeparin)	- SC dose: 2500–5000 IU OD		Same as Enoxaparin		

- **Caution:**
  - ➢ LMWH is less effective than UFH in **catheter thrombosis prevention** and is only **partially reversed by protamine sulfate**.



Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Fondaparinux (Arixtra)	- Synthetic pentasaccharide- SC bioavailability: **100%** - Peak effect: ~2 hours- **t½: 17 hours** (long-acting)- **Excreted unchanged by kidneys** - No metabolism- SC dose OD (2.5–10 mg)- No aPTT monitoring required	- Binds to **antithrombin III (AT-III)** - Causes irreversible conformational change- **Selectively inhibits factor Xa - Does not inhibit thrombin (IIa)**	**- DVT/PE prophylaxis and treatment - Acute coronary syndrome (ACS)** when no immediate intervention planned	**- Less thrombocytopenia** than LMWH- **Bleeding risk lower - Minimal osteoporosis risk -** Contraindicated in **renal failure**	**- Other anticoagulants or antiplatelets** → ↑ bleeding risk- **Avoid in renal impairment -** No reversal agent readily available
Danaparoid	- Heparan sulfate mixture- Derived from **pig gut mucosa** - Less potent anticoagulant than heparin- Used in special cases	- Indirect factor Xa inhibitor via AT-III- Does not act on thrombin- Less effect on platelet function	**Heparin-induced thrombocytopenia (HIT)** - Alternative to heparin in sensitive patients	- Rare bleeding- Low immunogenicity - Not for general use	- Anticoagulant effect may be potentiated by antiplatelet drugs- Use caution with NSAIDs, SSRIs

Heparin Antagonist

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Protamine Sulfate	**- Low molecular weight basic protein -** Obtained from **fish sperm -** Administered **IV-** Dose: **1 mg per 100 units of heparin -** Inject slowly at **≤5 mg/min**	**- Neutralizes heparin** by ionic binding- Forms a stable inactive complex- **Fully reverses UFH - Partially reverses LMWH - No effect on fondaparinux -** In absence of heparin, acts as a **weak anticoagulant**	**Heparin-induced bleeding - Rapid reversal of heparin** after surgery (e.g., cardiac/vascular)- Less often used in routine bleeding due to short action of heparin	**- Histamine release →** flushing, breathing difficulty- **Hypersensitivity reactions** (especially in fish allergy)- **Weak anticoagulant effect** if used alone- **Must be given slowly** to avoid adverse effects	**- Antagonizes heparin - Does not reverse fondaparinux -** Partial effect on **LMWH -** Interacts with **platelets and fibrinogen** (prolongs clotting if overdosed)- Caution with **allergy-prone** individuals

Direct Thrombin Inhibitors (DTIs)

- Unlike heparin, these drugs bind **directly to thrombin**, inhibiting its activity.
- They do **not require Antithrombin III (AT-III)** for action.
- DTIs **inactivate both circulating and clot-bound thrombin**.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Bivalirudin	- Synthetic 20 amino acid peptide- Short t½: ~25 min- Cleared by proteolysis & renal excretion- IV bolus + infusion- Not effective in renal failure without dose adjustment	**- Direct thrombin inhibitor (DTI) -** Binds **catalytic + substrate recognition sites** of thrombin- Inhibits **free and clot-bound thrombin - Does not require AT-III**	- Anticoagulation in **PCI for STEMI - Unstable angina/NSTEMI** when PCI is planned- Preferred in **patients at risk of HIT**	- Bleeding- Headache- Back pain- Hypotension	- No interaction with **protamine** (not reversed by it)- No specific **antidote** - Used with **antiplatelets** (aspirin, clopidogrel, GPI inhibitors)

Argatroban	- Synthetic non-peptide DTI- t½ ~45 min- Cleared by liver- Suitable for renal impairment- IV bolus + infusion	- Reversibly binds to **catalytic site of thrombin** only- Directly inhibits thrombin (independent of AT-III)	**- HIT prophylaxis & treatment -** Anticoagulation during **PCI** in HIT patients or high risk cases	- Bleeding- Requires INR monitoring during transition to warfarin	**- INR is prolonged,** caution needed when transitioning to **warfarin** - No reversal agent- May interact with **other anticoagulants** if overlapped

Vitamin K Antagonist

- First described in 1924 when cattle developed a hemorrhagic disease after feeding on spoiled sweet clover hay.
- The causative agent, **bishydroxycoumarin**, was identified in 1939.
- Clinical use began in 1941.
- **Warfarin**, initially used as a rat poison, was later found safe for human use and is now the principal coumarin oral anticoagulant.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Warfarin (racemic mix)	- Rapid & complete oral absorption - 99% protein bound - Crosses placenta & into milk - S-warfarin more potent, metabolized by CYP2C9 - R-warfarin less potent, metabolized by CYP1A, 3A4 - Undergoes enterohepatic circulation	Inhibits **Vitamin K epoxide reductase (VKOR)** → ↓ regeneration of active Vit K → ↓ γ-carboxylation of clotting factors II, VII, IX, X, Protein C & S	- Prophylaxis/treatment of DVT, PE - Post-MI, atrial fibrillation, prosthetic valves	- Bleeding (most common & serious) - Cutaneous necrosis - Teratogenic (foetal warfarin syndrome)	**Enhanced effect**: - Broad-spectrum antibiotics - Aspirin, NSAIDs - Phenytoin, sulfonamides (displace warfarin) - CYP inhibitors: cimetidine,

Dicumarol (Bishydroxycoumarin)	- Slow, unpredictable absorption - Dose-dependent metabolism - Poor GI tolerance		Rarely used now due to better Alternatives	- Bleeding - Poor GI tolerance	amiodarone, metronidazole **Reduced effect**: - CYP inducers: barbiturates, rifampin - Oral contraceptives – Griseofulvin
Ethyl Biscoumacetate	- Rapid, brief action - Occasionally used to initiate therapy - Difficult to maintain steady levels		Occasionally used for rapid onset	- Bleeding	
Acenocoumarol (Nicoumalone)	- Oral absorption - Parent drug t½: 8 hrs - Active metabolite extends effect to ~24 hrs - Acts faster than warfarin	VKOR inhibition → ↓ Vit K recycling → ↓ clotting factor activation	- Alternative to warfarin - DVT, PE, atrial fibrillation	- Bleeding - Generally well tolerated	

➤ Direct Factor Xa Inhibitors

- ✶ These are newer oral anticoagulants that directly inhibit activated Factor Xa.
- ✶ They have been introduced to overcome the limitations of warfarin (slow onset, narrow therapeutic range, need for frequent monitoring, and numerous drug interactions).

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Rivaroxaban	-Oral, peak effect in 3–4 hrs - t½: 7–11 hrs - Metabolized & partly excreted unchanged in urine - Once daily dosing	**Direct Factor Xa inhibitor** Inhibits thrombin generation by blocking activated factor Xa	-Prophylaxis of VTE after knee/hip surgery (10 mg OD) - Treatment of DVT/PE: 15 mg BD × 3 weeks → 20 mg OD -Stroke prevention in AF - Prophylaxis in ACS (2.5 mg with aspirin/clopidogrel)	-Bleeding Nausea Hypotension - Tachycardia - Edema	-Fewer than warfarin - Avoid in severe renal impairment - Interactions possible with CYP3A4 & P-gp modulators

Apixaban	-Oral bioavailability: 85% - Peak effect in ~3 hrs - t½: ~12 hrs - Partially metabolized (CYP3A4), excreted via feces & urine - Twice daily dosing	**Direct Factor Xa inhibitor**	-VTE prophylaxis post knee/hip surgery (2.5 mg BD) - Stroke prevention in AF (5 mg BD) - DVT/PE treatment: 10 mg BD × 7 days → 5 mg BD	-Bleeding Nausea	-Avoid in hepatic or significant renal impairment - Interacts with CYP3A4 inducers/inhibitors
General Class: NOACs (Factor Xa/Thrombin Inhibitors)	-Rapid onset & offset - Short half-lives - Fixed dosing, predictable kinetics - No INR monitoring needed	-Direct inhibition of **Factor Xa or Thrombin** (depending on drug)	-AF, DVT, PE - VTE prophylaxis post surgery - ACS (specific agents only)	-Lower risk of bleeding than warfarin	-Fewer than warfarin - Risk with CYP3A4 or P-gp modulators for some agents No antidote (for most)

- **Advantages of Newer Oral Anticoagulants (Direct Factor Xa Inhibitors and Direct Thrombin Inhibitors):**
  - Rapid onset and offset.
  - Short half-life.
  - No routine laboratory monitoring is required.
  - Fixed dosing.
  - Antithrombotic efficacy is comparable or superior to warfarin.
  - Lower bleeding risk.
  - Fewer drug interactions compared to warfarin.
- **Limitations:**
  - No widely available **reversal agent** (unlike warfarin, which can be reversed with vitamin K).
  - **Renal clearance dependency** makes them **unsuitable for severe kidney disease**.
  - More expensive compared to warfarin.

➤ Oral Direct Thrombin Inhibitor

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Dabigatran Etexilate	-Oral prodrug → converted to dabigatran - Onset: within 2 hours - Oral bioavailability: low but consistent - Excreted via kidney - t½ ~14 hrs, duration ~24 hrs - Dosing: → 110 mg OD for VTE prophylaxis → 75 mg OD in elderly (>75 yrs) → 150 mg BD for stroke prevention in AF	**Direct Thrombin Inhibitor** Reversibly binds to thrombin's catalytic site and inhibits fibrin formation	-Prevention of VTE after hip/knee surgery -Prevention of stroke & embolism in AF (nonvalvular) - Alternative to warfarin in eligible patients	- **Bleeding** (most important) - **Dyspepsia** (frequent) - **Hepatobiliary disorders** (occasional)	-Interacts with **P-gp inhibitors** (e.g., verapamil, amiodarone) → requires dose reduction - **No interaction** with CYP3A4 drugs

✶ **Antidote- Idarucizumab** (monoclonal antibody) is available for dabigatran reversal.

FIBRINOLYTIC DRUGS

✶ **Fibrinolytic drugs (thrombolytics)** are used to **dissolve thrombi/clots** in occluded blood vessels, especially in acute conditions like myocardial infarction (MI), pulmonary embolism (PE), and stroke.

✶ They work by **activating the body's natural fibrinolytic system**, converting plasminogen to **plasmin**, the enzyme that breaks down fibrin clots.

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Streptokinase (Stk)	From β-hemolytic Streptococci - Not fibrin specific - Antigenic - Requires loading dose	Forms complex with plasminogen →converts to plasmin (non-selective)	STEMI (now rarely used) - DVT - PE - Peripheral arterial occlusion (limited use now)	Bleeding - Hypersensitivity (anaphylaxis, fever) - Hypotension – Arrhythmias	Avoid repeated use (antibody neutralization) - Additive bleeding with anticoagulants or antiplatelets
Urokinase	From human urine/kidney cells - Non-fibrin specific - Out of use	Directly activates plasminogen to plasmin (non-selective)	Previously used in DVT, PE - Not preferred due to newer agents	Bleeding – Hypotension	Additive bleeding risk with anticoagulants

Alteplase (rt-PA)	Recombinant tPA - t½: 4–8 min - Moderately fibrin-specific - Requires slow IV infusion	Converts fibrin-bound plasminogen to plasmin → Clot-specific fibrinolysis	STEMI - Ischemic stroke (within 3–4.5 hrs) - PE - DVT - Peripheral arterial occlusion	Bleeding (0.5–5%) -Mild hypotension - Fever – Nausea	Additive effect with aspirin, heparin - Contraindicated with active bleeding, recent stroke, etc.
Reteplase	Deletion mutant of rt-PA - Longer t½: 13–16 min - Less fibrin selective than alteplase - Given as double bolus	Same as alteplase (less specific): activates plasminogen → plasmin Leads to thrombus lysis	STEMI - PE - Used when bolus administration is preferred	Bleeding - Hypotension	Heparin, aspirin coadministered - Adjust dose in hepatic/renal dysfunction
Tenecteplase	Mutant rt-PA - Highest fibrin selectivity - Longest t½ - PAI-1 resistant - Single IV bolus	Fibrin-specific plasminogen activation → localized clot dissolution	STEMI (preferred for ease of use) - PE	Bleeding (lower non-cerebral bleed risk in ASSENT-2) - Similar cranial bleed risk to others	Synergistic effect with aspirin/heparin - Avoid in high-risk bleeding conditions

- **Common Interactions:**
  - Additive bleeding risk with **antiplatelet drugs (aspirin, clopidogrel)** and **anticoagulants (heparin, warfarin)**
  - Avoid in patients with **recent surgery, trauma, stroke, or uncontrolled hypertension**
- **Contraindications:**
  - Intracranial hemorrhage history, recent stroke/head injury, bleeding disorders, active bleeding, uncontrolled HTN, etc.

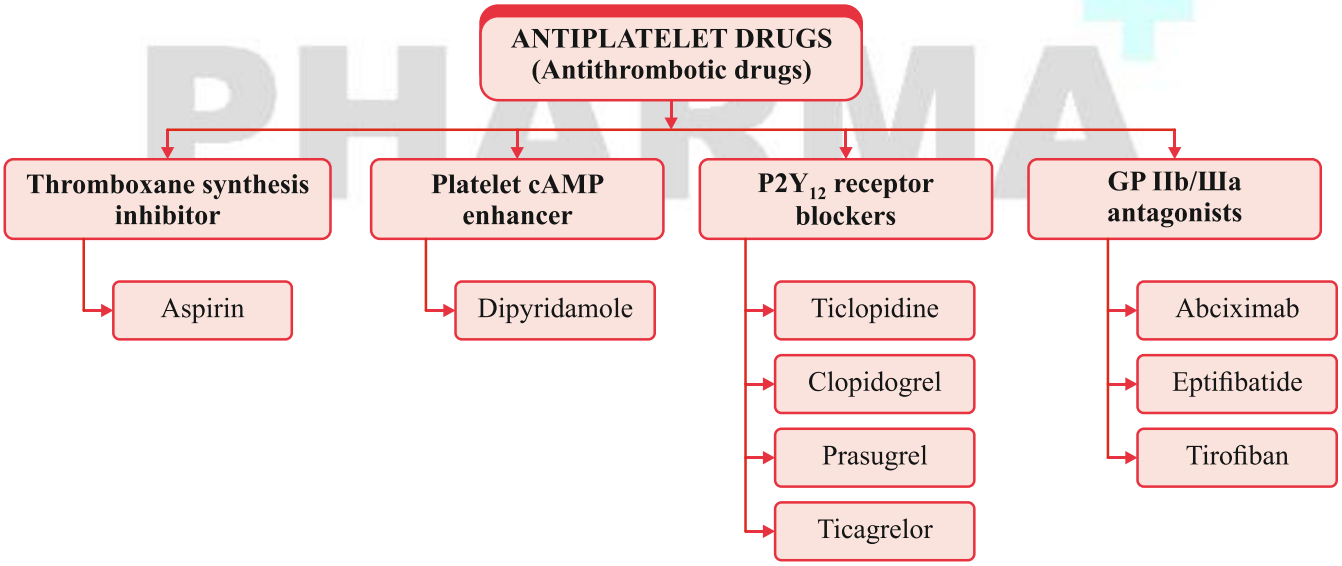
➤ Antifibrinolytic Drugs

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Epsilon Amino Caproic	Lysine analogue -Active orally and IV Excreted by kidney -	Binds to lysine-binding sites on plasminogen	Antidote to fibrinolytic drugs (streptokinase, alteplase, etc.) - Hyperplasminaemia	Intravascular thrombosis - Bradycardia, hypotension (if rapid IV) -	Risk ↑ in renal impairment (due to unlysed clots)

Acid (EACA)	Large dose needed	and plasmin → prevents their binding to fibrin → inhibits fibrinolysis	bleeding - Adjunct in hemophilia (tooth extraction, surgery, trauma)	Ureteric obstruction - Rare myopathy	- Additive prothrombotic effect with other antifibrinolytics
Tranexamic Acid	Lysine analogue -7× more potent than EACA Oral and IV (slow) use - TDS dosing	Same as EACA: Binds lysine site on plasminogen → prevents fibrin binding → blocks fibrinolysis	Bleeding due to fibrinolytics - Cardiopulmonary bypass, tonsillectomy, prostate surgery - Tooth extraction in hemophiliacs - IUCD-induced menorrhagia - Epistaxis, hyphema, peptic ulcer	Nausea, diarrhoea - Thromboembolism (rare) - Disturbed color vision - Thrombophlebitis (IV site)	Prothrombotic drugs ↑ risk - Avoid in active thrombosis or DIC unless benefits outweigh risks

ANTIPLATELET DRUGS

- Antiplatelet drugs, also known as antithrombotic drugs, interfere with platelet function and are primarily used for preventing thromboembolic disorders.
- They are more effective in arterial thrombosis, whereas anticoagulants are preferred for venous thrombosis.



Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Aspirin	-Absorbed from GI tract - Metabolized by liver - Excreted by kidney - Low doses: 75–150 mg/day	Irreversibly inhibits COX-1 → suppresses TXA2 formation → inhibits platelet aggregation	-CAD - Secondary prevention post-MI -Stroke prevention -ACS - Prevent reocclusion after stent placement	-GI irritation, ulcers - Bleeding - Tinnitus (overdose)	- Anticoagulants (↑ bleeding) - NSAIDs (reduce efficacy) Methotrexate (↑ toxicity)
Dipyridamole	-Rapid absorption - Metabolized by liver - Excreted by kidney	Inhibits phosphodiesterase →↑ cAMP → potentiates PGI2, inhibiting platelet aggregation	-Stroke prevention with aspirin Post-surgery thromboembolism - Prosthetic heart valves	-Nausea, dizziness, headache - GI upset, flushing - Hypotension	-Warfarin (enhances effects) - Antiplatelet drugs (synergistic effects)
Ticlopidine	-Absorbed well - Metabolized by liver Excreted by kidneys	Inhibits P2Y12 ADP receptor → prevents ADP-induced platelet aggregation	-Stroke prevention - Secondary prevention of MI - Prophylaxis in PCI (synergistic with aspirin)	-Neutropenia, thrombocytopenia -Diarrhoea, nausea Hemolysis, jaundice	-CYP450 inhibitors (e.g., omeprazole) Other antiplatelet drugs (↑ bleeding risk)
Clopidogrel	-Prodrug (activated by CYP2C19) - Absorbed well - Excreted via liver and kidneys	Irreversibly blocks P2Y12 ADP receptor → inhibits ADP-induced platelet aggregation	-ACS - Prevent stroke and MI recurrence - PCI with or without stent placement - Peripheral vascular disease	-Bleeding Diarrhoea, dyspepsia - Rare neutropenia, thrombocytopenia	-CYP2C19 inhibitors (e.g., omeprazole) - Anticoagulants, aspirin (↑ bleeding risk)
Prasugrel	-Prodrug Rapid absorption - Activated	Irreversibly blocks P2Y12 ADP receptor → stronger and	-ACS, particularly STEMI - PCI with or without	-Bleeding, including major - Hyperlipidemia - Risk of	-CYP2C19 inhibitors (reduced activation) -

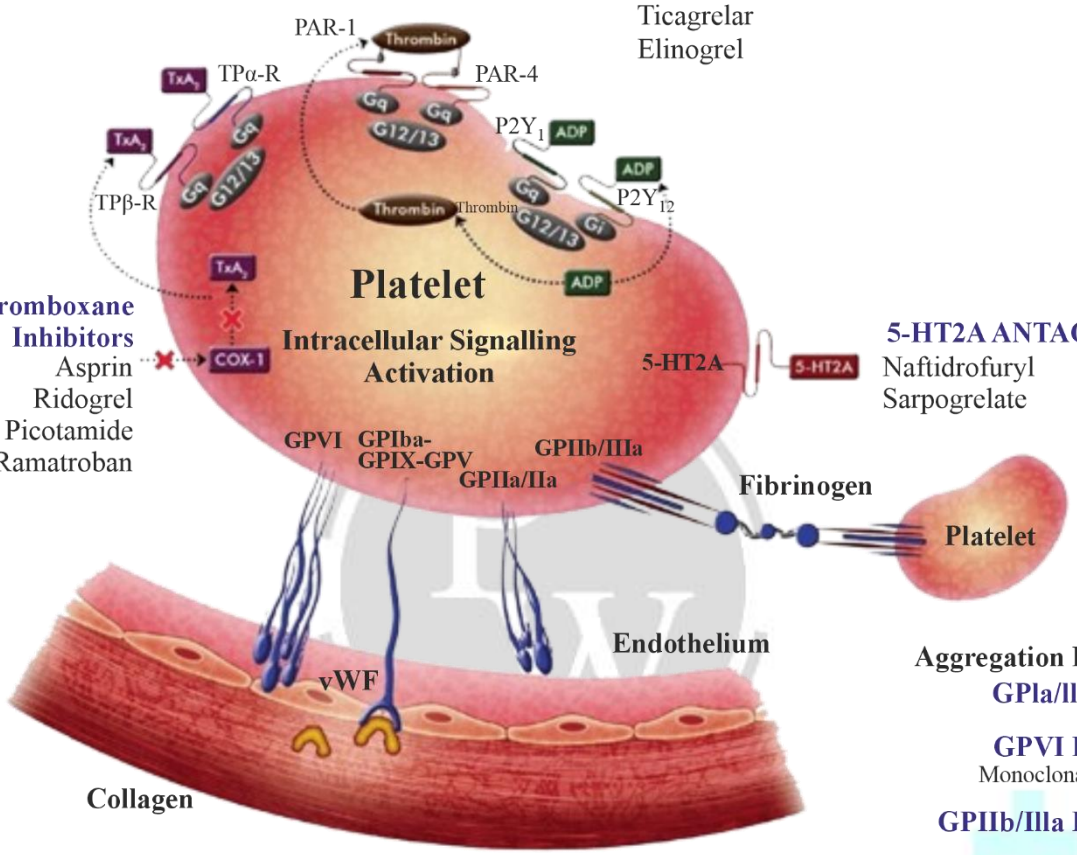
	quickly - Excreted by liver and kidneys	faster inhibition of platelet aggregation	stent placement - High-risk ACS patients	intracranial bleeding in ischemic stroke patients	Antiplatelet drugs (↑ bleeding risk)
Ticagrelor	-Rapid absorption - Does not require metabolic activation - Half-life 12 hours	Reversibly inhibits P2Y12 ADP receptor → faster onset and offset of action than clopidogrel	-ACS - PCI or stent placement Stroke prevention - Prophylaxis of MI recurrence	-Dyspnea Dizziness, headache Bleeding Arrhythmias	-High-dose aspirin (interferes with ticagrelor action) - Anticoagulants (↑ bleeding risk)
Abciximab	-Fab fragment of monoclonal antibody - IV administration Half-life 10-30 min	Blocks GP IIb/IIIa receptor on platelets → prevents fibrinogen and vWF binding →inhibits platelet aggregation	-ACS - PCI, stent placement Coronary artery bypass grafting (CABG)	-Bleeding (major) - Thrombocytopenia -Hypotension Constipation, ileus, arrhythmias	- Anticoagulants (enhances bleeding risk) - Other antiplatelet agents (synergistic effects)
Eptifibatide	-IV administration - Half-life 2.5 hours	Selectively inhibits GP IIb/IIIa receptor on platelets → prevents platelet aggregation	-ACS - PCI, angioplasty High-risk unstable angina	-Bleeding Thrombocytopenia -Hypotension Allergic reactions, rash	-Aspirin and heparin (used concurrently) Other antiplatelet drugs (synergistic effect)
Tirofiban	- IV administration - Half-life 2 hours	Inhibits GP IIb/IIIa receptor on platelets → prevents platelet aggregation	- ACS - PCI, angioplasty	- Bleeding Thrombocytopenia - Hypotension Allergic reactions, rashes	- Aspirin and heparin (used concurrently) Other antiplatelet drugs (synergistic effect)

Adhesion Antagonists

Activation Inhibitors
PAR-1 Antagonists

ADP P2Y $_{12}$ Receptor Antagonists
Ticlopidine
Clopidogrel
Prasugrel
Ticagrelar
Elinogrel

ADP P2Y$_1$ Receptor Antagonists



Thromboxane Inhibitors
Asprin
Ridogrel
Picotamide
Ramatroban

5-HT2A ANTAGONISTS
Naftidrofuryl
Sarpogrelate

Aggregation Inhibitors

GPIa/IIa Inhibitor

GPVI Inhibitors
Monoclonal antibodies

GPIIb/IIIa Inhibitors
Abciximab
Eptifibatide
Tirafikan

PHARMA

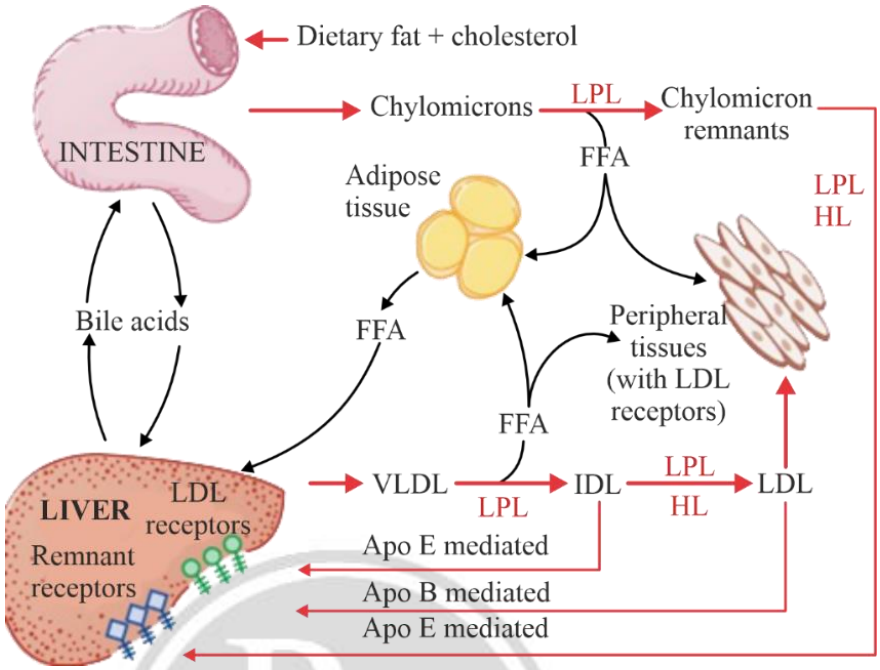
HYPOLIPIDAEMIC DRUGS

✶ **Lipid Transport:**

- Lipid transport in the body occurs via **lipoproteins**, which are complexes of lipids and proteins that facilitate the movement of lipids in the plasma.
- These lipoproteins consist of a hydrophobic core containing triglycerides (TG) and cholesteryl esters (CHE), while the outer polar layer comprises phospholipids, free cholesterol (CH), and apoproteins.
- **Types of Lipoproteins and Their Functions:**

Lipoprotein Type	Size	Lipid Content	Source	Function
Chylomicrons (Chy)	100–500 nm	TG > CHE	Diet	Transport dietary triglycerides from the intestine to peripheral tissues.
Chylomicron Remnants	30–50 nm	CHE > TG	Diet, Chylomicrons	Transport dietary cholesterol to the liver.
Very Low-Density Lipoproteins (VLDL)	40–80 nm	TG > CHE	Liver	Transport endogenous triglycerides from the liver to adipose and muscle.
Intermediate-Density Lipoproteins (IDL)	30–35 nm	CHE > TG	VLDL	Precursor to LDL; transports cholesterol and triglycerides to the liver.
Low-Density Lipoproteins (LDL)	20–25 nm	CHE	IDL	Transports cholesterol to peripheral tissues and liver; excess causes atherosclerosis.
High-Density Lipoproteins (HDL)	5–10 nm	Phospholipids, CHE	Tissues, Cell Membranes	Removes excess cholesterol from tissues and returns it to the liver.

- **Lipid Transport Mechanism:**
  - ➢ **Dietary Lipid Absorption:**
    - Lipids from food are absorbed in the intestine and packaged into chylomicrons.
  - ➢ **Chylomicron Metabolism:**
    - Lipoprotein lipase (LPL) in capillary endothelium hydrolyzes triglycerides into fatty acids, which are taken up by adipose and muscle tissues.



➢ **Conversion of Lipoproteins:**

- Chylomicron remnants are absorbed by the liver.
- The liver releases VLDL, which is hydrolyzed by LPL to form IDL and subsequently LDL.

➢ **LDL Metabolism:**

- LDL is taken up by tissues via LDL receptors for cellular cholesterol needs.

➢ **Reverse Cholesterol Transport:**

- HDL collects excess cholesterol and delivers it back to the liver for excretion or recycling.

○ **Clinical Relevance:**

➢ **Hyperlipoproteinemia:**

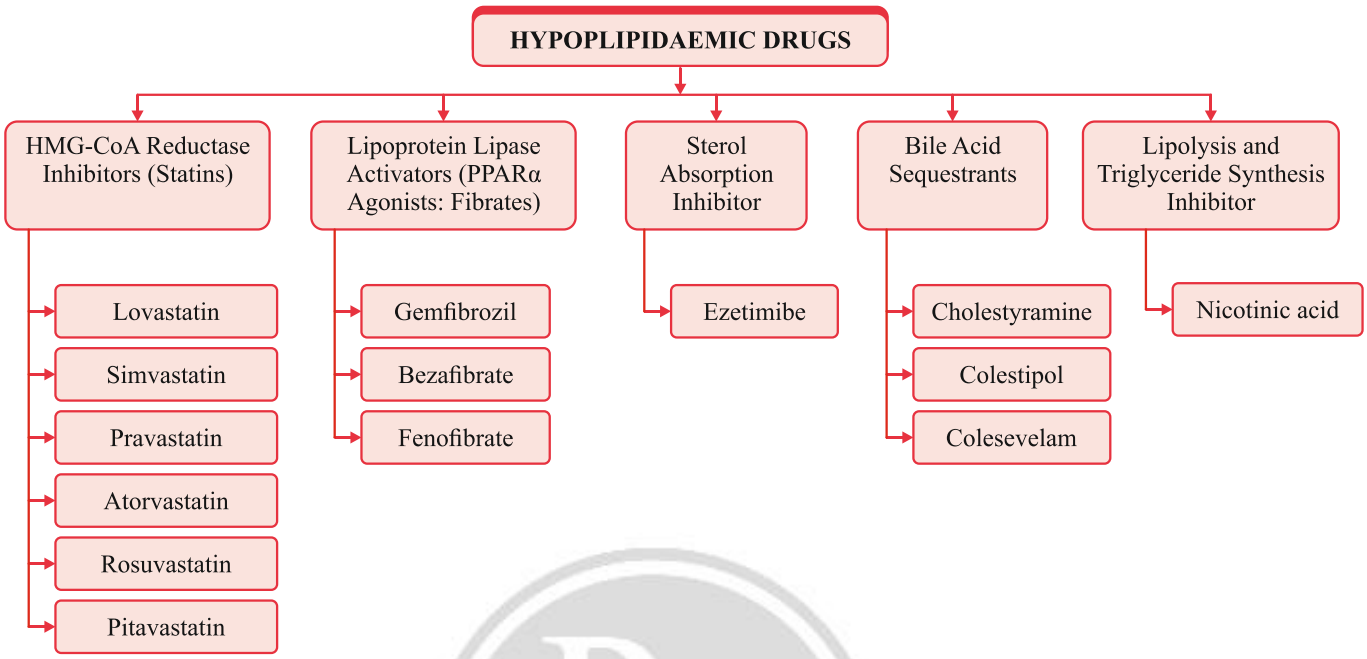
- Elevated levels of lipoproteins (especially LDL and VLDL) contribute to atherosclerosis.

➢ **Protective Role of HDL:**

- Higher HDL levels are associated with reduced cardiovascular risk.

➢ **Statins and Lipid-Lowering Drugs:**

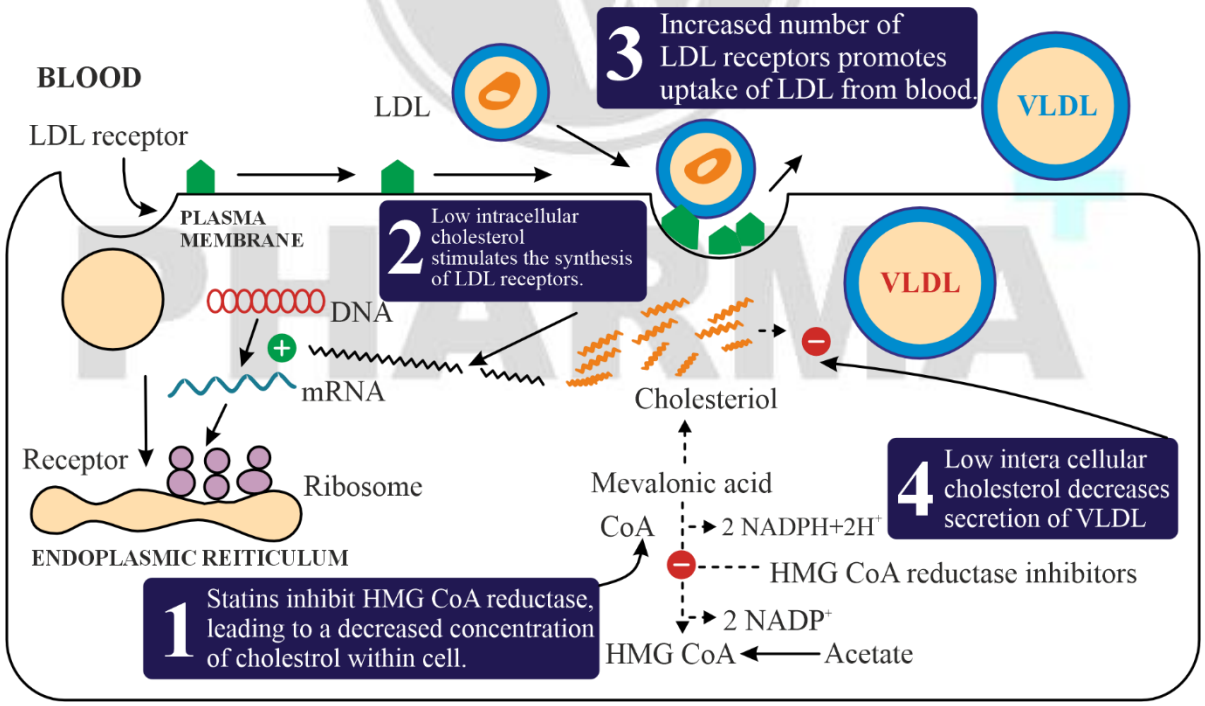
- These medications reduce LDL cholesterol and increase HDL to prevent cardiovascular diseases.



➤ HMG-COA REDUCTASE INHIBITORS

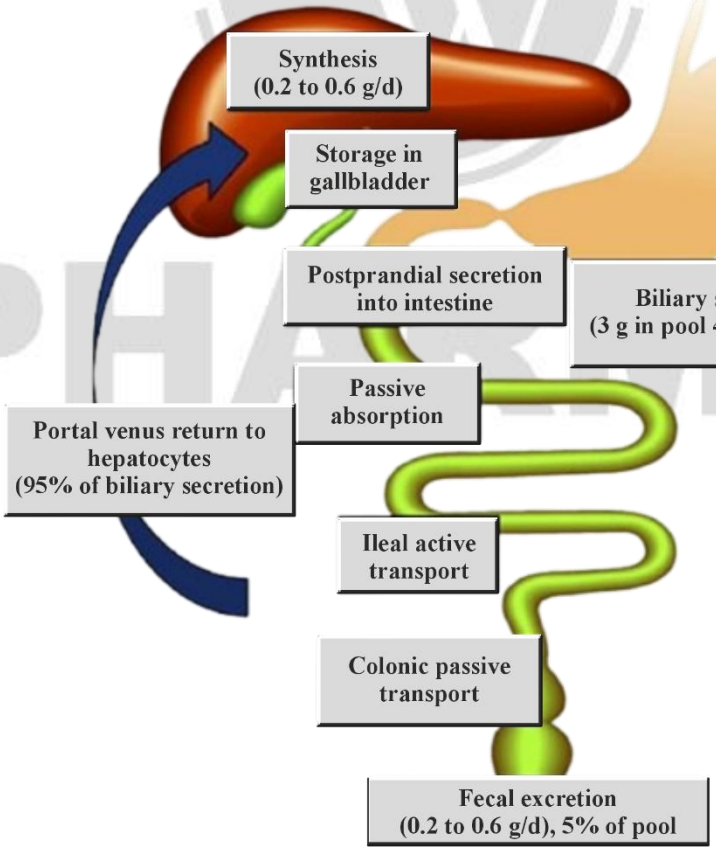
Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Lovastatin	Lipophilic; lactone prodrug; t½: 2–4 hrs; extensive first-pass metabolism; excreted in bile	Competitive inhibition of HMG-CoA reductase →↓ mevalonate → ↓ cholesterol synthesis →↑ LDL receptor expression → ↓ LDL-C	Primary/ secondary hypercholesterolaemia, ASCVD prevention	GI upset, headache, rash, sleep disturbances, ↑ transaminases, myopathy (rare), rhabdomyolysis (very rare)	CYP3A4 inhibitors ↑ levels (e.g. ketoconazole); gemfibrozil ↓ clearance; avoid with strong CYP3A4 inhibitors
Simvastatin	Lipophilic; lactone prodrug; t½: 2–3 hrs; better oral absorption		More effective than lovastatin; raises HDL more	Same as above; higher risk of myopathy at 80 mg/day	CYP3A4 inhibitors, gemfibrozil, erythromycin, protease inhibitors, cyclosporine
Pravastatin	Hydrophilic; active drug; t½: 1–3 hrs	Same as above + ↓ fibrinogen levels	Similar to lovastatin; added benefit in reducing plasma fibrinogen	Better tolerated, fewer CNS effects due to hydrophilicity	Fewer CYP interactions; minimal risk of drug interactions

Atorvastatin	Lipophilic; t½: 14–18 hrs; high efficacy	Same as above + antioxidant properties	High LDL & TG reduction; effective in mixed dyslipidaemia	As above; well tolerated overall	CYP3A4 interactions; avoid gemfibrozil; prefer fenofibrate if combination needed
Rosuvastatin	Longest t½: 18–24 hrs; most potent; excreted unchanged mostly	Same as above; higher HDL rise than others; long duration	Severe hypercholesterolaemia, post-surgical VTE prevention	Similar profile; low incidence of side effects	Least CYP involvement; preferred in complex patients; less interaction potential
Pitavastatin	t½: ~12 hrs; most potent per mg; limited to max 4 mg/day		Moderate LDL-C reduction; no distinct advantage over others	Similar to others; limited clinical experience	Avoid with gemfibrozil (↓ clearance); limited CYP metabolism



➤ BILE ACID SEQUESTRANTS

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Cholestyramine Colestipol Colesevelam	Not absorbed or digested; supplied as chloride form; act locally in gut; excreted in feces	Bind bile acids in intestine → interrupt enterohepatic circulation → ↑ fecal excretion of bile salts and cholesterol → ↑ hepatic conversion of cholesterol to bile acids → ↑ LDL receptor expression →↑ clearance of LDL, IDL, VLDL	-Primary hyperlipidaemia (esp. ↑ LDL)- Adjunct in combined therapy- Atherosclerosis (modest benefit)- Bile salt diarrhea, pruritus in cholestasis	-Unpalatable- GI discomfort: bloating, flatulence, constipation- Poor patient compliance	-Impair absorption of fat-soluble vitamins (A, D, E, K)- Interfere with absorption of many oral drugs (e.g., warfarin, thiazides, digoxin, iron)- Space administration time apart (1–2 hrs before or 4–6 hrs after other drugs)



➤ LIPOPROTEIN-LIPASE ACTIVATORS

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Gemfibrozil	Completely absorbed orally; glucuronidated; enterohepatic circulation; t½: 1–2 hrs	Activates **PPARα** → ↑ lipoprotein lipase → ↑ VLDL catabolism → ↓ TGs; ↓ hepatic TG synthesis	- Type III, IV, V hyperlipoproteinaemi a- Severe hypertriglyceridaemi a- Chylomicronaemia- Metabolic syndrome	- GI upset- Rash, myalgia, headache- Myopathy (esp. with statins)- Gallstones	↑ risk of myopathy with **statins**; avoid comboEnhances effect of **oral anticoagulants**
Bezafibrate	Oral; requires dose reduction in elderly/renal disease	Same as gemfibrozil + ↓ LDL-CH + ↓ fibrinogen & glucose	- Mixed hyperlipidaemia (III, IV, V)- Low HDL-CH with high TGs- Atherosclerosis slowing	- GI upset- Myalgia- Rash	Same as gemfibrozil; monitor with anticoagulants
Fenofibrate	Prodrug; t½: ~20 hrs	Strong **PPARα** activator↑ HDL, ↓ LDL, ↓ TGsMinimal ↑ in LDL in high TG pts	- Same as gemfibrozil- Preferred for combining with statins	- Myalgia- Hepatitis- Rare: rhabdomyolysis, gallstones	**Safe to combine with statins** (less myopathy risk) Minimal CYP interference
Saroglitazar	Oral; once daily; t½ not well established	Dual **PPARα** + **PPARγ** agonist → ↓ TG, ↓ glucose, ↑ HDL	- Diabetic dyslipidaemia- Hypertriglyceridaemi a uncontrolled by statin	- Weakness- Fever- Gastritis(No edema or weight gain seen yet)	Profile not fully known; avoid in absence of long-term safety data

➤ LIPOLYSIS AND TRIGLYCERIDE SYNTHESIS INHIBITOR

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Nicotinic Acid (Niacin)	- Absorbed orally- Requires high doses (2–4 g/day)- SR/ER forms reduce flushing- Should be taken after meals	- Inhibits intracellular lipolysis in adipocytes → ↓ FFA flow to liver- ↓ TG synthesis in liver- ↓ VLDL, LDL; ↑ HDL (20–35%)- Activates **GPR109A (niacin receptor)** → ↓ cAMP → ↓ lipolysis- ↓ Lp(a) levels	- Severe hypertriglyceridemi a (types III, IV, V)- Raise HDL-CH- Prevent acute **pancreatitis** due to chylomicronemia **Not** recommended by NICE for routine primary/secondary CVD prevention or use in diabetes/CKD	- **Flushing**, heat, itching (↓ with aspirin, laropiprant, SR forms)- **Dyspepsia**, nausea, vomiting, diarrhea- **Liver dysfunction**, jaundice- **Hyperglycemia**, worsened diabetes- **Hyperuricemia**, gout- **Arrhythmias**, dry skin, hyperpigmentation	- ↑ **Statin-induced myopathy** risk- ↑ **Postural hypotension** with antihypertensives
Acipimox	- Nicotinic acid derivative- Better tolerated- Weaker lipid-lowering action	Similar to niacin, but less potent:- ↓ TGs and VLDL- Modest ↑ HDL-CH	- Used in **hypertriglyceridemia** where niacin is poorly tolerated	- Better tolerated than niacin- Fewer flushing and GI effects	Similar interactions as niacin, but milder due to lower potency

➤ STEROL ABSORPTION INHIBITOR

Drug	PK Properties	Mechanism of Action	Therapeutic Uses	Side Effects	Potential Drug Interactions
Ezetimibe	- Poor aqueous solubility- Absorbed after glucuronidation in intestinal mucosa- Undergoes enterohepatic circulation- Excreted mainly in faeces- t½ ~22 hrs	- Inhibits **NPC1L1** cholesterol transporter in intestinal mucosa- ↓ absorption of dietary & biliary cholesterol and phytosterols- Compensatory ↑ CH synthesis in liver	- As **adjunct to statins** for primary hypercholesterolemia- **When statins not tolerated -** To supplement **dietary management**	- Generally well tolerated- Rare: **Reversible hepatic dysfunction, myositis**	- **Synergistic** LDL-C lowering with statins- No major drug interactions reported

GUIDELINES FOR THE USE OF HYPOLIPIDAEMIC DRUGS

- **Raised plasma cholesterol (CH) is a major risk factor** for coronary artery disease (CAD) and stroke. The **higher the cholesterol level, the greater the risk**.
- Studies (HPS, 2002; ASCOT-LLA, 2003) have demonstrated that **lowering LDL cholesterol (LDL-CH) reduces cardiovascular mortality and morbidity**.
- **Statins are now a standard therapy** post-acute coronary event, **regardless of lipid levels**.
- **Lipid Profile Targets (NCEP-ATP III, 2001):**

Lipid Levels (mg/dL)	Total CH	LDL-CH	HDL-CH	TGs
Optimal	<200	<100 (<70 for CAD pts)	>40 (Men), >50 (Women)	<150
Borderline High	200-239	130-159	-	150-199
High	≥240	160-189	>60	200-499
Very High	-	≥190	-	≥500

- **Treatment Guidelines:**
  - **Lifestyle Modification:** First-line approach **regardless of drug therapy:**
    - Low-fat, low-cholesterol diet
    - Reduction in saturated and trans fats
    - Regular exercise
    - Weight management
    - Smoking cessation and limited alcohol intake.
  - **Pharmacotherapy Considerations:**
    - Low-dose aspirin is recommended for CAD or stroke-risk patients unless contraindicated.
    - LDL-CH levels alone do not determine treatment-associated risk factors like diabetes, hypertension, and peripheral/cerebral vascular disease are also considered.
  - **Statin Therapy Classification (ACC/AHA 2013 & NICE 2014):**
    - Statins are categorized based on **LDL reduction efficacy**:

Statin Therapy	High-Intensity (≥50% LDL reduction)	Moderate-Intensity (30–50% LDL reduction)	Low-Intensity (<30% LDL reduction)
Atorvastatin	40–80 mg	10–20 mg	-
Rosuvastatin	20–40 mg	5–10 mg	-
Simvastatin	-	20–40 mg	10 mg
Pravastatin	-	40–80 mg	10–20 mg
Lovastatin	-	40 mg	20 mg
Pitavastatin	-	2–4 mg	1 mg

- High-intensity statins (Atorvastatin, Rosuvastatin) are preferred for high-risk patients.
- **Major Risk Groups for Statin Therapy (ACC/AHA 2013):**
  - Patients with ASCVD (Atherosclerotic Cardiovascular Disease).
  - LDL-CH ≥190 mg/dL.
  - Diabetics (age 40-75) with LDL-CH 70-189 mg/dL.
  - Non-diabetic individuals with ASCVD risk ≥7.5% (age 40-75, LDL-CH 70-189 mg/dL).
- **Key Clinical Studies Supporting Statin Use:**
  - **JUPITER Trial (2008):**
    - High-dose Rosuvastatin **reduced cardiovascular events by 44%.**
  - **Cholesterol Treatment Trialists (CTT) Meta-analysis:**
    - Standard statin therapy (LDL reduction by 30-40%) reduces CV events by **30-35%**.
    - Intensive statin therapy (LDL reduction ~50%) reduces CV events by **~50%**.