

Pharmacology Of Drugs Acting on Blood and Blood Forming Agents

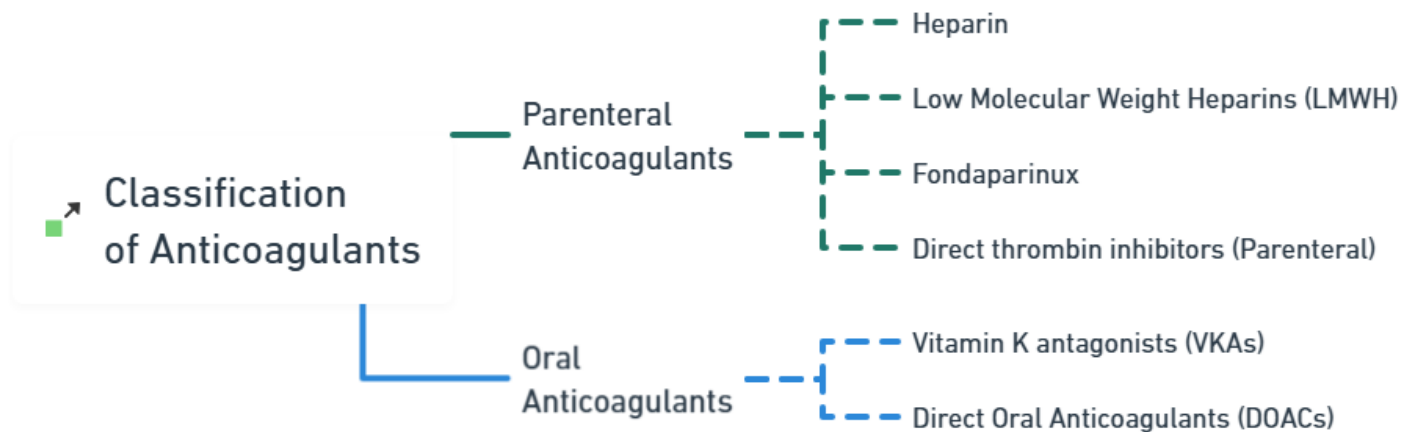
Anticoagulants

Introduction:

- Anticoagulants are drugs that prevent the formation of new blood clots or stop existing clots from growing larger.
- They do not dissolve existing clots but are crucial in the management and prevention of thromboembolic disorders like deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation, and stroke.

Classification:

Anticoagulants can be classified based on their mechanism and route:



A. Parenteral Anticoagulants

- Heparin (Unfractionated Heparin, UFH)
- Low Molecular Weight Heparins (LMWH) (e.g., Enoxaparin, Dalteparin)
- Fondaparinux
- Direct thrombin inhibitors (Parenteral) (e.g., Bivalirudin, Argatroban, Lepirudin)

B. Oral Anticoagulants

- Vitamin K antagonists (VKAs): Warfarin, Acenocoumarol
- Direct Oral Anticoagulants (DOACs):
 - **Direct thrombin inhibitors:** Dabigatran
 - **Factor Xa inhibitors:** Rivaroxaban, Apixaban, Edoxaban

Mechanism of Action:

A. Heparin (Unfractionated Heparin):

- Heparin activates antithrombin III (AT III), a natural inhibitor of clotting.

- This complex inhibits thrombin (factor IIa) and factor Xa, preventing conversion of fibrinogen to fibrin.

B. Low Molecular Weight Heparins (LMWH):

- Also activate AT III, but preferentially inhibit factor Xa.
- Less effect on thrombin due to shorter chain length.

C. Fondaparinux:

- Synthetic pentasaccharide; selectively inhibits factor Xa via AT III activation.
- Does not inhibit thrombin.

D. Warfarin:

- Inhibits vitamin K epoxide reductase, blocking activation of vitamin K.
- This prevents gamma-carboxylation of clotting factors **II, VII, IX, and X**, and proteins C and S (all vitamin K-dependent).
- Delayed onset as already synthesized clotting factors must degrade.

E. Direct Oral Anticoagulants (DOACs):

- **Dabigatran:** Directly inhibits thrombin (factor IIa).
- Rivaroxaban, Apixaban, Edoxaban: Direct factor Xa inhibitors, preventing prothrombin to thrombin conversion.

Pharmacokinetics:

Drug	Absorption	Onset	Half-life	Metabolism	Excretion
Heparin (IV/SC)	Poor oral, SC/IV only	Immediate (IV)	1–2 hrs	Hepatic	Renal
LMWH	SC	3–5 hrs	4–6 hrs	Minimal	Renal
Fondaparinux	SC	2 hrs	17 hrs	No metabolism	Renal
Warfarin	Oral	24–72 hrs	36–42 hrs	Hepatic (CYP450)	Renal, bile
Dabigatran	Oral	1–2 hrs	12–17 hrs	Esterases	Renal
Rivaroxaban/Apixaban	Oral	2–4 hrs	8–15 hrs	Hepatic (CYP3A4)	Renal, fecal

Pharmacodynamics:

- Anticoagulants **prolong clotting times**, assessed by:
 - **Heparin:** aPTT (activated Partial Thromboplastin Time)
 - **Warfarin:** PT/INR (Prothrombin Time/International Normalized Ratio)

- **DOACs:** Specific assays (e.g., anti-Xa assay), though not routinely required

Adverse Effects:

- Bleeding (major and minor)
- Heparin-induced thrombocytopenia (HIT) (UFH > LMWH)
- Osteoporosis (long-term heparin)
- Skin necrosis (warfarin, due to protein C depletion)
- GI symptoms (DOACs, dabigatran in particular)
- Hepatotoxicity (rare)
- Hypersensitivity reactions

Contraindications:

- Active bleeding
- Severe thrombocytopenia
- Uncontrolled hypertension
- Recent surgery with bleeding risk (e.g., eye, brain, spine)
- Liver disease (warfarin – impaired metabolism)
- Renal impairment (dose adjustment for LMWH, DOACs)
- Pregnancy (warfarin – teratogenic, especially in first trimester)

Therapeutic Uses:

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Atrial fibrillation (prevention of stroke)
- Mechanical heart valves (mainly warfarin)
- Myocardial infarction (MI) – adjunctive therapy
- Post-surgery prophylaxis – LMWH, DOACs
- Disseminated intravascular coagulation (DIC) – heparin (selectively)

Drug Interactions:

Warfarin:

- Highly interactive; metabolized by CYP450 enzymes
- **Increased effect** (↑ INR): NSAIDs, antibiotics (e.g., erythromycin), amiodarone, cimetidine, alcohol (acute)
- **Decreased effect** (↓ INR): Rifampin, barbiturates, carbamazepine, alcohol (chronic), vitamin K

- **Protein displacement:** NSAIDs can displace warfarin from albumin

Heparin/LMWH:

- Increased bleeding with other anticoagulants, antiplatelets

DOACs:

- CYP3A4 and P-glycoprotein interactions (e.g., ketoconazole ↑ effect, rifampin ↓ effect)

Dose and Route of Administration:

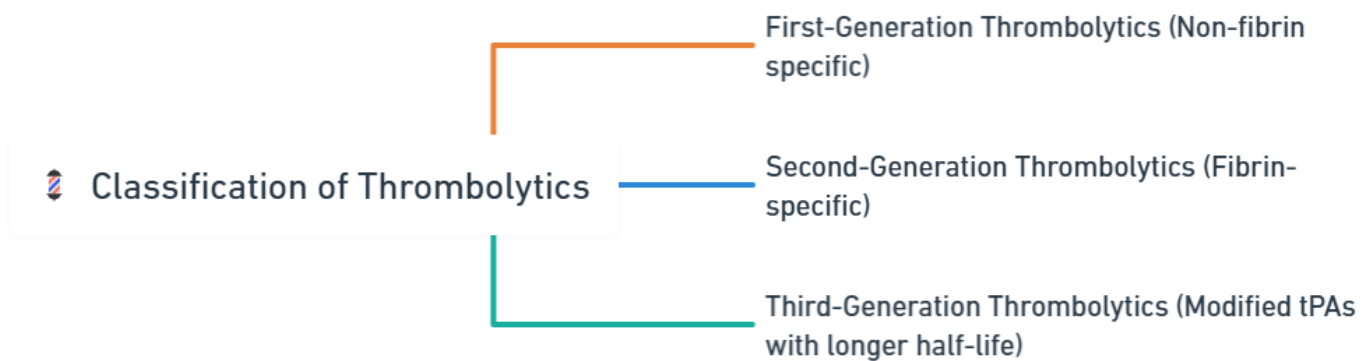
Drug	Route	Dose
Unfractionated Heparin (UFH)	IV bolus	5,000 units, then continuous infusion adjusted to aPTT
	SC (prophylaxis)	5,000 units 2–3 times/day
LMWH (Enoxaparin)	SC (treatment)	1 mg/kg every 12 hours
	SC (prophylaxis)	40 mg once daily
Warfarin	Oral (initial)	5 mg/day, adjusted to maintain INR 2–3
	Oral (maintenance)	2–10 mg/day (individualized)
Fondaparinux	SC	2.5–10 mg once daily depending on indication
Dabigatran	Oral	150 mg twice daily (adjust for renal function)
Rivaroxaban	Oral	15–20 mg once daily with food (depending on indication)
Apixaban	Oral	5 mg twice daily

Thrombolytics (Fibrinolytic Agents)

Introduction

- Thrombolytic agents are a class of drugs that dissolve already formed thrombi (blood clots) in blood vessels.
- They are primarily used in life-threatening thrombotic conditions, such as:
 - **Acute myocardial infarction (MI)**
 - **Ischemic stroke**
 - **Massive pulmonary embolism (PE)**
- Thrombolytics exert their action by enhancing the body's natural fibrinolytic system, which breaks down fibrin — the main protein component of blood clots.

Classification of Thrombolytics



A. First-Generation Thrombolytics (Non-fibrin specific)

- **Streptokinase** (from *Streptococcus* bacteria)
- **Urokinase** (from human kidney or recombinant cells)

B. Second-Generation Thrombolytics (Fibrin-specific)

- **Alteplase** (recombinant tissue plasminogen activator, rtPA)

C. Third-Generation Thrombolytics (Modified tPAs with longer half-life)

- Reteplase
- Tenecteplase
- Lanoteplase

Mechanism of Action

Thrombolytics act primarily by converting plasminogen (inactive zymogen) to plasmin (active protease).

Plasmin:

- **Degrades fibrin** → dissolves the meshwork of the thrombus.
- Also degrades fibrinogen and other clotting factors (with systemic activation).



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