Feature	Unfractionated Heparin (UFH) (Heparin)	Low Molecular Weight Heparins (LMWH) (Enoxaparin, Dalteparin)	Fondaparinux / Rivaroxaban (Synthetic pentasaccharide)	Warfarin Sodium (Marivan, Dendivan)
	1- INDIRECT THROMBIN INHIBITORS			**2- Oral anticoagulants** Vitamin K antagonist
Pharmacokinetics		Fragments of unfractionated heparin which composed of shorter polysaccharide chains with average MW about 5000d		Prototype of cumarine anticoagulants (synthetic)
Route of Administration	* Due to highly negative charge (ionized) of heparin and its large molecular size, it is not given orally. It is given parenterally I.V. →immediate onset of action	S.C.	S.C. injection → fondaparinux oral → Rivaroxaban	Oral only, **No more benefits from parenteral administration effective only in vivo**
Onset of Action	(5 hours duration) - in emergency * S.C. -> delayed onset (1-2h) but for long-term maintenance. * I.M. injection must be avoided (cause painful hematomas).	**Longer duration of action: 24 H; single daily dose**	Single daily dose without coagulation monitoring.	Slow (dependent on factor half-lives)
Half-life	1-1.5 H (short acting)	Longer t1/2 so they are used S.C. once / day.		40 hours
Duration of Action	5 hours (I.V.)			2-5 days
BBB/Placenta Passage	Not Passing			
Elimination	Liver and Kidney			Kidneys (inactive metabolites)
Bioavailability	Not given orally	They have **high bioavailability and predictable anticoagulant effect**, so no need for routine lab monitoring or dose adjustment.		Very high (orally)
Plasma Protein Binding				~99%
Metabolism				Liver (inactive metabolites)
Enterohepatic Circulation				Yes (accounts for long half-life)
Mechanism of Action	These agents **bind to antithrombin-III (protease)**: naturally occurring inhibitor of clotting factors: **2**, 9,**10**, 11, 12. **no intrinsic anticoagulant activity**.			
Antithrombin-III Binding	Yes	No	No	
Inhibition of Factor II (Thrombin)	Equal to Factor Xa	Little effect	No	Indirect (via Vit K antagonism)
Inhibition of Factor Xa	Equal to Thrombin Factor Xa inhibition is more specific than thrombin inhibition.	Primarily only. by antithrombin with little effect on thrombin. **less risk for thrombocytopenia and less osteoporosis**	Specific Only.	Indirect (via Vit K antagonism)
Vitamin K Antagonist	No	No	No	Yes
Affects Vit K-dependent Factors (II, VII, IX, X)	No	No	No	Yes
Slow Onset due to Factor Half-lives	No	No	No	Yes (5-100 hours)
Monitoring				
Monitoring Required	aPTT (especially I.V.) (activated partial thromboplastin time)	Anti-factor Xa activity (not aPTT)	Not routinely needed	Prothrombin Time (PT) / INR
Therapeutic Goal (aPTT)	1.5-2.5 times normal control value			INR usually 2.0-3.0
Normal aPTT	30-40 sec			
aPTT in Heparin Therapy	60-100 sec			
Dosage Adjustment Based On	aPTT			PT (INR)
Adverse Effects				
Bleeding	Dose-dependent dosage adjustment based on aPTT monitoring	Lesser risk	Less likely	Yes

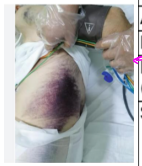
because its effect is dependent on the tip of these factors (from 5-100 hours).

(heparin + warfarin) must be given for first 4-5 days followed by warfarin alone.

inhibits the enzyme Vit k epoxide reductase which is responsible for the production and activation of vit k-dependent coagulatior factors (II, VII, IX, and X) by the liver.

monitoring: should be twice the control (IN= 1-1.5)

based on prothrombin time (PT) (INR: International Normalized Ratio).



Heparin-Induced Thrombocytopenia (HIT) immune-based reactions)	Yes (0.5% after 5 days) of starting drug therapy. Management: heparin must be stopped, and the patient must be given alternative anticoagulant.	Less risk	Much less likely **Advantages**:	No
Osteoporosis	Yes	Lesser risk		Yes
Alopecia	Yes			Yes
Hypersensitivity	Yes			
Muscle Hematoma (IM)	Yes (avoid IM) if given IM			
Skin Reactions				Hemorrhagic skin necrosis, purple toe syndrome, alopecia urticaria, dermatitis (infrequent)
Pregnancy Category				X (Teratogenic: fetal warfarin syndrome)
Abortion/Birth Defects/ intrauterine fetal death				Yes
CNS Hemorrhage (Fetus)				Yes
Sudden Withdrawal				rebound synthesis vitamen K- dependent clotting factors thrombosis
Antidote for Bleeding Dose : (1 mg protamine/100 units heparin) required to neutralize the heparin present in the plasma.	Protamine sulfate (a mixture of basic (positively charged) polypeptides isolated fromsalmon sperm) is used to overcome bleeding because it binds tightly (electrostatic bond)to heparin and neutralizes its anticoagulant effect.	protamine only partially reverses the anticoagulant activity of LMWHs and has no effect on that of fondaparinux.	No effect	Vitamin K1 (3-5 mg IV)
Advantages	Rapid onset (I.V.), first choice for thromboembolic disorders	Longer duration, less thrombocytopenia/osteoporosis, predictable effect	Less likely to cause HIT, no routine monitoring	Oral administration
Disadvantages	Parenteral administration, requires monitoring (aPTT), risk of HIT	Parenteral administration, effect incompletely neutralized by protamine	Parenteral administration (injection only) **Indications**	Slow onset, requires monitoring (INR), many drug interactions, teratogenic
Indications	• Treatment of thromboembolic disorders: ○ First choice because of its rapid onset of action. ○ Used for 4-5 days followed by oral anticoagulant warfarin: a)Deep venous thrombosis (DVT) b)Pulmonary embolism (PE) c)Primary prophylaxis of DVT or PE. • Prevention of venous thromboembolism in high risk patients: After orthopedic (hip or knee surgery) or gynecological surgery. • Initial management of : a)Unstable angina and atrial fibrillation & in mitral valve disease, especially with atrial fibrillation. b)During and after cardiac surgery e.g., Prosthetic heart valves, coronary angioplasty or stent placement, cardiopulmonary bypass grafts. c)Transient ischemic attacks (TIA) or Cerebral infarction. d)In disseminated intravascular coagulation (DIC) • DVT during pregnancy. • To prevent occlusion of hemodialysis machine.	Thromboprophylaxis (hip/knee surgery), initial therapy for PE/DVT	Thromboprophylaxis (hip/knee surgery), initial therapy for PE/DVT pulmonary embolism	
Administration Notes	I.M. injection must be avoided	S.C. once daily	S.C. single daily dose	Taken only orally
Monitoring Notes	Very important in I.V. administration	Monitored by anti-factor Xa activity		INR should be twice the control (INR= 1-1.5 normal)
Use with Heparin	Often followed by oral anticoagulant warfarin			Given with heparin for first 4-5 days

Indications

1. **Prevention of DVT or pulmonary embolism recurrence following initiation course of heparin.**
2. **Prevention of venous thromboembolism in high risk patients after orthopedic (hip or knee surgery) or gynecological surgery.**

❑ **Factors that decrease warfarin effectiveness:**

* **Cholestyramine** inhibits warfarin absorption.
* **Genetic resistance to vit K epoxide reductase**.
* ↑ **metabolic clearance of warfarin** by **enzyme inducers** (phenobarbitone, rifampicine, phenytoin and chronic alcohol ingestion.

❑ **Factors that increase warfarin effectiveness:**

* ↓ **vit k** due to damage of intestinal flora by **broad spectrum antimicrobial agents.**
* ↑ **displacement of warfarin from plasma protein binding by NSAIDs**.
* ↓ metabolism of warfarin by **enzyme inhibitors** (metronidazole, cimetidine, allopurinol, amiodarone and acute ingestion of alcohol

avoided during pregnancy. (teratogenic): fetal warfarin syndrome