Drugs Used in Thromboembolic Disease I

Drug		MOA	Administration	Uses	Side Effects	Notes
Heparin	**Unfractionated High Molecular Weight Heparin (UFH | HMWH)**	**Indirect** thrombin inhibitor: -Increases the **electronegative** potential of the vessel wall -Causes the release of (**TFPI**), which works on factor **Xa, platelets & endothelium** and inhibits factor **VIIa** -I**nhibits** platelets aggregation -Activates **Lipoprotein Lipase** which **reduces** platelets adhesiveness -Activates **antithrombin** by binding and causing a conformational change → inhibits thrombin (IIa), IXa and Xa *HMWH has high affinity → inhibits 3 factors *LMWH → inhibit factor Xa mainly (less effect on thrombin & IXa)	-**Initial** bolus injection:80-100units/kg -**Continuous** infusion through a pump: 15-22 unit/kg/hr (aPTT*: 2-2.25 time of the control) *Not by intramuscular injection -Low dose **prophylaxis**: (subcutaneous) 5000 units every 8-12 hrs -Monitoring is **needed**: by aPTT*, protamine titration and Anti-Xa units	-Anticoagulant: in arterial and venous thrombosis (**Drug of choice**)	*Toxicity: -Bleeding. -Allergic reactions: fever, anaphylaxis -Alopecia, or loss of hair -Osteoporosis and ostealgia -Mineralocorticoid deficiency -Thrombocytopenia: less in LMWH, **more in UFH** from bovine *Contraindications: -Thrombocytopenia -Hypersensitivity -Active bleeding -Severe hypertension -Hemophilia, purpura -Infective endocarditis, active TB -Ulcerative lesions of GIT -Threatened abortion -Visceral carcinoma -Advanced liver or renal disease	-**Composed** of sulfated glucosamine and D-glucoronic acid by sulfaminic bridges. **-LMWH:** has **equal** efficacy, **more predictable** effects, **higher bioavailability**, given **less frequently**, treatment not monitored -Found inactively in **mast cells** -Released with **anaphylaxis** -Obtained from cow lung and pig intestinal mucosa -**T1/2 = 1 hr** -**Distribution** → intravascular -**Doesn't cross** the placenta and **not excreted** in breast milk. -**Eliminated** by rapid metabolism by **heparinase** enzyme (liver, kidney) some of it is uptaken by RES -Functions as a cofactor → **not consumed** ***aPTT:** activated Partial Thromboplastin Time
	Low Molecular Weight Heparins **-Tinzaparin** **-Deltaparin** **-Enoxaparin**		-Almost completely absorbed after subcutaneous injection -Usually given once or twice daily -Monitoring is by Xa inhibition assay (not routinely) ***No antidote**			
Protamine Sulfate		-Binds mainly to UFH (HMWH) -Binds poorly to LMWH → ineffective		-Antidote for heparin (HMWH) -Protamine titration is used to monitor UFH		-A highly basic, low molecular weight compound

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Fondaparinux		**Indirect** thrombin inhibitor -Binds antithrombin with high specific activity, resulting in more selective inactivation of factor Xa (no effect on thrombin)		-Anticoagulant: in arterial and venous thrombosis		-Synthetic pentasaccharide fragment of heparin -Does not affect thrombin at all -Has a long half-life of 15 hours
IV Direct Thrombin Inhibitors	**Hirudine** **Lepirudin** **Argatroban** **Bivalirudin**	-**Directly** inhibit thrombin: they bind at both the catalytic site and the substrate recognition site of thrombin	IV	-Anticoagulant: in arterial and venous thrombosis	Can cause allergy and anaphylaxis	-Bivalent compounds -Hirudine is extracted from leeches -Lepirudin is the recombinant form of Hirudine
Dabigatran		-**Directly** inhibits thrombin: binds only at the active site of thrombin	Oral	-Anticoagulant: in arterial and venous thrombosis		-A small molecule
Factor Xa Inhibitors	**Rivaroxaban "Xarelto"** **Apixaban** **Edoxaban**	-**Directly** Inhibit factor Xa, in the final common pathway of clotting	Given orally at fixed doses and do not require monitoring	-Anticoagulant: in arterial and venous thrombosis -To prevent stroke in atrial fibrillation		-Eliminated by the kidneys

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