Hemostasis	MCC of death in the western world – MI secondary to thrombotic occlusion is the #1 cause of death **Virchow's Triad:** Endothelial injury, stasis, hypercoagulability Degradation of the thrombus: Plasminogen → plasmin which then degrades fibrin

Anticoagulants: Indirect Thrombin Inhibitors - Uses → DVT, Atrial Fib, Mechanical heart valves, Clotting disorders

Drug	MOA	Pharmacokinetics & Structure	Adverse Effects/ Contraindications
Unfractionated Heparin (UFH) **DOC in pregnancy**	Binds to antithrombin III and acts as a catalyst → enhance **inactivation coagulation factors** *(speeds up the complex formation btwn antithrombin & coag factors)* Prevents conversion of fibrinogen → fibrin Requires 5 pentasaccharide repeats to bind to antithrombin III to be active	Endogenous sulfated mucopolysaccharide produced by mast cells IV for rapid anticoagulation SQ variable F Bind to endothelial cells & plasma proteins → variable response	Excessive bleeding & complications → tx with protamine sulfate ↑Risk of thrombus due to long term use and ↓antithrombin III activity Thrombocytopenia (HIT) → **Type II** = non-immune – immune mediated causing ↓platelet count, can lead to gangrene (Bovine >porcine > LMWH) **Type I** = immune- no major complications, will recover even with continued administration, usually due to high dose IV Osteoporosis
Low Molecular Weight Heparin (LMWH) **Use in Unstable Angina*** Enoxaparin Dalteparin Tinzaparin Fondaparinux (pentasaccharide)	Catalyze inhibition of Factor Xa via Antithrombin III Less able to inactivate Factor II compared to UFH	Don't bind to plasma proteins, endothelial cells or macrophages → longer t ½ Renal clearance	

Warfarin

MOA	Clinical Use	Pharmacokinetics	Adverse Effects/ Contraindications
Prevents reduction of vitamin K → inhibition of γCarboxylation (slows thrombin production)	PPX & TX DVT & PE PPX & TX for atrial fib Valvular stenosis MI	Coumarin derivative Chemically related to vitamin K Highly plasma protein bound **T ½ of 1 week (modulated by drugs- *see chart*)**	Narrow TI → monitor INR Bleeding & warfarin skin necrosis Teratogenicity (not in breast milk) **CI:** PUD, intracranial bleeding, Liver disease, HTN, renal failure

CYP450 Inducers (↓ Efficacy of warfarin)	CYP450 Inhibitors (↑ risk of bleeding on warfarin)
Barbiturates Carbamazepine Phenytoin Rifampicin Grisofulvin	Ketoconazole Metronidazole Cotrimoxazole Statins Omeprazole Cimetidine Amiodraone Allopurinol

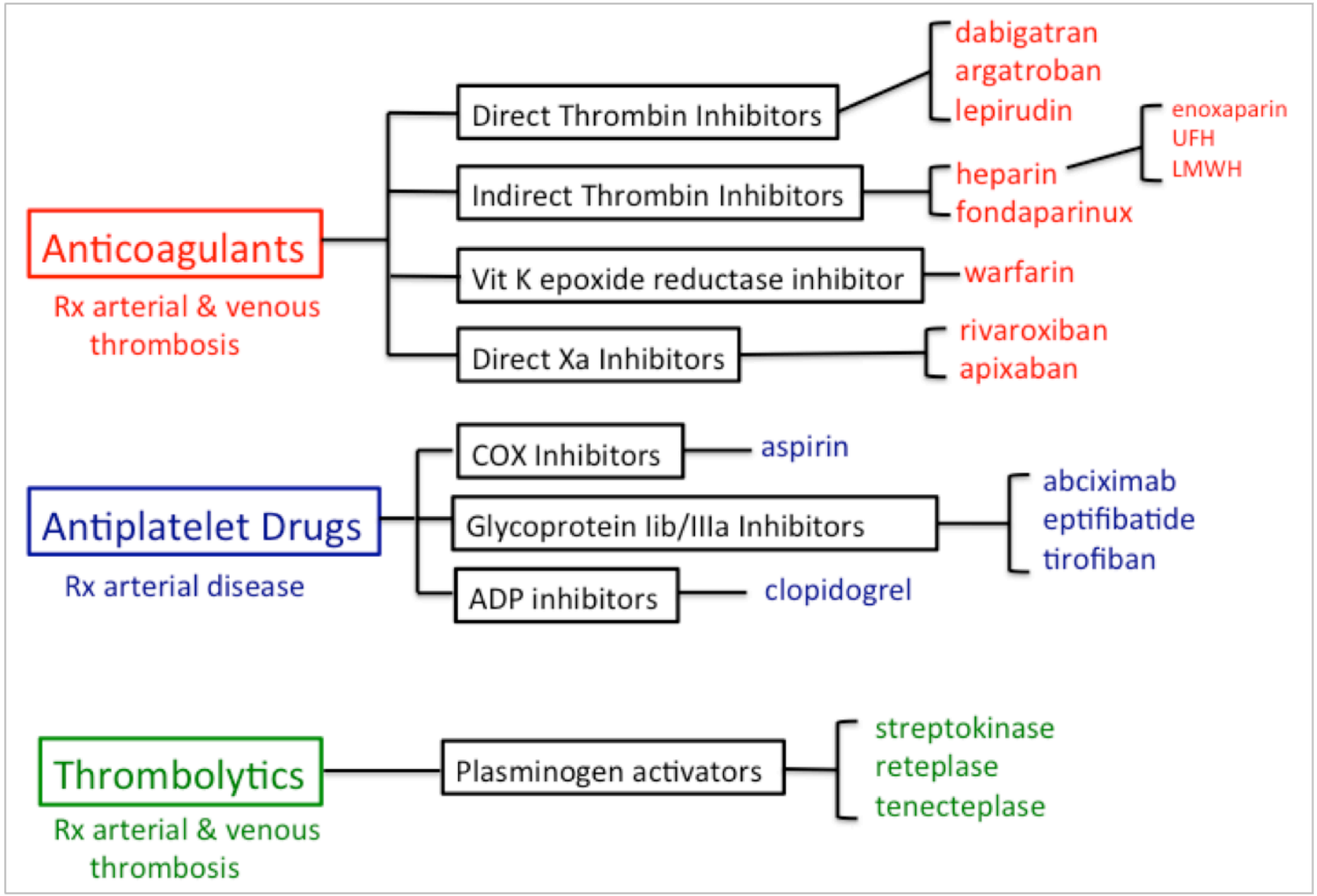
Antithrombotics: Direct Thrombin Inhibitors: inhibit both circulating and clot bound thrombin			
Drug	MOA	Clinical Uses	Adverse Effects/ Contraindications
Hirudin	Bivalent Bind to catalytic site of thrombin & substrate recognition		
Bivalirudin		PCI in HIT patients	Bleeding & HSR Back pain Safe in liver disease Monitor Activated clotting time (ACT)
Lepirudin		HIT	CI in renal impaired HSR & bleeding Monitor aPTT
Dabigatran	Small molecules that bind at the thrombin active site	Stroke/ thromboembolism Alternative to warfarin	Bleeding CI in renal disease
Argatroban		PPX & TX of HIT PCI *(percutaneous coronary intervention)*	GI bleeding Hematuria Monitor aPTT
Melagatran			

Antiplatelets: Glycoprotein IIb/IIIa Receptor Antagonists			
Drug	**MOA**	**Clinical Use**	**Adverse Effects/ Contraindications**
Abciximab	Ab against glycoproteinIIb/IIIa → prevents binding of fibrinogen to IIb/IIIa IV administration with heparin/aspirin	Precuteanous transluminal coronary angiography	Bleeding Thrombocytopenia
Eptifibatide			
Tirofiban			

Unstable Angina*

Antiplatelet Drugs: P2Y Antagonists			
Drug	**MOA**	**Clinical Use**	**Adverse Effects/ Contraindications**
Aspirin	Irreversibly inhibits COX1 → inhibits TXA2 synthesis → ↓platelet aggregation	Prevent arterial thrombosis in IDH & stroke PPX in angina, TIA & atrial arrhythmias	GI upset & bleeding
Ticlopidine	Block binding of ADP to P2Y (receptor) → inhibits activation of GPIIb/IIIa Pro drugs	Alternative to aspirin in ppx Combined with aspirin in ppx of coronary stent thrombosis	Aplastic anemia Agranulocytosis TTP
Clopidogrel		***clopidogrel is preferred due to t ½**	*Activated by 2C19 → can be inhibited by omeprazole
Prasugrel		Used with aspirin for acute coronary syndrome	
Ticagrelor	Same MOA as above but not a prodrug	Used with aspirin in post MI	
Dipyridamole	Inhibits ADP induced platelet aggregation via inhibition of phosphodiesterase (↑cAMP) **Promotes vasodilation** via ↑cAMP in arterial smooth muscle	Thromboembolism ppx after valve replacement Alternative to treadmills in stress testing	
Cilostazol		Peripheral vascular disease PDE3 inhibitor	

Fibrinolytics:			
Drug	**Duration of action/ Location Derivative**	**Clinical Use**	**Adverse Effects/ Contraindications**
Urokinase	Synthesized by kidney	Short term emergency management of → coronary thrombses in MI, DVT, Acute MI, PE, acute ischemic stroke	Bleeding & hemorrhage CI: surgery planned within 10 days, GI bleed within last 3 months, Active bleeding, previous cerebrovascular accident, aortic dissection
Alteplase (rTPA)	tPA (tissue plasminogen activator) 5 minutes		
Reteplase	Deletion mutant- 15 minutes		
Streptokinase	Enzyme from Group C streptococci 20 minute duration Low clot specificity→ acts on free & bound plasminogen Depletes factors V & VIII		
Anisteplase	Streptokinase/plasminogen complex		
Tenecteplase	Substitution mutant 20 minutes		
E-Aminocaproic Acid (EACA)	Competitively blocks plasminogen activation → inhibits fibrinolysis	Tx of fibrinolysis induced bleeding *Tranexamic acid also used in dental extractions for hemophilia patients*	
Tranexamic Acid	Same MOA as above + antifibrinolytic		


Anticoagulants
Rx arterial & venous thrombosis
Direct Thrombin Inhibitors
dabigatran
argatroban
lepirudin
Indirect Thrombin Inhibitors
heparin
enoxaparin
UFH
LMWH
fondaparinux
Vit K epoxide reductase inhibitor
warfarin
Direct Xa Inhibitors
rivaroxiban
apixaban
Antiplatelet Drugs
Rx arterial disease
COX Inhibitors
aspirin
Glycoprotein IIb/IIIa Inhibitors
abciximab
eptifibatide
tirofiban
ADP inhibitors
clopidogrel
Thrombolytics
Rx arterial & venous thrombosis
Plasminogen activators
streptokinase
reteplase
tenecteplase