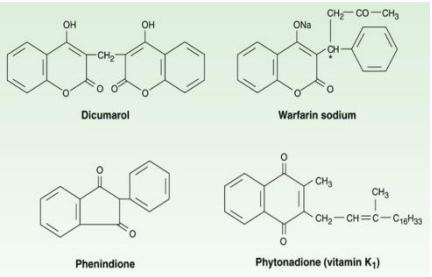
Oral Anticoagulant Drugs



*Spoiled sweet clover caused hemorrhage in cattle(1930s).

*Substance identified as bishydroxycoumarin.

*Initially used as rodenticides, still very effective, more than strychnine.

*Warfarin was introduced as an antithrombotic agent in the 1950s.

1. Warfarin:

About the drug	• Is one of the most commonly prescribed drugs, usually underprescriped. • 100% bioavailability, beaks after one hour. • 99% bound to plasma protiens, leading to small volume of distribution and long 1/2 life (36 hr). • Doesn't cross BBB, but crosses placenta. • Hydroxylated in the liver. • Present in 2 enantiomorphs.
Mechanism of Action	Act in the liver, not in the circulation. Structure is similar to vitamin K. • Block the ɣ-carboxylation which is a final synthetic step that transforms a common precursor into various factors: prothrombin, VII, IX, and X as well as the endogenous anticoagulant proteins C and S. • This blockade results in incomplete coagulation factor molecules that are biologically inactive. • The protein carboxylation reaction is coupled to the oxidation of vitamin K. • The vitamin must then be reduced to reactivate it. • Therefore, warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form.
Onset of Action	• Time to maximal effect depends on factor degradation half-lives in the circulation. VII=6, IX=24, X= 40 and II=60 hrs. • Action starts after about 48 hrs i.e. after elimination of most of the factors in the circulation. So, do not increase the dose. • Effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K dependent clotting factors.
Administration and Dosage	• Treatment is initiated with small doses of 5-10mg, not large loading doses. • Warfarin resistance seen in cancer patients. • Response monitored by Prothrombin Time. • International Normalized Ratio (INR)= Patient PT/ Mean of normal PT for the lab.
Toxicity	• Bleeding. • Teratogenicity. • Cutaneous necrosis, infarction of breast, fatty tissues, intestine and extremities. This is due to inhibition of Protein C and S, especially in patients genetically deficient in them.
Reversal of action	• Vitamin K. • Fresh-frozen plasma • Prothrombin complex concentrates. • Recombinant factor VII.

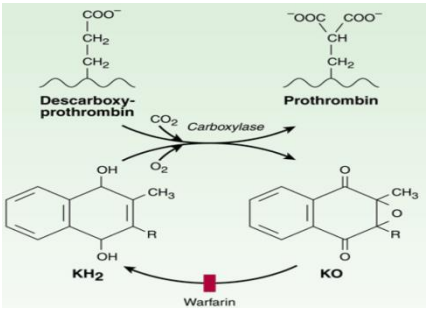


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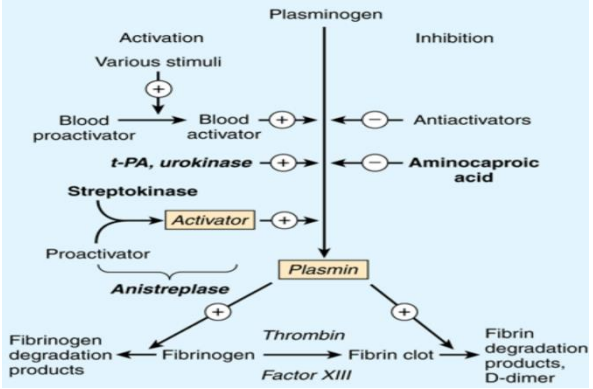
TABLE 34-2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	*Pharmacodynamic*	*Pharmacokinetic*	*Pharmacodynamic*
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

2. Fibrinolytic Agents:



*These drugs rapidly lyse thrombi by catalyzing the formation of the serine protease Plasmin from its precursor zymogen, Plasminogen.

*They create a generalized lytic state.

*Aspirin will be still required.

*Indications: -Pulmonary embolism with hemodynamic instability. -Deep venous thrombosis. -Ascending thrombophlebitis. -Acute myocardial infarction.

Drug	Source	Action	Side Effects	Notes
Streptokinase	Protein synthesized by Streptococcus	*Binds with the proactivator plasminogen in plasma to activate it. *Not fibrin - specific > Bleeding.	Highly antigenic : -Can cause allergic reactions . -Can result in inactivation of the drug.	Early administration is important.
Anistreplase **(Anisoylated Plasminogen Streptokinase Activator Complex,ASPAC)**		Deacylated at fibrin surface > Active complex released.		-More active and selective. -Long action, t½: 6h
Urokinase	A human enzyme synthesized by the kidneys.	Directly converts plasminogen into plasmin.	Not antigenic	Expensive
Tissue-type Plasminogen Activators (t-PA) **Ateplase/ Reteplase/ Tenecteplase**	Synthesized by the endothelial cells, also recombinant.	*Bind to fibrin and activate plasminogen at the fibrin surface. *Action less affected by age of thrombus. *Specific action: within the thrombus, avoids systemic activation.		-Short action t½ = 8 min -Given by infusion over 1-3 hours. -Very Expensive.

3. Antiplatelet Drugs:

Types of Platelet Regulators:

1. Agents generated outside platelets which interact with membrane receptors: Catecholamines, collagen, thrombin, and prostacyclin.

2. Agents generated inside and interact with membrane receptors: ADP, PGD2, PGE2 and serotonin.

3. Agents generated within and interact within platelets: TXA2, cAMP, cGMP and calcium.

Factors that play a role in platelet adhesion and aggregation:

1. GPIa/IIa and GPIb: are platelet receptors that bind to collagen and von Willebrand factor (vWF), causing platelets to adhere to the subendothelium of a damaged blood vessel.

2. P2Y1 and P2Y12 are receptors for ADP. When stimulated by agonists, these receptors activate the fibrinogen-binding protein GPIIb/IIIa and cyclooxygenase-1 (COX-1) to promote platelet aggregation and secretion.

3. PAR1 and PAR4 are protease-activated receptors that respond to thrombin (IIa).

4. Thromboxane A2 (TxA2) is the major product of COX-1 involved in platelet activation.

5. Prostaglandin I2(prostacyclin, PGI2), synthesized by endothelial cells, inhibits platelet activation

Drug	Site of action	Details about action	Notes
Aspirin = Acetyl Salicylic Acid	inhibits thromboxane A2(TXA2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA2 release attenuates platelet activation and recruitment to the site of vascular injury.	Causes irreversible acetylation of COX in platelets. Platelets do not have DNA or RNA, so aspirin causes permanent inhibition of platelets' COX (half-life 7-10 days). Endothelium can synthesize new COX, so PGI2 production is not affected.	Dose: 80 ¾ 325 mg.
Clopidogrel (Plavix) Ticlopidine (Ticlid) prasugrel	irreversibly block P2Y12, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12.	Irreversibly block ADP receptors on platelets.	Useful in TIAs, completed stroke, unstable angina and after placement of coronary stents. *Useful for patients who cannot tolerate aspirin. * Can cause leukopenia, GI irritation and skin rash.
Abciximab	inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa.	C7E3 monoclonal antibody of the glycoprotein IIb/IIIa receptor complex	
Eptifibatide		Synthetic peptide	
Tirofiban			
SCH530348 and E5555	inhibit thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR1), the major thrombin receptor on platelets.		
Dipyridamole Cilostazole		Work by inhibiting adenosine uptake and phosphodiesterase enzyme > c AMP in platelets and elsewhere. *They also work as vasodilators	
Dazoxiben		Inhibits TX synthetase enzyme.	
Sulotroban		Inhibits TXA2 receptor.	
Anagrelide		Reduces platelet production by decreasing megakaryocyte maturation.	
Lipid Lowering Agents			

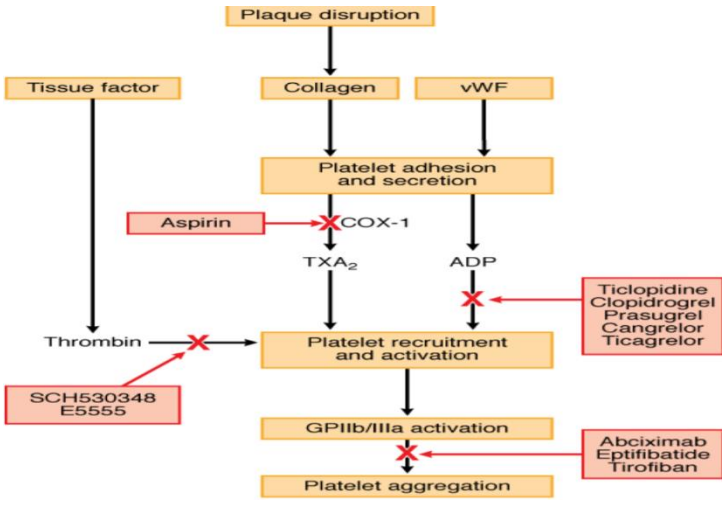
4. Hemostatic Agents:

*Whole Blood *Fresh Frozen Plasma . *Plasma fractions. *Vitamin K.

*Absorbable Gelatin Foam *Absorbable Gelatin Film *Oxidized Cellulose *Thrombin

5. Plasmin Inhibitors:

*a2 Antiplasmin: Physiological. *Aprotinin: Bovine parotid gland. *Aminocaproic Acid *Tranexamic Acid



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