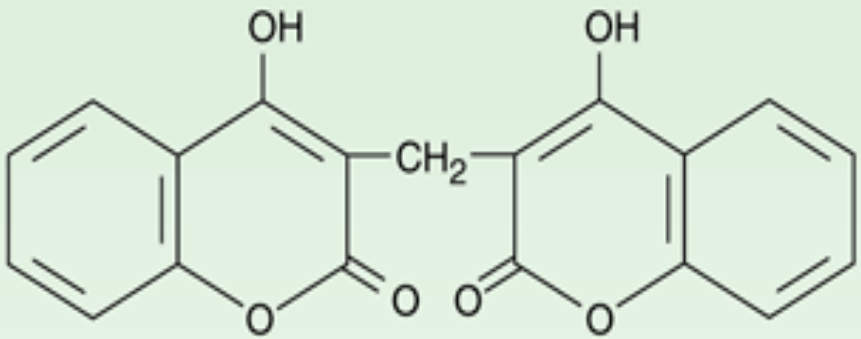
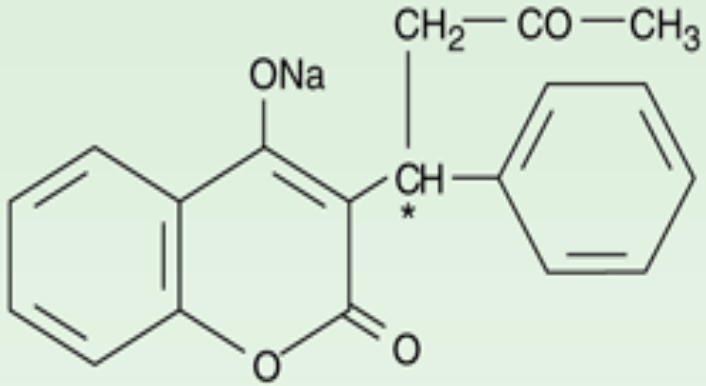
Oral Anticoagulant Drugs

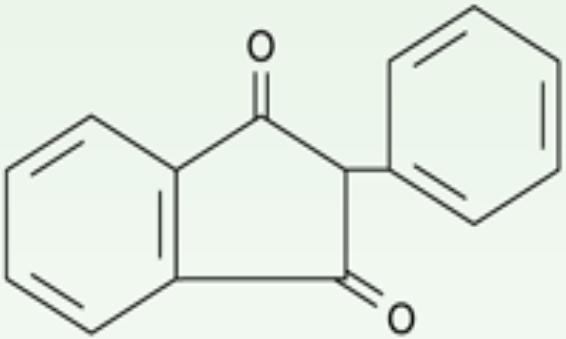
- **Spoiled sweet clover caused hemorrhage in cattle(1930s).**
- **Substance identified as bishydroxycoumarin.**
- **Initially used as rodenticides, still very effective, more than strychnine.**
- **Warfarin was introduced as an antithrombotic agent in the 1950s.**



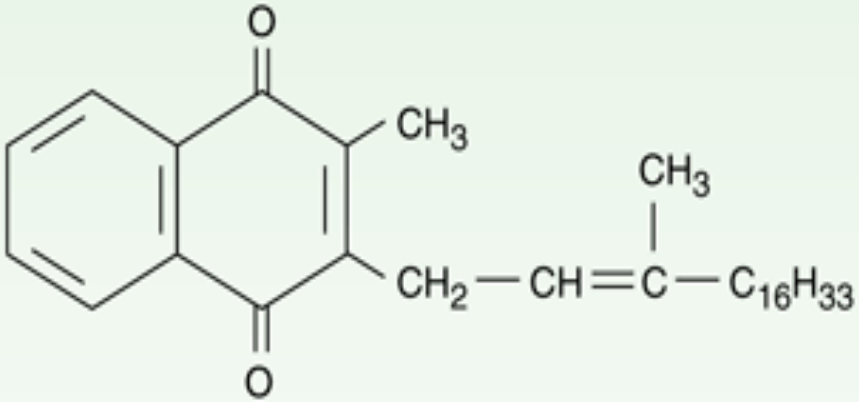
Dicumarol



Warfarin sodium



Phenindione



Phytonadione (vitamin K_1)

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Oral Anticoagulant Drugs

- **Warfarin:**
  - **Is one of the most commonly prescribed drugs, usually *underprescribed*.**
  - **100% bioavailability, peaks after one hour.**
  - **99% bound to plasma proteins, leading to small volume of distribution and long half life(36hr). Does not cross BBB, but crosses the placenta.**
  - **Hydroxylated in the liver.**
  - **Present in two enantiomorphs.**

Oral Anticoagulant Drugs

Mechanism of Action:

Act in the liver, not in the circulation.

Structure is similar to vitamin K.

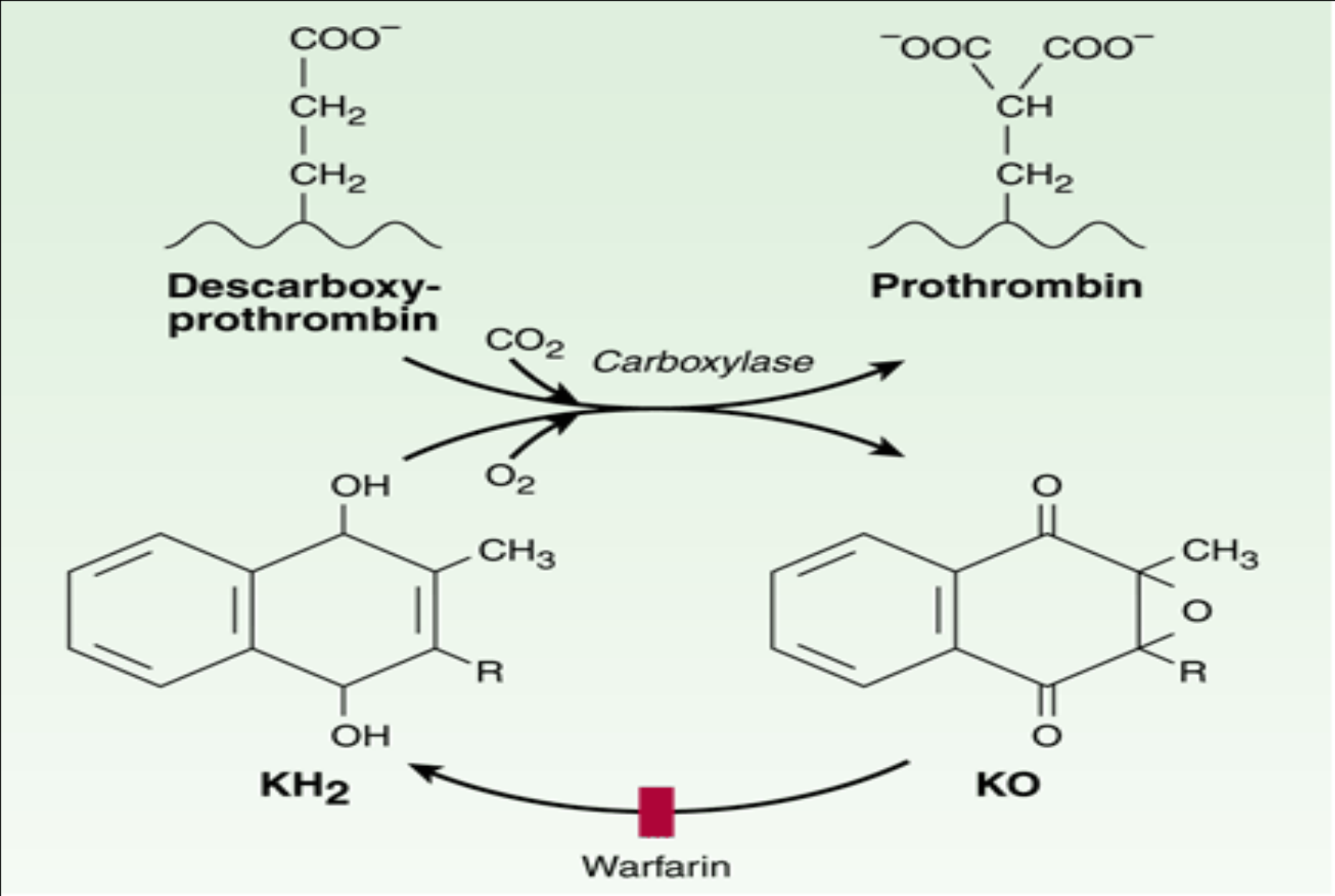
- **Block the γ-carboxylation which is a final synthetic step that transforms a common precursor into various factors: prothrombin, VII, IX, and X as well as the endogenous anticoagulant proteins C and S.**
- **This blockade results in incomplete coagulation factor molecules that are biologically inactive.**

Oral Anticoagulant Drugs

Mechanism of Action:

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.**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Warfarin

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.**

Warfarin

- **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.**

Warfarin

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.**

Table 10-1. CD

Clinically Significant Interactions with Warfarin by Level of Causation and Drug Group

Level of Causation	Anti-infectives	Cardiovascular Drugs	Analgesics, Anti-inflammatories, and Immunologics	CNS Drugs
		Potentiation		
I Highly Probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid (600 mg/d) Metronidazole Miconazole oral gel Miconazole vaginal suppositories Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline
II Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Acetylsalicylic acid Celecoxib Dextropropoxyphene Interferon Tramadol	Disulfiram Choral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)
III Possible	Amoxicillin Amoxicillin/ tranexamic rinse Chloramphenicol Gatifloxacin Miconazole topical gel193 Nalidixic acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Celecoxib Indomethacin Leflunomide Propoxyphene Rofecoxib Sulindac Tolmetin Topical salicylates	Felbamate
IV Highly Improbable	Cefamandole Cefazolin Sulfisoxazole	Bezafibrate Heparin	Levamisole Methylprednisolone Nabumetone	Fluoxetine/diazepam Quetiapine
		Inhibition		
I Highly Probable	Griseofulvin Nafcillin Ribavirin Rifampin	Cholestyramine	Mesalamine	Barbiturates Carbamazepine
II Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chlordiazepoxide
III Possible	Terbinafine	Telmisartan	Sulfasalazine	
IV Highly Improbable	Cloxacillin Nafcillin/dicloxacillin Teicoplanin	Furosemide		Propofol

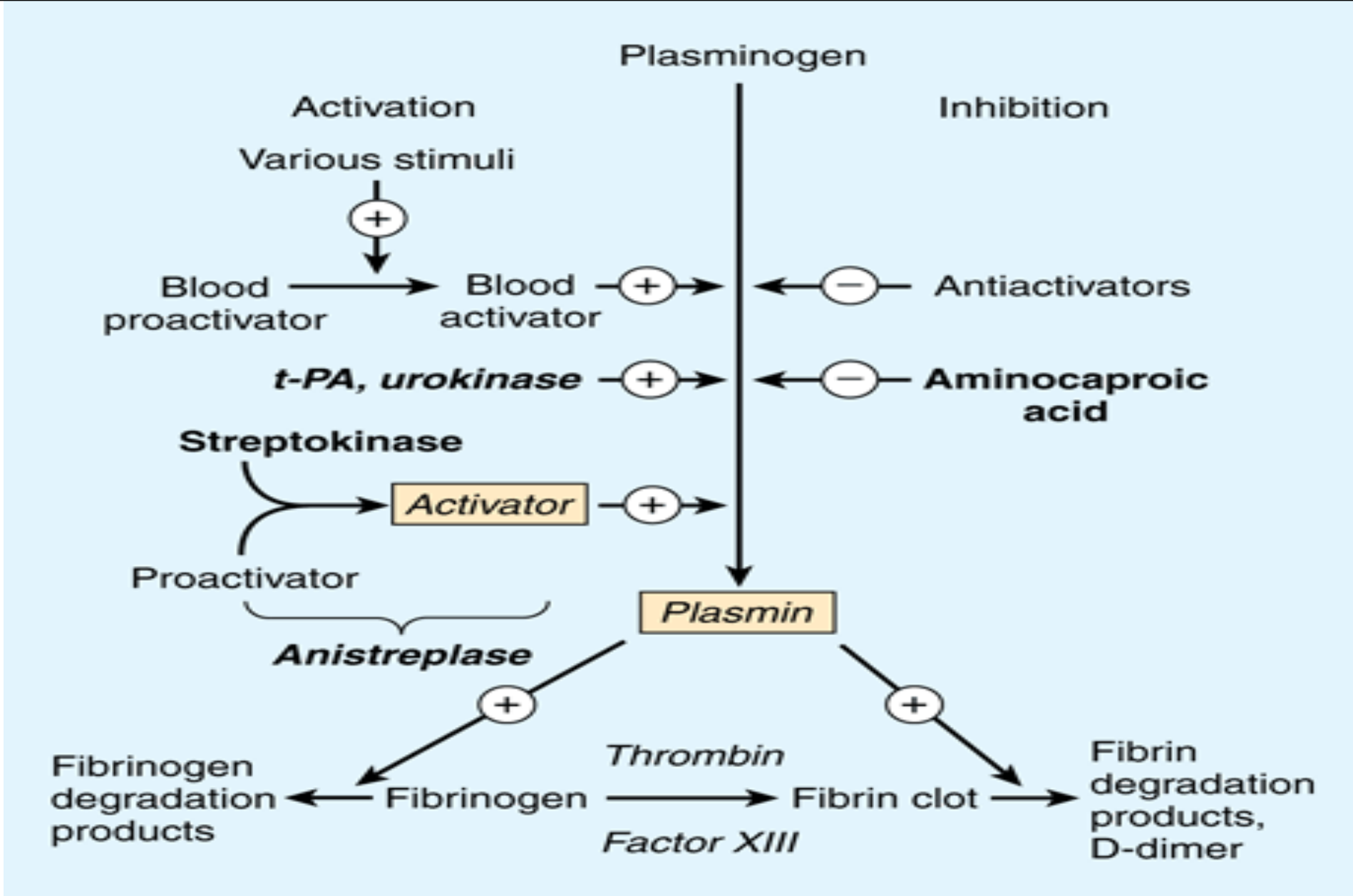
Source: Adapted with permission from reference 30.

Warfarin

- **Reversal of Action:**
  - **Vitamin K.**
  - **Fresh-frozen plasma.**
  - **Prothrombin complex concentrates.**
  - **Recombinant factor VII.**

Fibrinolytic Agnets

- **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.**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Fibrinolytic Agents

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.**

Fibrinolytic Agents

Urokinase:

- **Is a human enzyme synthesized by the kidneys.**
- **Directly converts plasminogen into plasmin.**
- **Not antigenic.**
- **Expensive.**

Fibrinolytic Agents

Anistreplase (Anisoylated Plasminogen Streptokinase Activator Complex,ASPAC):

- **Deacylated at fibrin surface → Active complex released.**
- **More active and selective.**
- **Long action, t½ → 6h**

Fibrinolytic Agnets

- **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.**

Fibrinolytic Agnets

Indications:

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

Antiplatelet Drugs

Types of Platelet Regulators:

- **Agents generated outside platelets which interact with membrane receptors:**

  Catecholamines, collagen, thrombin, and prostacyclin.

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

- **Agents generated within and interact within platelets: TXA_2, cAMP, cGMP and calcium.**

Platelet adhesion and aggregation

- **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.**

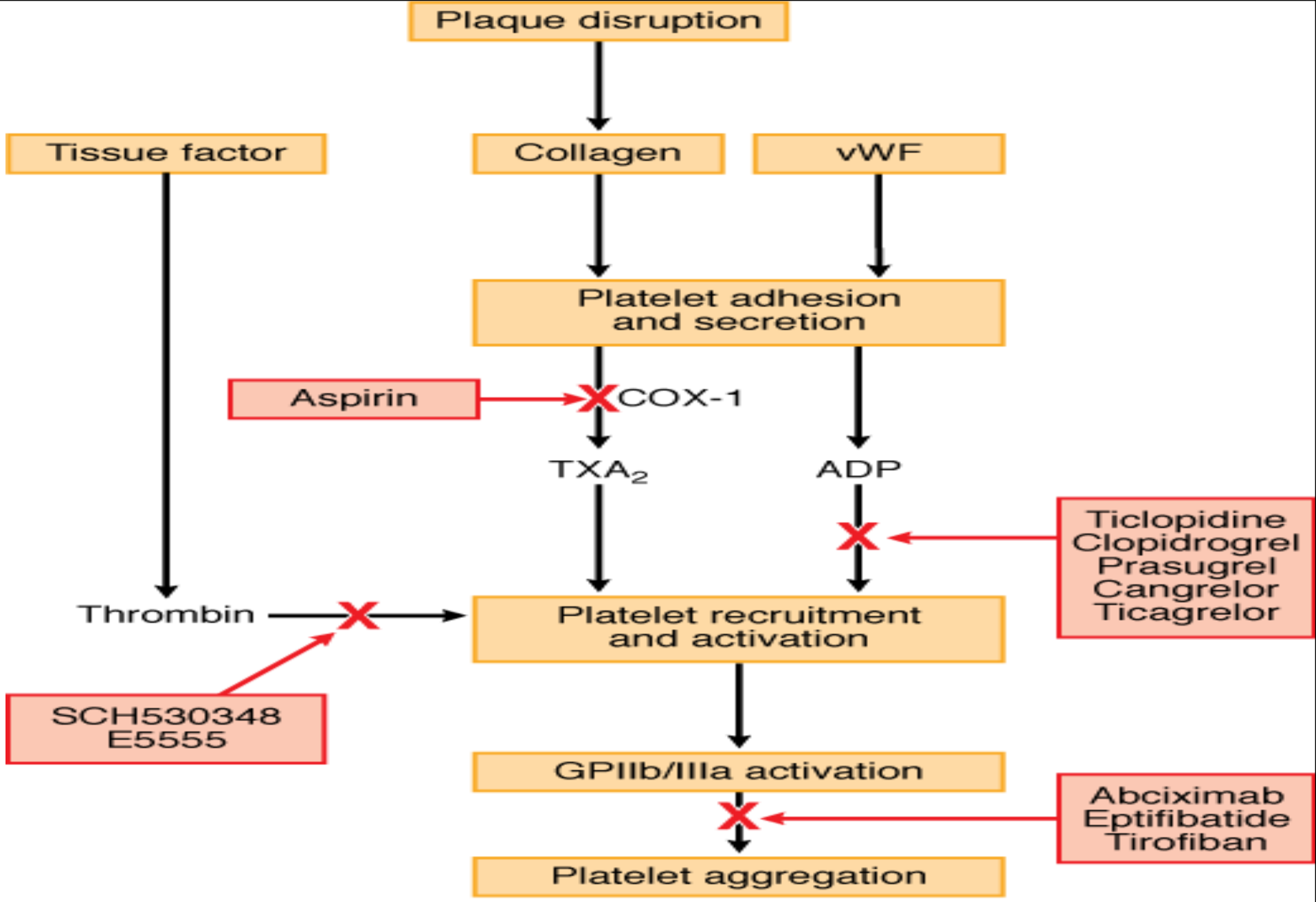
- **P2Y1 and P2Y12 are receptors for ADP. When stimulated by agonists, these receptors activate the fibrinogen-binding protein GPIIb/IIIa and cyclooxygenase-1 (COX-1) to promote platelet aggregation and secretion.**

Platelet adhesion and aggregation

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

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

- **Prostaglandin I2(prostacyclin, PGI2), synthesized** by **endothelial cells, inhibits platelet activation**



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Sites of action of antiplatelet drugs.

- **Aspirin 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.**
- **Ticlopidine, clopidogrel, and prasugrel irreversibly block P2Y12, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12.**

Sites of action of antiplatelet drugs.

- **Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa.**

- **SCH530348 and E5555 inhibit thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets.**

Antiplatelet Drugs

- **Aspirin = Acetyl Salicylic Acid**
  - **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 — 325 mg.**

Antiplatelet Drugs

- Clopidogrel (Plavix).
- Ticlopidine (Ticlid).
  - 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.

Antiplatelet Drugs

- **Abciximab.**
  - **C7E3 monoclonal antibody of the glycoprotein IIb/IIIa receptor complex.**
- **Eptifibatide.**
  - **Synthetic peptide.**
- **Tirofiban.**
  - **All inhibit the platelet glycoprotein IIb/IIIa complex, which works as a receptor mainly for fibrinogen and vitronectin as well as for fibronectin and von Willebrand factor.**

Antiplatelet Drugs

Dipyridamole

Cilostazole

Also work as vasodilators.

- **Work by inhibiting adenosine uptake and phosphodiesterase enzyme $\rightarrow\uparrow$c AMP in platelets and elsewhere.**

Antiplatelet Drugs

Dazoxiben:

Inhibits TX synthetase enzyme.

Sulotroban:

Inhibits TXA2 receptor.

Anagrelide:

Reduces platelet production by decreasing megakaryocyte maturation.

Lipid Lowering Agents

Hemostatic Agents

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

Table 34–3. Therapeutic products for the treatment of coagulation disorders.

Factor	Deficiency State	Hemostatic Levels	Half-Life of Infused Factor	Replacement Source
I	Hypofibrinogenemia	1 g/dL	4 days	Cryoprecipitate FFP
II	Prothrombin deficiency	30–40%	3 days	Prothrombin complex concentrates (intermediate purity factor IX concentrates)
V	Factor V deficiency	20%	1 day	FFP
VII	Factor VII deficiency	30%	4–6 hours	FFP Prothrombin complex concentrates (intermediate purity factor IX concentrates) Recombinant factor VIIa
VIII	Hemophilia A	30–50% 100% for major bleeding or trauma	12 hours	Recombinant factor VIII products Plasma-derived high purity concentrates Cryoprecipitate[1] Some patients with mild deficiency will respond to DDAVP
IX	Hemophilia B Christmas disease	30–50% 100% for major bleeding or trauma	24 hours	Recombinant factor IX products Plasma-derived high purity concentrates
X	Stuart-Prower defect	25%	36 hours	FFP Prothrombin complex concentrates
XI	Hemophilia C	30–50%	3 days	FFP
XII	Hageman defect	Not required		Treatment not necessary
Von Willebrand	Von Willebrand disease	30%	Approximately 10 hours	Intermediate purity factor VIII concentrates that contain von Willebrand factor Some patients respond to DDAVP Cryoprecipitate[1]
XIII	Factor XIII deficiency	5%	6 days	FFP Cryoprecipitate

Hemostatic Agents

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

Plasmin Inhibitors

- α2 Antiplasmin
  - **Physiological.**
- Aprotinin:
  - **Bovine parotid gland.**
- Aminocaproic Acid
- Tranexamic Acid