Drugs used in Thromboembolic Disease II

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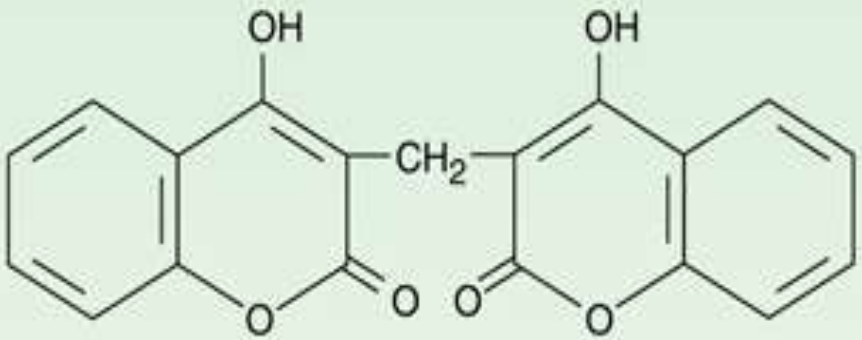
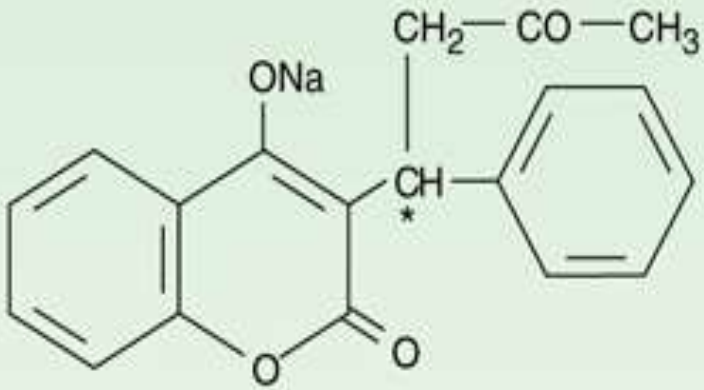
Oral Anticoagulant Drugs

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

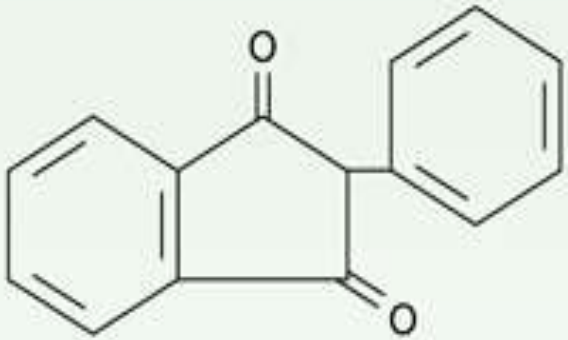
- 27/10/2021



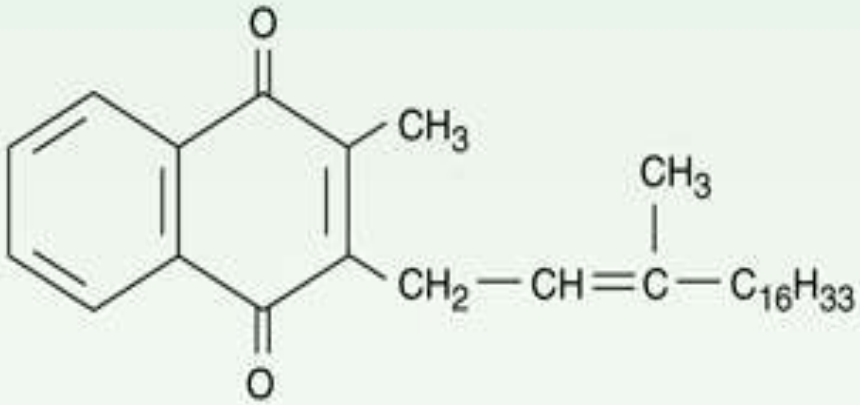
Dicumarol



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, actually it is *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.

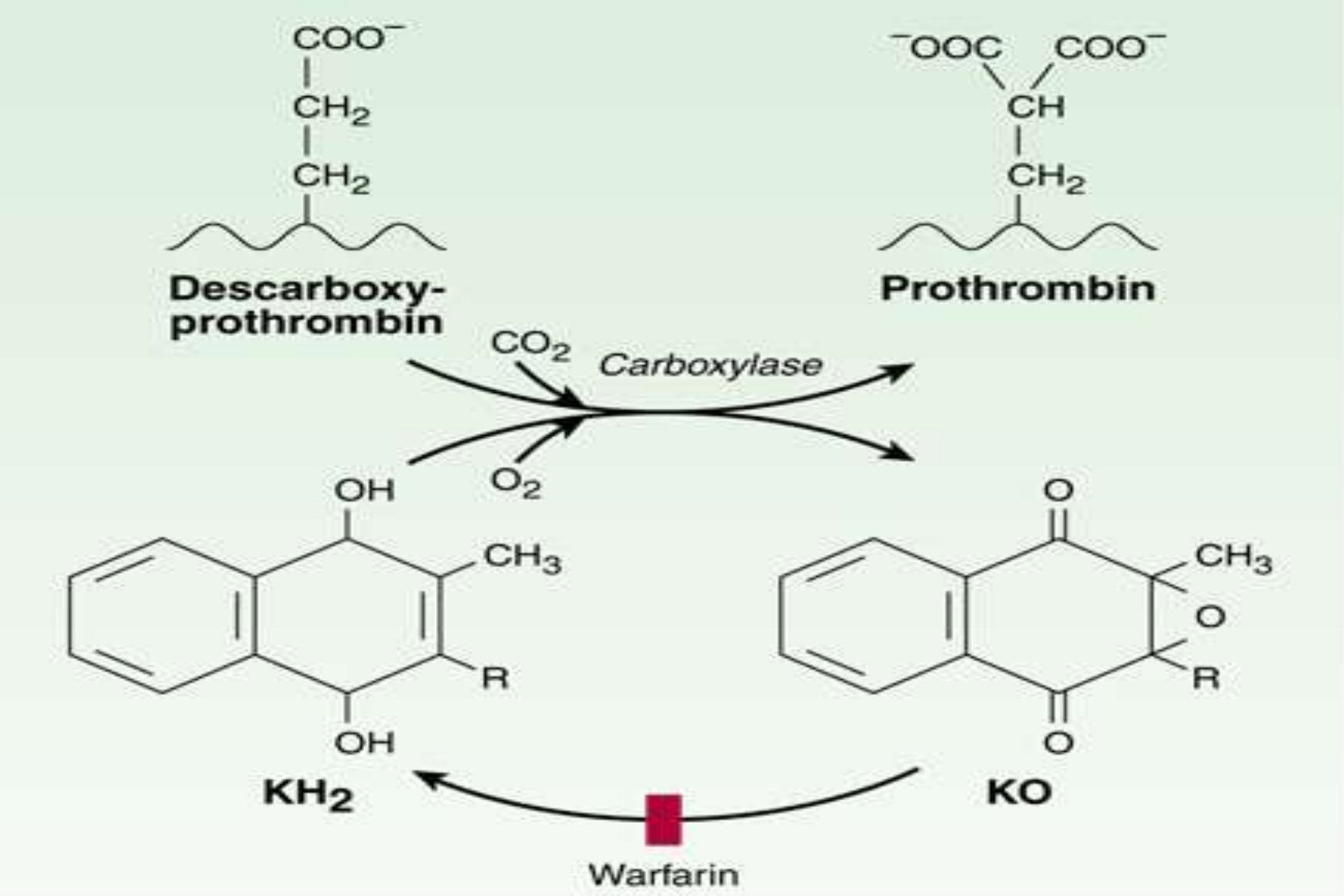
- Block the ɣ-carboxylation which is a final synthetic step that transforms a common precursor into various factors: prothrombin, VII, IX, and X as well as the endogenous anticoagulant proteins C and S.
- This blockade results in incomplete coagulation factor molecules that are biologically inactive.

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

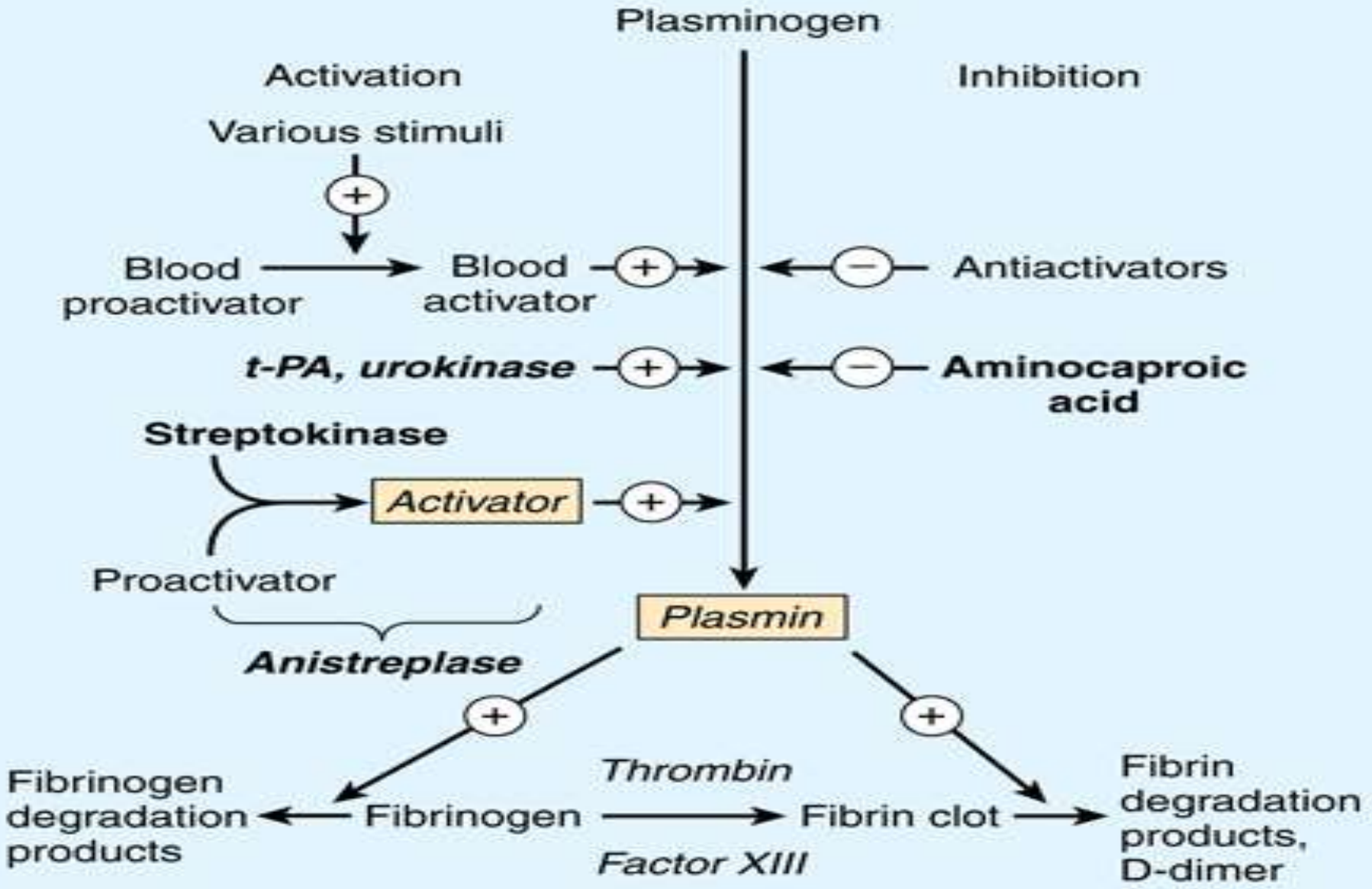
Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	***Pharmacodynamic***	***Pharmacokinetic***	***Pharmacodynamic***
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K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

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 .
  - This 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):

- More active and selective.
- Deacylated at fibrin surface → Active complex released.
- 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.

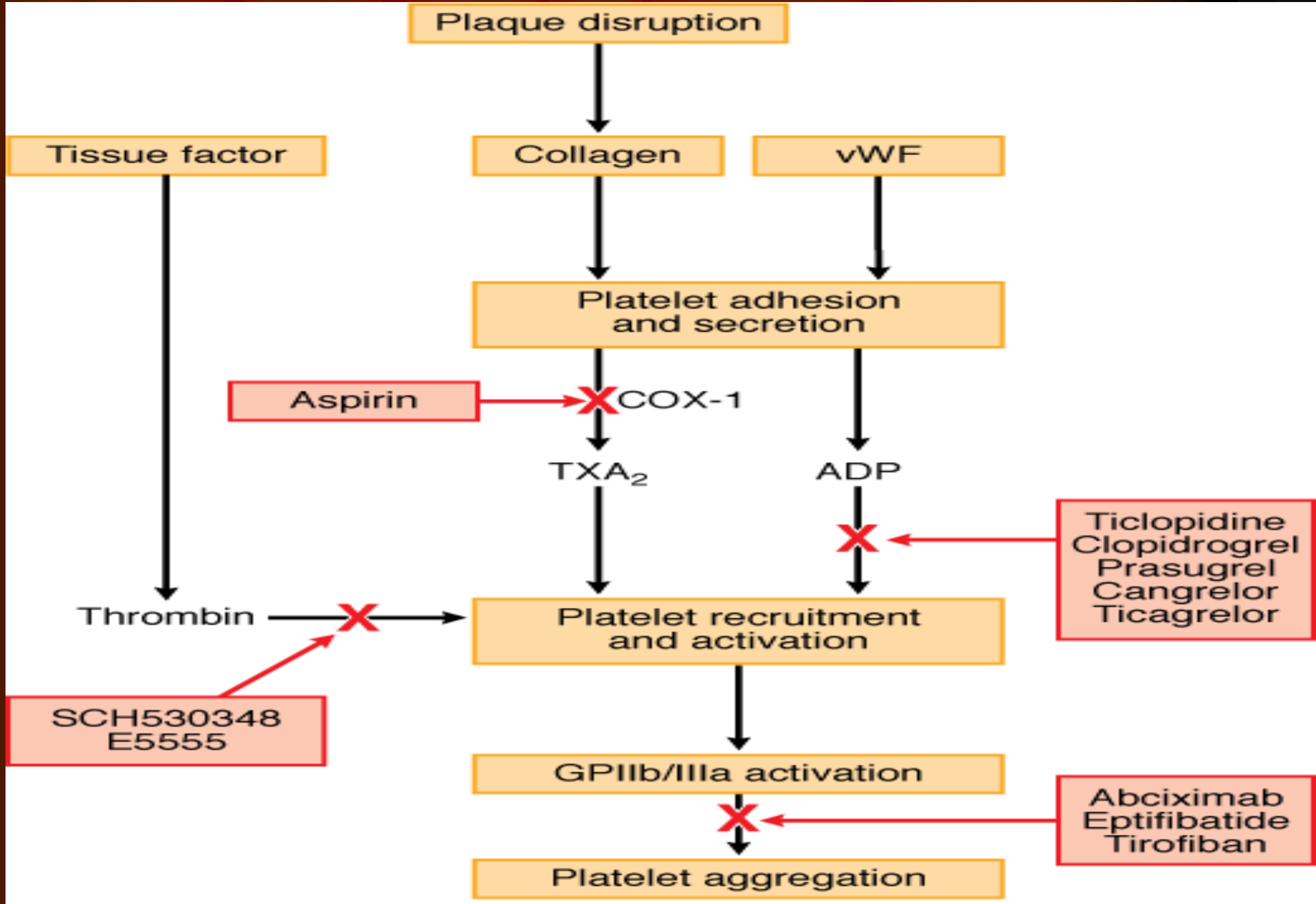
Platelet adhesion and aggregation

- **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** Block fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa.

- **Zontivity** 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.

- Monoclonal antibody

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