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.
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 (36 hr). Does not cross BBB, but crosses the placenta.
  - Hydroxylated in the liver.
  - Present in two enantiomorphs.

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Oct-13
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.
Dicumarol

Warfarin sodium

Phenindione

Phytonadione (vitamin K₁)

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

Onset of Action:

- Action starts after about 48 hrs after elimination of the factors in the circulation.
- Effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K dependent clotting factors.
- Time to maximal effect depends on factor degradation half-lives in the circulation. $\text{VII}=6$, $\text{IX}=24$, $\text{X}=40$ and $\text{II}=60$. 
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>
<thead>
<tr>
<th>Level of Causation</th>
<th>Anti-infectives</th>
<th>Cardiovascular Drugs</th>
<th>Analgesics, Anti-inflammatory, and Immunologics</th>
<th>CNS Drugs</th>
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</thead>
<tbody>
<tr>
<td>I Highly Probable</td>
<td>Ciprofloxacin</td>
<td>Amiodarone</td>
<td>Phenybutazone</td>
<td>Alcohol (if concomitant liver disease)</td>
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<td>Cotrimoxazole</td>
<td>Clofibrate</td>
<td>Piroxicam</td>
<td>Citalopram</td>
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<td>Diltiazem</td>
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<td>Fluconazole</td>
<td>Fenofibrate</td>
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<td>Sertraline</td>
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<td></td>
<td>Isoniazid (600 mg/d)</td>
<td>Propafenone</td>
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<td>Metronidazole</td>
<td>Propranolol</td>
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<tr>
<td></td>
<td>Miconazole oral gel</td>
<td>Sulfipyrazone</td>
<td>(biphasic with later inhibition)</td>
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<tr>
<td></td>
<td>Miconazole vaginal suppositories</td>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II Probable</td>
<td>Amoxicillin/clavulanate</td>
<td>Fluvastatin</td>
<td>Acetaminophen</td>
<td>Disulfiram</td>
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<tr>
<td></td>
<td>Azithromycin</td>
<td>Quinidine</td>
<td>Acetylsalicylic acid</td>
<td>Choral hydrate</td>
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<td>Clarithromycin</td>
<td>Ropinirole</td>
<td>Celecoxib</td>
<td>Fluoxamine</td>
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<tr>
<td></td>
<td>Clarithromycin</td>
<td>Simvastatin</td>
<td>Dextropropoxyphene</td>
<td>Phenytin (biphasic with later inhibition)</td>
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<td>Itraconazole</td>
<td>Metolazone</td>
<td>Interferon</td>
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<td>Levofloxacin</td>
<td>Keloximide</td>
<td>Tolmetin</td>
<td></td>
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<tr>
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<td>Ritonavir</td>
<td>Tetrazycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III Possible</td>
<td>Amoxicillin</td>
<td>Amiodarone-induced toxicosis</td>
<td>Celecoxib</td>
<td>Felbamate</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/tranexamic rinse</td>
<td>Disopyramide</td>
<td>Indomethacin</td>
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<tr>
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<td>Clarithromycin</td>
<td>Gemfibrozil</td>
<td>Leflunomide</td>
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<td>Metolazone</td>
<td>Propoxyphene</td>
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<td>Itraconazole</td>
<td>Rofecoxib</td>
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<td>Levofloxacin</td>
<td>Sulindac</td>
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<td>Ritonavir</td>
<td>Tolmetin</td>
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<tr>
<td></td>
<td>Tetrazycline</td>
<td>Topical salicylates</td>
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<tr>
<td>IV Highly Improbable</td>
<td>Cefamandole</td>
<td>Bezafibrate</td>
<td>Levamisole</td>
<td>Fluoxetine/diazepam</td>
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<td>Cefazolin</td>
<td>Heparin</td>
<td>Methylprednisolone</td>
<td>Quetiapine</td>
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<td>Sulfoxazole</td>
<td>Levamisole</td>
<td>Nabumetone</td>
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**Inhibition**

<table>
<thead>
<tr>
<th>Level of Causation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>I Highly Probable</td>
<td>Griseofulvin</td>
<td>Cholestyramine</td>
<td>Mesalamine</td>
<td>Barbiturates</td>
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<td>Nafcillin</td>
<td></td>
<td></td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td>Ribavirin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II Probable</td>
<td>Dicloxacillin</td>
<td>Bosentan</td>
<td>Azathioprine</td>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
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<td></td>
<td></td>
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<tr>
<td>III Possible</td>
<td>Terbinafine</td>
<td>Telmisartan</td>
<td>Sulfasalazine</td>
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<tr>
<td>IV Highly Improbable</td>
<td>Cloxacillin</td>
<td>Furosemide</td>
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<td>Propofol</td>
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<tr>
<td></td>
<td>Nafcillin/dicloxacillin</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Teicoplanin</td>
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</tbody>
</table>

Source: Adapted with permission from reference 30.
Warfarin

**Reversal of Action:**

- Vitamin K.
- Fresh-frozen plasma.
- Prothrombin complex concentrates.
- Recombinant factor VII.
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.
Fibrinolytic Agents

**Streptokinase:**
- Protein synthesized by *Streptococcus*.
- Binds with the proactivator plasminogen in plasma to activate it.
- Not fibrin-specific → Bleeding.
- Highly antigenic:
  - Allergic reactions
  - Can be inactivated.
- 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):

- Deacetylated at fibrin surface → Active complex released.
- More active and selective.
- Long t½ Action → 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 $t^{1/2} = 8$ min.
- Given by infusion over 1-3 hours.
- Very Expensive.
- Should add Aspirin.
Fibrinolytic Agnets

Indications:

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

Platelet Regulators:

- Agents generated outside platelets and 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.
Sites of action of antiplatelet drugs.

- **Aspirin** inhibits thromboxane A2 (TxA2) synthesis by irreversibly acetylation 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**
  - Irreversible acetylation of COX in platelets.

Platelets do not have DNA or RNA, so 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 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**

Vasodilator.

- Inhibit adenosine uptake and phosphodiesterase enzyme → ↑ 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>
<thead>
<tr>
<th>Factor</th>
<th>Deficiency State</th>
<th>Hemostatic Levels</th>
<th>Half-Life of Infused Factor</th>
<th>Replacement Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hypofibrinogenemia</td>
<td>1 g/dL</td>
<td>4 days</td>
<td>Cryoprecipitate</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>FFP</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin deficiency</td>
<td>30–40%</td>
<td>3 days</td>
<td>Prothrombin complex concentrates (intermediate purity factor IX concentrates)</td>
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<td>V</td>
<td>Factor V deficiency</td>
<td>20%</td>
<td>1 day</td>
<td>FFP</td>
</tr>
<tr>
<td>VII</td>
<td>Factor VII deficiency</td>
<td>30%</td>
<td>4–6 hours</td>
<td>FFP</td>
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<td>Prothrombin complex concentrates (intermediate purity factor IX concentrates)</td>
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<td></td>
<td>Recombinant factor VIIa</td>
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<td>VIII</td>
<td>Hemophilia A</td>
<td>30–50%</td>
<td>12 hours</td>
<td>Recombinant factor VIII products</td>
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<td></td>
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<td>100% for major bleeding or trauma</td>
<td></td>
<td>Plasma-derived high purity concentrates</td>
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<td></td>
<td>Cryoprecipitate</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Some patients with mild deficiency will respond to DDAVP</td>
</tr>
<tr>
<td>IX</td>
<td>Hemophilia B Christmas disease</td>
<td>30–50%</td>
<td>24 hours</td>
<td>Recombinant factor IX products</td>
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<td>100% for major bleeding or trauma</td>
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<td>Plasma-derived high purity concentrates</td>
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<tr>
<td>X</td>
<td>Stuart-Prower defect</td>
<td>25%</td>
<td>36 hours</td>
<td>FFP</td>
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<tr>
<td>XI</td>
<td>Hemophilia C</td>
<td>30–50%</td>
<td>3 days</td>
<td>FFP</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman defect</td>
<td>Not required</td>
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<td>Treatment not necessary</td>
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<td>Von Willebrand disease</td>
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<td>Approximately 10 hours</td>
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<td>Some patients respond to DDAVP</td>
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<td>Factor XIII deficiency</td>
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<td>秋-13</td>
<td>FFP</td>
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<td>Cryoprecipitate</td>
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Plasmin Inhibitors

- $\alpha_2$ Antiplasmin
  - Physiological.
- Aprotinin:
  - Bovine parotid gland.
- Aminocaproic Acid
- Tranexamic Acid
Hemostatic Agents

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