<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prototype</th>
<th>Action</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anticoagulant</td>
<td><strong>Parenteral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td>Inactivation of clotting factors</td>
<td>Prevent DVT</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td>Warfarin</td>
<td>Decrease synthesis of clotting factors</td>
<td>Prevent DVT</td>
</tr>
<tr>
<td>2. Antiplatelet</td>
<td>Aspirin</td>
<td>Decrease platelet aggregation</td>
<td>Prevent arterial thrombosis</td>
</tr>
<tr>
<td>3. Thrombolytic</td>
<td>Streptokinase</td>
<td>Fibinolysis</td>
<td>Breakdown of thrombi</td>
</tr>
</tbody>
</table>
I. Anticoagulants

1. Heparin

Structure
Mucopolysaccharide

Metabolism
Partially in the liver by heparinase to uroheparin, \textit{which has only slight antithrombin activity}. 20-50 \% is excreted unchanged.

{The heparin polysaccharide chain is degraded in the gastric acid} administered IV or SC. Heparin should not be given IM {danger of hematoma formation}. 
Unfractionated heparin (UFH)

Mol weight:

3000-30000

Mechanism of action:
• Primarily: interaction with antithrombin III: alters the molecular configuration of antithrombin III, making it 1,000 to 4,000 times more potent as an inhibitor of thrombin formation: limits conversion of fibrinogen to fibrin: prolongs aPTT
• Also inhibits the effects of factor Xa on the coagulation cascade & limits platelet aggregation.

Half-life:
IV: 1 hr
SC: 3 hrs.
UFH inactivate factor IIa through formation of a tertiary complex (unlike LMWH).

UFH binds more to plasma proteins, endothelium and macrophages: reduced bioavailability & greater patient variability to a given dose.

UFH inactivates factors IIa and Xa & affects the aPTT (measure of anti-factor IIa activity).
Dosing options.

Preoperative: 5,000U 2 hours before surgery. 
*{The single preoperative dose seems to be as effective as multiple preoperative doses}.*

Postoperative: 8 to 12 hrs after surgery & every 8 to 12 hrs until the patient is fully ambulatory.

Antidote: 
Protamine sulphate

Monitor: 
aPTT

Use in pregnancy: *{does not cross the placenta}* 
safe
Low-Molecular-Weight Heparin

- Molecular weight
  1000-10000 Da.
- Produced by concentrating the low molecular component of UFH. Enzymatic or chemical controlled hydrolysis of UFH.
- The mechanism of action
  Primarily by inhibiting factor Xa, which is higher in the coagulation cascade than antithrombin: LMWH is more efficient than UFH.

{the molecular configuration of antithrombin III is not altered by LMWH} thrombin conversion is minimally inhibited and aPTT is not appreciably affected.
LMWH inhibits factor Xa and minimally affects factor IIa; thus aPTT is not used to measure its anticoagulant activity.
<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Manufacturer</th>
<th>Mol Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Lovenex, Clexane</td>
<td>Rhone-Poulence-Rorer</td>
<td>4500</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Logiparine</td>
<td>Novo</td>
<td>4850</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>Kabi</td>
<td>6370</td>
</tr>
</tbody>
</table>
Half-life:
4 hrs, by any route: longer dosing interval.

Bioavailability
More consistent than that of UFH: dosing is based on lean body mass & Less thrombocytopenia.

**Use in pregnancy:**
Does not cross the placenta: safe.

**Dosing options.**
Prophylaxis: Once a day
Therapy: Twice-daily.

**Enoxaparin** is an LMWH
Moderate risk: 20 mg/d
High risk: 40 mg/d.

• **Advantage**
Decreased need for monitoring
Fondaparinux

- Fondaparinux is given via injection once daily
- It is licensed for initial treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for venous thromboembolism prevention in patients undergoing surgery for hip fracture or hip/knee replacement
Hirudin

• Medicinal leeches:
  – Used since ancient times to relieve body of “bad humors”
    • Egyptians, Greeks
  – Reached peak popularity in mid-19th century

Hirudo medicinalis
• 1884: John Haycraft in Birmingham demonstrated that medicinal leeches, *Hirudo medicinalis*, secrete a substance that prevents blood from clotting

• 1904: Substance named hirudin

• 1957: Markwardt isolated the active anticoagulant substance, determined it to be a polypeptide 65 AAs long which inhibited thrombin
• Estimated to require 50,000 leeches annually for diagnostics and treatment

• 1986: DNA isolated and cloned

• Today recombinant hirudin is made in yeast cells
  – Lepirudin, desirudin, bivalirudin
History of Anticoagulants

- Warfarin has been the drug of choice for the prevention and treatment of arterial and venous thrombotic disorders for more than 40 years.
- It was initially marketed as a pesticide against rats and mice, and is still popular for this purpose.
The vitamin K antagonists or coumarins were first isolated by Karl Paul Link at the University of Wisconsin in the 1930s. The observation that cows bled to death after eating mouldy clover had led Link’s team to isolate the anticoagulant factor from the contaminated clover. Link later developed a synthetic coumarin derivative. This was patented by the Wisconsin Alumni Research Foundation who named it warfarin as a contraction of the organization’s acronym, WARF, and the word coumarin. The use of coumarins became widespread in the 1940s.
2. Oral anticoagulants

- **Coumarins - warfarin, dicumarol**

**Structure:**
small, lipid-soluble molecules, Structurally related to vitamin K, isolated from clover leaves

**Mechanism:**
- Inhibits production of active clotting factors
- blocks the Vitamin K-dependent glutamate carboxylation of precursor clotting factors e.g. FII, VII, IX , X

**Metabolism:**
- Absorption: rapid
- Binds to albumin
- Clearance is slow: 36 hrs
- Delayed onset: 8-12 hr \{T1/2 of clotting factors in plasma\}
blocks the Vitamin K-dependent glutamate carboxylation of precursor clotting factors
Use:
To prevent the formation, recurrence or extension of DVT & PE
Not used in pregnant women {cross placenta}
Not used for arterial thrombi {No effect on platelets}

Toxicity:
bleeding
birth defects

Overdose:
Reversed by vitamin K infusion
Recovery needs synthesis of new clotting factors
Warfarin tablets, 5, 3 and 1mg
<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Representative Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that Increase Warfarin Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease binding to Albumin</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Inhibit Degradation</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Decrease synthesis of Clotting Factors</td>
<td>Cimetidine, Disulfiram</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotics (oral)</td>
</tr>
<tr>
<td>Drugs that promote bleeding</td>
<td>Inhibition of platelets</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Inhibition of clotting Factors</td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>Induction of metabolizing Enzymes</td>
<td>Antimetabolites</td>
</tr>
<tr>
<td>Drugs that decrease Warfarin activity</td>
<td>Promote clotting factor Synthesis</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>Reduced absorption</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin K</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholestyramine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colestipol</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Parenteral only</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Vol of distribution</strong></td>
<td>Plasma vol (0.07 L/kg)</td>
<td>7.6 - 13.9 L</td>
</tr>
<tr>
<td><strong>Metabolism/Clearance</strong></td>
<td>Hepatic metabolism &amp; uptake by reticulo endothelial system</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Also by thrombin &amp; other clotting factors</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination t1/2</strong></td>
<td>50 - 90 min</td>
<td>36 - 42 hr</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>Bound to antithrombin III &amp; other serine proteases</td>
<td>99.4% bound to albumin</td>
</tr>
<tr>
<td><strong>Plasma concentration (therapeutic)</strong></td>
<td>0.2 - 0.4 U/ml</td>
<td>1.5 mg/L</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Bleeding</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Thrmbocytopenia</td>
<td>Skin necrosis</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Drug interactions</td>
</tr>
<tr>
<td><strong>Treatment of bleeding</strong></td>
<td>• Mild: Slow or stop infusion</td>
<td>• Mild: hold 1-2 doses, observe, restart at lower dose</td>
</tr>
<tr>
<td></td>
<td>• Severe: Protamine 1 mg/100 u of estimated heparin remaining in body</td>
<td>• Severe: Vit K or fresh frozen plasma</td>
</tr>
</tbody>
</table>
Activation and aggregation of platelets is a major component of thrombosis especially in arteries.

**Targets** for platelet inhibitory drugs:

(a) inhibition of prostaglandin metabolism through inhibition of cyclooxygenase (aspirin)

(b) inhibition of ADP-induced platelet aggregation (ticlopidine), (clopidogrel)
Platelet Activation:

- **Endothelial damage** of vessel: exposes collagen
- **Activated platelets** release ADP, serotonin (5-HT) & thromboxane A2 (TXA2-) from arachidonic acid: platelet aggregation by causing the appearance of binding sites for fibrinogen on platelet membrane
- **Fibrinogen** is involved: platelet to platelet adhesion (aggregation)
- **Thrombin** causes further platelet activation by releasing platelet ADP & stimulating PG synthesis

*prostacyclin (PGI2) - synthesized within vessel walls inhibits thrombogenesis by increasing platelet cAMP. Nitric oxide (NO) - released by endothelium - increases cAMP*
III. Thrombolytic Agents

Agents which reduce the formation of arterial platelet thrombi

**Mechanism:**
- Rapid lysis of thrombi by catalyzing the formation of plasmin from plasminogen
- Endogenous plasmin breaks down fibrin promoting clot dissolution

**Use:**
- Emergency treatment of coronary artery thrombosis in M.I.
- IV or intracoronary injection
- DVT: rapid recanalization of occluded vessels

**Toxicity:**
- Bleeding (intracranial, G.I.)
- Allergic reactions (i.e. streptokinase)
Streptokinase:
Purified from bacteria
Continuous use: immune reaction
Forms a complex with plasminogen & catalyzes it: rapid conversion to plasmin

Urokinase:
From cultured human kidney cells
No immune response
Directly converts plasminogen to plasmin

tPA:
Produced by recombinant techniques
No immune reaction - EXPENSIVE
Promotes conversion of plasminogen (that is found to fibrin) to plasmin
In theory, selective for formed clots
The future for anticoagulants

- Molecular targets are factor IIa (thrombin) and factor Xa
- The two candidate compounds, one direct thrombin inhibitor (dabigatran etexilate) and one direct factor Xa inhibitor (rivaroxaban) are hoping to be approved as new oral anticoagulants in the near future
The future for anticoagulants

- Factor Xa also regulates thrombin generation via binding to factor Va followed by activation of prothrombin to thrombin
Fibrinogen → Fibrin

Common Pathway

New Oral Agents

Apixaban
Rivaroxaban

Xa Blocker

Prothrombin → Thrombin

Dabigatran

Clot

Fibrinogen → Fibrin
MANY CHOICES

The coagulation cascade is complex, but anticoagulant drugs in late-stage development hit it at just two points: Factor Xa or thrombin.

Factor XIIa → Factor XIa

Factor IXa → Factor VIIIa → Factor VIIa → Tissue factor

Factor Xa → Factor Va → Thrombin → Fibrin

Dabigatran etexilate

Apixaban

Rivaroxaban

Betrixaban
# Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Disadvantage of Warfarin</th>
<th>Ideal Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Fast onset of action, allowing for acute treatment of VTE and use post-procedures</td>
</tr>
<tr>
<td><strong>Need for Injectable agent</strong></td>
<td></td>
</tr>
<tr>
<td>Slow resolution of action</td>
<td>Fast resolution of action, allowing for use pre-procedures</td>
</tr>
<tr>
<td>Regular blood monitoring</td>
<td>No routine blood monitoring</td>
</tr>
<tr>
<td>Many drug interactions</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Interactions with diet</td>
<td>No interactions with diet</td>
</tr>
<tr>
<td>Wide range of therapeutic doses</td>
<td>Narrow-ranged, fixed doses</td>
</tr>
<tr>
<td>Unpredictable dose-response</td>
<td>Predictable dose-response</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Safe in pregnancy</td>
</tr>
<tr>
<td>Slow reversibility via vitamin K</td>
<td>Immediate reversibility</td>
</tr>
</tbody>
</table>
DABIGATRAN ETEXILATE  
(Pradaxa®, Boeringher-Ingelheim)

PHARMACOLOGY:
- Prodrug, converted to the active dabigatran moiety by hydrolysis via nonspecific esterases.
- Dabigatran is a reversible and selective direct thrombin inhibitor.
- Dabigatran inhibits human thrombin and thrombin-induced platelet aggregation.
- Dabigatran inhibits both clot-bound and fluid-phase thrombin.

FDA indication (Approved October 2010):
- Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Dabigatran: Ensuring Appropriate Use

Capsule Stability

- Dabigatran exetilate requires an acid environment for absorption
- Capsules contain multiple drug pellets
- Each pellet has a tartaric acid core (coated with drug) that creates an acid microenvironment to improve dissolution and absorption independent of gastric pH

DO NOT CRUSH, CHEW OR BREAK CAPSULES
Dabigatran: Ensuring Appropriate Use Capsule Stability

- Once bottle is opened, contents must be used within 30 days
  - Cap on bottle contains desiccant to reduce moisture and avoid degradation
# Comparison of Oral Anticoagulants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of action</td>
<td>Vitamin K antagonist</td>
<td>Direct thrombin inhibitor (IIa)</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Maximum time to onset</td>
<td>2–5 days</td>
<td>2 hours</td>
<td>2.5–4 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>2–5 days</td>
<td>14–17 hours</td>
<td>5–9 hours in healthy patients; 9–12 hours in elderly patients</td>
<td>8–15 hours</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Acetaminophen; aspirin; NSAIDs; anti-infectives; SSRIs; phenytoin; multiple other drugs (and diet)</td>
<td>P-gp inducers (eg, rifampin); dronedarone; ketoconazole; aspirin; NSAIDs; clopidogrel</td>
<td>Strong inhibitors and inducers of CYP3A4 and P-gp; aspirin; NSAIDs; clopidogrel</td>
<td>Aspirin; clopidogrel; potentially, strong inhibitors and inducers of CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors (antidepressants); P-gp = P-glycoprotein
Potential Advantages of New Oral Anticoagulants

- Oral administration
- Rapid onset of action
  - Eliminates 2 AC regimen
- Predictable effect with fixed or weight-based dosing
  - No monitoring
- Less food/drug interactions
- Short half-life
  - Ease of reversal/ no bridging
- More convenient
  - Potentially leading to greater use
- More cost effective
  - No routine monitoring
  - Fewer ADEs requiring ER visits and hospitalizations
- Possible superior efficacy
- Possible superior safety
The Future for Warfarin?

- Warfarin will not disappear!
- Use will continue in many circumstances, including:
  - Mechanical heart valves and other un-studied indications
  - Patients who ‘fail’ therapy on a new AC
  - A monitored drug may be preferred for patients with:
    - Compliance issues
    - Drug interaction issues
    - Changing/ poor renal or hepatic function (dialysis?)
  - There may be initial resistance to new agents
    - Especially to convert over a stable warfarin patient
Overview

The American Heart Association defines an anticoagulant as a medication that prevents blood from clotting. Anticoagulants are given to people who are at risk for blood clotting, people with artificial heart valves, and people with atrial fibrillation. Common anticoagulants include Coumadin and heparin. According to Nutrition411, some foods and supplements have anticoagulant properties and can affect blood clotting. If you are taking anticoagulants, you should avoid these foods unless a doctor says otherwise.
Ginger is the underground stem of the Zingiber plant. It has been used for its medicinal properties in Asian cultures for thousands of years. Ginger is most commonly recommended as an aid for stomach upset like nausea and vomiting. According to the University of Maryland Medical Center, preliminary studies show ginger may help prevent blood from clotting. They go on to say that it is too early to make firm recommendations to heart patients, but these affects may help protect against blood vessel blockage that can lead to heart attack and stroke.
Garlic is another food that has been used for its medicinal purposes for thousands of years. The University of Maryland Medical Center says garlic is recommended to help prevent heart disease. In addition to decreasing bad cholesterol and increasing good cholesterol, garlic helps prevent platelet aggregation, also known as blood clotting. According to the University of Maryland Medical Center, allicin appears to be the chemical property in garlic with the anticoagulant powers.
Vitamin E is a fat-soluble vitamin naturally found in some foods. There are many health claims related to vitamin E, most notably its antioxidant and anti-inflammatory properties. According to the Office of Dietary Supplements, vitamin E has been shown to prevent or delay the onset of coronary heart disease by preventing the formation of blood clots. Food sources of vitamin E include almonds, wheat germ, sunflower seeds, peanuts, safflower oil, spinach and mangoes.
Fish Oil

Fatty fish like salmon, tuna, and halibut contain an essential fatty acid called omega 3 fatty acid. Recently, studies have shown that omega 3 fatty acids reduce the risk of heart disease, says the University of Maryland Medical Center. The American Heart Association recommends eating fish twice a week for heart health. In addition to lowering triglyceride levels and blood pressure, omega 3 fatty acids in fish contain anticoagulant properties that slow down the development of blood clots to help prevent and treat atherosclerosis.