ANTICOAGULANT, THROMBOLYTIC, 
and ANTI-PLATELET DRUGS

Katzung (9th ed.) Chapter 34

**** THIS VERSION HAS BEEN CHANGED COMPARED TO THE ONE MADE AVAILABLE ON WEDNESDAY APRIL 26 (sorry!) ****

CRITICAL FACTS

(if med school is a Minnesota forest with millions of trees, these are the red pines)

1. These drugs are used to treat strokes, myocardial infarctions, pulmonary embolisms, disseminated intravascular coagulation (DIC) and deep vein thrombosis (DVT) --- all potentially life-threatening conditions.

2. The effectiveness of thrombolytics ("clot busters") is inversely related to the time elapsed since the thrombic crisis began; these drugs are most effective within 6 hours of onset of symptoms.

3. The major classes of anticoagulant drugs have distinctly different mechanisms of action, routes of administration and adverse effects. The mechanisms of action include: activation of anticoagulating factors (especially antithrombin III), direct inhibition of thrombin, inhibition of synthesis of blood coagulation factor precursors (zymogens), and activation of protein C.

4. A unique side effect to the use of HEPARIN is a transient thrombocytopenia (HIT) that occurs in 25% of patients.

5. The approved use of direct thrombin inhibitors (DTIs) is for the treatment of heparin-induced thrombocytopenia (HIT).

6. WARFARIN:
   • has a NARROW THERAPEUTIC INDEX
   • is NEARLY COMPLETELY (99%) BOUND TO PLASMA ALBUMIN
   • is ELIMINATED BY HEPATIC METABOLISM (cytP450)

   ➔ WARFARIN IS THE PROTOTYPE FOR DRUG-DRUG INTERACTIONS!

7. DROTRECOGIN ALFA is approved for use in disseminated intravascular coagulation or DIC (fatal complication of septic shock). The use of activated protein C as a drug occurred as a result of a change in our understanding of the pathophysiology of sepsis, particularly the intricate interplay between activation of coagulation and inflammation.
DRUGS YOU NEED TO KNOW:

**ANTICOAGULANTS**
- ARGATROBAN
- BIVALIRUDIN (Angiomax)
- DALTEPARIN (Fragmin)
- DROTRECOGIN ALFA (ACTIVATED PROTEIN C) (Xigris)
- ENOXAPARIN (Lovenox)
- FONDAPARINUX
- HEPARIN (Calciparine, Hepathrom, Lipo-Hepin, Liquaemín, Panheparin)
- HIRUDIN (Desirudin)
- 4-HYDROXYCOUMARIN (Coumadin)
- LEPIRUDIN (Refludan)
- WARFARIN (Athrombin-K, Panwarfin)
- XIMELAGATRAN (Exanta)

**ANTIPLATELET DRUGS**
- ABCIXIMAB (Centocor)
- ACETYLSALICYLIC ACID (Aspirin)
- CLOPIDOGREL (Plavix)
- DIPYRIDAMOLE (Persantine)
- EPTIFIBATIDE (Integrilin)
- TICLOPIDINE (Ticlid)
- TIROFIBAN (Aggrastat)

**ANTIDOTES**
- PHYTONADIONE (Vitamin K1)
- PROTAMINE SULFATE
- AMINOCAPROIC ACID (EACA) (generic, Amicar) (in bleeding disorders handout!)
- THROMBOLYTICS
  - ANISTREPLASE (APSAC; Eminase)
  - STREPTOKINASE (Streptase, Kabikinase)
  - TISSUE PLASMINOGEN ACTIVATORS (tPAs): ALTEPLASE (Activase), RETEPLASE (Retavase), TENECTEPLASE (TNKase), UROKINASE (Abbokinase)

IMPORTANT MATERIAL FROM OTHER LECTURES:
1. Principles of pharmacokinetics and pharmacodynamics, esp. therapeutic index, drug metabolism, the cytochrome P450 system (Dr. Knych, Principles), and types of biological variability (Dr. Eisenberg, Principles).
2. Coagulation and thrombosis (Drs. Krafts and Prohaska, Hematopoiesis).

OBJECTIVES:
1. Be able to diagram the coagulation and fibrinolytic pathways and the interaction of protein C with those pathways. Define how different classes of anticoagulant and fibrinolytic drugs interact with specific clotting factors and naturally occurring anticoagulants in the context of these pathways.
2. Be able to describe the biochemical mechanisms of action, therapeutic uses, contraindications and adverse effects of the specific anticoagulant and fibrinolytic agents listed above. Know the properties of agents that can reverse the actions of heparin and the oral anticoagulants.
3. Describe the empirical rationale for thrombolytic therapy, its limitations and the agents that are currently approved for this purpose. Be able to identify both the common and the distinguishing characteristics of thrombolytic agents.

4. Compare and contrast:
   a. heparin and low molecular weight heparins
   b. heparin and warfarin

   with respect to mechanism of action, administration, time to onset of activity, method of monitoring, antidotes and use during pregnancy.

5. Understand why particular disease states and co-administration of other drugs can alter the efficacy and side effects of warfarin. Be able to describe specific pharmacokinetic and pharmacodynamic principles governing the interactions of warfarin with specific drugs listed in the main section of the handout. Be able to use cytochrome P450 interaction tables to identify the interactions of other drugs with both R- and S-warfarin.

6. Know the specifics of the anti-coagulant, fibrinolytic and anti-inflammatory actions of drotrecogin alfa.

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**THERAPEUTIC STRATEGIES**

These drugs are used to treat strokes, myocardial infarctions, pulmonary embolisms, disseminated intravascular coagulation (DIC) and deep vein thrombosis (DVT) --- all potentially life-threatening conditions.

- **Degrade fibrinogen/fibrin (fibrinolytic agents)**
  
  **GOAL:** eliminate formed clots

- **Inhibit clotting mechanism (anticoagulants)**
  
  **GOAL:** prevent progression of thrombosis

- **Interfere either with platelet adhesion and/or aggregation (antiplatelet drugs)**
  
  **GOAL:** prevent initial clot formation
Activation

Platelets → Fibrinogen (I) → Fibrin (Ia) → Clot

... Prothrombin (II)

Thrombin (IIa)

Degradation

Plasminogen → Plasmin → FDPs
THROMBOLYTIC DRUGS

tPAs: ALTEPLASE, RETEPLASE, TENECTEPLASE, ANISTREPLASE, STREPTOKINASE, UROKINASE

Common Features

- dissolve existing life-threatening thrombi
- activate plasminogen to plasmin → hydrolysis of fibrin and several other coagulation factors
- plasmin formed inside a thrombus is protected from plasma antiplasmins
- short activation times, and short half-lives
- recommended for patients with:
  - recent acute MI (selection of patients is critical!!! Some can be harmed)
  - extensive pulmonary emboli
  - severe deep vein thrombosis
  - thromboembolic stroke (tPAs only)

Common Contraindications/Precautions

- cause BLEEDING (particularly hemorrhagic stroke) – can be antagonized by AMINOCAPROIC ACID (for tPAs) or APROTININ (for STREPTOKINASE)
  - inhibitory control system can be overwhelmed producing a systemic lytic state → not for use in:
  1. recent surgery (10 days)
  2. GI bleeding (3 months)
  3. active bleeding or hemorrhagic disorder
  4. previous cerebrovascular accident or active intracranial process
  5. history of hypertension (diastolic > 110 mmHg)
  6. pregnancy
  7. aortic dissection
  8. acute pericarditis

- thrombolytic therapy is expensive (particularly tPAs)
1. **ANISTREPLASE, STREPTOKINASE**

*Mechanism of Action*

- binds to and induces a conformational change in plasminogen resulting in exposure of the active site and conversion to plasmin (**STREPTOKINASE** itself is not intrinsically active)

- **ANISTREPLASE** is an inactive complex of **STREPTOKINASE** and human lys-plasminogen - more convenient (shorter infusion time) but far more expensive with an increased tendency for systemic thrombolysis

*Adverse Effects*

- may evoke allergic hypersensitivity reactions, fever and anaphylaxis

2. **UROKINASE**

*Mechanism of Action*

- kidney enzyme that directly converts plasminogen to active plasmin

- primarily indicated only for patients allergic to **STREPTOKINASE**

*Adverse Effects*

- febrile episodes are common but infusion reactions and hypersensitivity (anaphylaxis) are rare

3. **TISSUE PLASMINOGEN ACTIVATORS (tPAs): ALTEPLASE, RETEPLASE, TENECTEPLASE**

- genetically engineered from human melanoma cells
  - **ALTEPLASE** is unmodified human tPA
  - **RETEPLASE** has several amino acid sequences deleted
  - **TENECTEPLASE** is a recombinant version of human tPA with 3 amino acid substitutions
Mechanism of Action

- causes “selective” activation of fibrin-bound plasminogen
- poor plasminogen activator in the absence of fibrin, i.e., theoretically confines fibrinolysis to the formed thrombus and decreases systemic activation

ANTICOAGULANT DRUGS

The major classes of anticoagulant drugs have distinctly different mechanisms of action, routes of administration and adverse effects.
Mechanisms of Action:

1. Activation of anticlotting factors (especially antithrombin III) e.g. **HEPARIN**
2. Direct inhibition of thrombin e.g. **HIRUDIN**
3. Inhibition of synthesis of blood coagulation factor precursors (zymogens) e.g. **WARFARIN**
4. Activated Protein C i.e., **DROTECOCIN ALFA**

1. **DRUGS THAT ACTIVATE ANTICLOTTING FACTORS:**
   - **HEPARIN, DALTEPARIN, ENOXAPARIN, FONDAPARINUX**

**Generalities**

**HEPARIN**
- most commonly given anticoagulant for short term use (>12 million patients/year)
- is a complex mixture of mucopolysaccharides
- isolated from bovine lung or porcine intestine
- normally found in mast cells - unknown physiologic role
- strongly acidic

**DALTEPARIN, ENOXAPARIN**
- low MW fragments of **HEPARIN**

**Fondaparinux**
- synthetic formulation of the key pentasaccharide that appears to be the active component in all heparins

**Mechanisms of Action**

1. Bind to antithrombin III, a protease inhibitor that complexes with activated clotting factors II, IX, X and XI (i.e., heparins are **INDIRECT** thrombin inhibitors)
   - conformational change in ATIII
   - exposure of ATIII active site
   - more rapid formation of ATIII-protease complexes
• release of HEPARIN; activated clotting factors remain bound to ATIII

2. Coat blood vessel wall (prevents platelet binding or causes permeabilization?)

Pharmacokinetics

• activity is standardized by bioassay
• must be given IV (not active orally; IM administration causes hematomas)
• rapid effect (within minutes); instantaneously in vitro
• metabolized in liver; excreted in urine
• HEPARIN dose is adjusted to double partial thromboplastin time (monitored by aPTT)

DALTEPARIN, ENOXAPARIN

Greater than heparin
• Anti-factor Xa activity
• Bioavailability (SC administration)
• Half-life (decreased dosing)
• More predictable pharmacology
  (less need for monitoring)

Less than heparin
• Inactivation of thrombin (IIa)
• Platelet inhibition
• Vascular permeabilization
• Plasma protein binding

Therapeutic Indications

• for an immediate hypotrombic response:
  o massive deep-vein thrombosis
  o pulmonary infarct
  o post-operative acute MI (except brain, spinal cord or eye)
  o prior to cardioversion of atrial fibrillation
• effective anticoagulant in vitro

Adverse Effects

• HEMORRHAGE (esp. hemorrhagic stroke)
• hypersensitivity
• transient HIT occurs in about 25% of the patients during first 5 days of treatment – severe HIT occurs in 5% of patients

  o small % of patients develop antibody-mediated thrombocytopenia that is associated with thrombosis (paradoxical)

  o in those patients, **HEPARIN** should be discontinued, and treatment initiated with **HIRUDIN** or **LEPIRUDIN**, but not **WARFARIN** (may exacerbate the prothrombotic state)

• prolonged administration of high doses may cause

  o osteoporosis

  o progressive reduction in antithrombin III \(\rightarrow\) decreased effectiveness, increased clotting

  o mineralocorticoid deficiency

**PROTAMINE SULFATE**

• highly basic peptide that combines with **HEPARIN** as an ion pair

• lasts about 2 hours

• routinely used following cardiac surgery and other vascular procedures

• excess protamine also has an anticoagulant effect, since it can interact with platelets, fibrinogen and other plasma proteins

• anaphylactic reactions can occur - approximately 1% of patients with diabetes mellitus who have received protamine-containing insulin experience anaphylaxis

• cannot reverse many LMWH!
2. DIRECT THROMBIN INHIBITORS (DTIs): ARGATROBAN, BIVALIRUDIN, HIRUDIN, LEPIRUDIN, XIMELAGATRAN

Mechanism of Action

- **HIRUDIN** was originally isolated from leech; **LEPIRUDIN** is the recombinant form; **BIVALIRUDIN** is a synthetic analogue
- work by 1) inhibiting fibrin binding to thrombin and 2) interacting with the thrombin active site → inhibiting thrombin activity even in the presence of bound fibrin
- **ARGATROBAN** is a synthetic derivative of L-arginine - **ARGATROBAN** and **XIMELAGATRAN** bind reversibly to the thrombin active site
- advantages over **HEPARIN:**
  1. inhibition of coagulation via a single mechanism of action
  2. actions are independent of antithrombin III, which means they can reach and inactivate fibrin-bound thrombin inside clots
  3. little effect on platelets or bleeding time
  4. elimination of HIT as a side effect of treatment
  5. not inactivated by platelet or plasma proteins
  6. more uniform potency and increased safety
  7. rebound coagulation after discontinuation of the drug is less likely with direct thrombin inhibitors

Pharmacokinetics

- given IV (note: **XIMELAGATRAN** is first oral agent in this class → promoted as a replacement for both **WARFARIN** and **HEPARIN** because of its immediate anticoagulant action
- metabolized by hydrolysis in liver, excreted in urine

The approved use of DTIs is for the treatment of heparin-induced thrombocytopenia (HIT).
• monitored by aPTT – **ARGATROBAN** causes elevated INRs because of test interference, making the transition to warfarin difficult

**Adverse Effects**

• **HEMORRHAGE**: dose related; increased in patients with renal insufficiency, liver injury, or recent trauma and/or treatment with other anticoagulants

3. **DRUGS THAT INHIBIT SYNTHESIS OF COAGULATION FACTOR PRECURSORS: 4-HYDROXYCOUMARIN, WARFARIN**

**Mechanism of Action**

• inhibit epoxide hydrase

• interfere with the synthesis of vitamin K and thus inhibits activation of vitamin K-dependent clotting factors (II, VII, IX, X)

• also decreases the activity of protein C (activated by thrombin) – responsible for some side effects

**Pharmacokinetics**

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→ **WARFARIN IS THE PROTOTYPE FOR DRUG-DRUG INTERACTIONS!**

• rapid, complete absorption from GI; peak plasma drug concentration in ≤ 1 hr

• **WARFARIN** is a racemic mixture of R- and S-forms – S is the active enantiomer

• S- and R- **WARFARIN** are metabolized differently; **S is metabolized primarily by CYP2C9**, and R by CYP1A2, CYP2C19 and CYP3A4

• several genes play a role in **WARFARIN** metabolism:
• polymorphisms in **CYP2C9** cause about 30% of patients to be slow metabolizers (causes ↑ serum concentrations)

• polymorphisms in the **vitamin K epoxide reductase multiprotein complex** (VKOR) can confer resistance (↓ serum concentrations)

• recent clinical studies show that testing for **CYP2C9** polymorphisms allows physicians to better predict the appropriate starting dose for **WARFARIN**, allowing the achievement of stable blood levels more quickly than the current method of trial-and-error dosing

• defects in the coagulation cascade can also confer resistance to **WARFARIN**: the most common are: APC resistance (factor V Leiden), protein S deficiency, protein C deficiency, antithrombin III deficiency

• no *in vitro* effect

• readily crosses placenta

• delayed hypothrombic effect (1-3 days); \( t_{1/2} \) 35 hr, biological \( t_{1/2} \) 6-6O hrs

• small daily doses – adjustment of prothrombin time takes ~ 1 week

**Therapeutic Indications**

• rodenticides
• long-term oral treatment of deep-vein thrombosis

• for 2-6 months following myocardial infarction

• atrial fibrillation

Adverse Effects

• HEMORRHAGE

• flatulence and diarrhea are common

• decreased protein C causes cutaneous necrosis caused during first weeks of treatment; rarely can progress to infarction (venous thrombosis) in fatty tissues, intestine and extremities

• bone defects (chondrodysplasia punctata) and hemorrhagic disorders in infants born to mothers taking the drug during first trimester of pregnancy

→ ABSOLUTELY CONTRAINDICATED IN PREGNANCY
• DISEASE STATE and DRUG INTERACTIONS

**PHARMACOKINETIC**

• **ABSORPTION**
  \( \uparrow \) binding in intestine

• **DISTRIBUTION**
  \( \downarrow \) plasma protein binding

• **ELIMINATION**
  cytP450 inhibition
  cytP450 induction

**PHARMACODYNAMIC**

• **SYNERGISM**
  \( \downarrow \) platelet/clotting factor function

• **ANTAGONISM**
  \( \uparrow \) concentration of clotting factors

• **ALTERED VITAMIN K**
  \( \downarrow \) availability of vitamin K
## Drug Interactions

### Importance of Cytochrome P450 Isozymes

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<tr>
<th>CYP3A4 Inhibitors</th>
<th>Inducers</th>
<th>Substrates</th>
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<tr>
<td>amiodarone</td>
<td>barbiturates</td>
<td>carbamazepine</td>
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<td>aramiprenarin</td>
<td>carbamazepine</td>
<td>dexamethasone</td>
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<tr>
<td>carthromycin</td>
<td>diazepam</td>
<td>efavirenz</td>
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<tr>
<td>cyclosporine</td>
<td>indinavir</td>
<td>efavirenz</td>
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<td>delavirdine</td>
<td>nelfinavir</td>
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<td>efavirenz</td>
<td>ritonavir</td>
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<td>etravirine</td>
<td>saquinavir</td>
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<td>etravirine</td>
<td>troleandomycin</td>
<td>verapamil</td>
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<td>fentanyl</td>
<td>zafirlukast</td>
<td>verapamil</td>
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<th>CYP2C9 Inhibitors</th>
<th>Inducers</th>
<th>Substrates</th>
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<tr>
<td>cilostazol</td>
<td>barbiturates</td>
<td>cimetidine</td>
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<tr>
<td>cilostazol</td>
<td>ethinyl estradiol</td>
<td>cimetidine</td>
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<td>diltiazem</td>
<td>fluoxetine</td>
<td>cimetidine</td>
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<td>diltiazem</td>
<td>nifedipine</td>
<td>diltiazem</td>
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<td>verapamil</td>
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<tr>
<td>alprazolam</td>
<td>amitriptyline</td>
<td>diphenhydramine</td>
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<td>chlorpromazine</td>
<td>diphenhydramine</td>
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<td>clozapine</td>
<td>diphenhydramine</td>
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<td>codeine</td>
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### Import of Cytochrome P450 Isozymes

- **Inhibitors**: Cimetidine, citalopram, clomipramine, doxepin.
- **Inducers**: Rifampin, phenobarbital, phenytoin, St. John's wort.
- **Substrates**: Barbiturates, carbamazepine, dexamethasone.

### Key Points
- **Important**:
  - Cytochrome P450 isozymes play a crucial role in drug metabolism.
  - Certain drugs can inhibit or induce these enzymes, affecting how other medications are metabolized.
  - Understanding these interactions is crucial for effective drug therapy.

### Metabolism of Drugs by CYP2D6
- Many drugs are metabolized by subfamilies of hepatic cytochrome P450.
- A drug that inhibits the activity of a specific enzyme can block the metabolism of other drugs, potentially causing toxicity.
- A drug that induces the activity of a specific enzyme can stimulate the metabolism of other drugs, potentially reducing their efficacy.
ILLUSTRATIVE CASE

- A 74-year-old woman with insulin-dependent (type 2) diabetes had been taking \textit{METOPROLOL} and \textit{WARFARIN} for atrial fibrillation and \textit{AMITRIPTYLINE} for diabetic neuropathy for several years. On the death of her husband, she presented with symptoms of depression and \textit{PAROXETINE} was added to her medication regimen.

- Three days after the initiation of paroxetine therapy, the woman was brought to the emergency department by her daughter, who had \textit{found her asleep at 11 am}. On awakening, the patient complained of \textit{dry mouth and dizziness}.

- The ER physician, noting that paroxetine had been added recently, changed the patient to \textit{FLUVOXAMINE}, which he thought would be \textit{less sedating}.

- Three days later, the patient was still very sedated and dizzy, and complained of difficulty urinating. She was again brought to the ER, where bladder catheterization yielded two liters of dark urine. Her INR was 4.0.

“Classic” cytochrome P450 interactions

- alcohol, barbiturates, cimetidine, fluvoxamine, phenytoin

Drugs that ALWAYS Interact with Warfarin

- aspirin, cimetidine, phenytoin

Drugs that are LIKELY to be co-administered with Warfarin (due to co-morbidity, high prescription rate and/or OTC status)

- By class: other anticoagulants, antiplatelet drugs, analgesics and NSAIDS, sedative-hypnotics, anti-arrhythmics, antibiotics/antifungals, antihyperlipidemics, GI drugs (esp. antacids), uricosurics (anti-gout), diuretics, thyroid medications

- Specifically: abciximab, alcohol (acute and chronic), allopurinol, aspirin, carbamazepine, cephalosporins, cholestyramine, cimetidine, ciprofloxacin, clofibrate, erythromycin, fluconazole, gemfibrozil, \textit{HEPARIN, HIRUDIN}, lovastatin, metronidazole, miconzaole, NSAIDS, phenytoin, phytonadione, sulfonamides,
thyroid hormones, trimethoprim-sulfamethoxazole

Many herbal supplements: black cohosh, chamomile, dong quai, feverfew, garlic, ginger, gingko biloba, ginseng (only one that decreases efficacy)

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<thead>
<tr>
<th>Pharmacokinetic INCREASES in Effect</th>
<th>Pharmacokinetic DECREASES in Effect</th>
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<td><strong>Inhibition of metabolism</strong></td>
<td><strong>Decreased Plasma Protein Binding</strong></td>
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<tr>
<td>Acute alcohol</td>
<td>Clofibrate</td>
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<td>Allopurinol</td>
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<td>Cimetidine</td>
<td>Phenytoin (initially)</td>
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<td>Ciprofloxacin</td>
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<td>Erythromycin</td>
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<td>Fluconazole</td>
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<td><strong>Decreased availability of vitamin K</strong></td>
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<td>Cephalosporins</td>
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<td>Chronic alcohol</td>
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<td>Phenytoin (ultimately)</td>
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<td><strong>Decreased platelet/clotting factor function</strong></td>
<td><strong>Increased concentrations of clotting factors</strong></td>
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<tr>
<td>Abciximab</td>
<td>Diuretics</td>
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<td>ASA</td>
<td>Vitamin K</td>
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<td>DISEASE STATES</td>
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<td><strong>DECREASE ANTICOAGULANT EFFICACY</strong></td>
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<tr>
<td>Blood dyscrasias$^2$ (hemophilia, von Willebrand's disease, thrombocytopenia)</td>
<td>Alcoholism (chronic)$^4$</td>
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<td>Diarrhea$^1$</td>
<td>Edema$^2$</td>
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<tr>
<td>Elevated temperature$^3$</td>
<td>Hyperlipemia$^1$</td>
</tr>
<tr>
<td>Hepatic disease$^{2,4}$</td>
<td>Hereditary resistance$^*^2$</td>
</tr>
<tr>
<td>Hyperthyroidism$^3$</td>
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</tr>
<tr>
<td>Inadequate diet$^1$ (esp. vitamin K deficiency)</td>
<td>Nephrotic syndrome$^4$</td>
</tr>
<tr>
<td>Jaundice$^2$</td>
<td></td>
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<tr>
<td>Small bowel disease$^1$</td>
<td></td>
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<tr>
<td>Steatorrhea$^1$</td>
<td></td>
</tr>
</tbody>
</table>

1. ↓ vitamin K levels
2. ↓ synthesis/function of clotting factors and/or platelets
3. ↑ clotting factor turnover
4. ↓ drug metabolism/elimination

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* Hereditary resistance to warfarin has been shown to be due to defects in the coagulation cascade, the most common of which are: APC resistance (factor V Leiden), protein S deficiency, protein C deficiency, antithrombin III deficiency

**PHYTONADIONE** (Vitamin K$_1$)

- pharmacodynamic antagonist (not due to disappearance of warfarin, but rather the reestablishment of normal clotting factor activity) – takes 24 hours
- fresh-frozen plasma or factor IX concentrates are also effective
4. DROTRECOGIN ALFA (ACTIVATED PROTEIN C)

**Mechanism of Action**

- recombinant version of protein C; activated by thrombin; requires Ca\(^{2+}\), phospholipid and protein S as cofactors
- anti-coagulant actions:
  1) destroys activated factors Va and VIIIa, resulting in ↓ thrombin formation
  2) inhibits platelet activation
  3) suppresses tissue factor expression
- fibrinolytic actions
  1) attenuates thrombin-catalyzed activation of tPA inhibitors
  2) decreases PAI-1 concentrations
- anti-inflammatory actions:
  1) inhibits synthesis of tumor necrosis factor
  2) inhibits neutrophil activation
  3) blocks the release of cytokines from macrophages

**Therapeutic Indications**

- decreases relative risk of death by 20% (up to 50% of patients die of sepsis within 6 months)

**Adverse Effects**

- **HEMORRHAGE:** dose related, no increase in patients with renal or liver insufficiency
ANTIPLATELET DRUGS
ASA, ABCIXIMAB, CLOPIDOGREL, DIPYRIDAMOLE, EPTIFIBATIDE, TICLOPIDINE, TIROFIBAN

Mechanisms of Action

Inhibit platelet adhesion and aggregation by:

1. Inhibiting cyclooxygenase: e.g. **ASA**
2. Blocking glycoprotein IIb/IIIa receptor: e.g. **ABCIXIMAB, EPTIFIBATIDE**
3. Inhibiting the binding of fibrinogen to activated platelets: e.g. **CLOPIDOGREL, TICLOPIDINE**
4. Inhibiting cyclic nucleotide phosphodiesterase: e.g. **DIPYRIDAMOLE**