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 anticlotting 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, Liquaemin, Panheprin)

HIRUDIN (Desirudin)

4-HYDROXYCOUMARIN (Coumadin)

LEPIRUDIN (Refludan)

WARFARIN (Athrombin-K, Panwarfin)

XIMELAGATRAN (Exanta)

ANTIDOTES

PHYTONADIONE (Vitamin K_1)

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)

ANTIPLATELET DRUGS

ABCIXIMAB (Centocor)

ACETYLSALICYLIC ACID (Aspirin)

CLOPIDOGREL (Plavix)

DIPYRIDAMOLE (Persantine)

EPTIFIBATIDE (Integrilin)

TICLOPIDINE (Ticlid)

TIROFIBAN (Aggrastat)

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.

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)

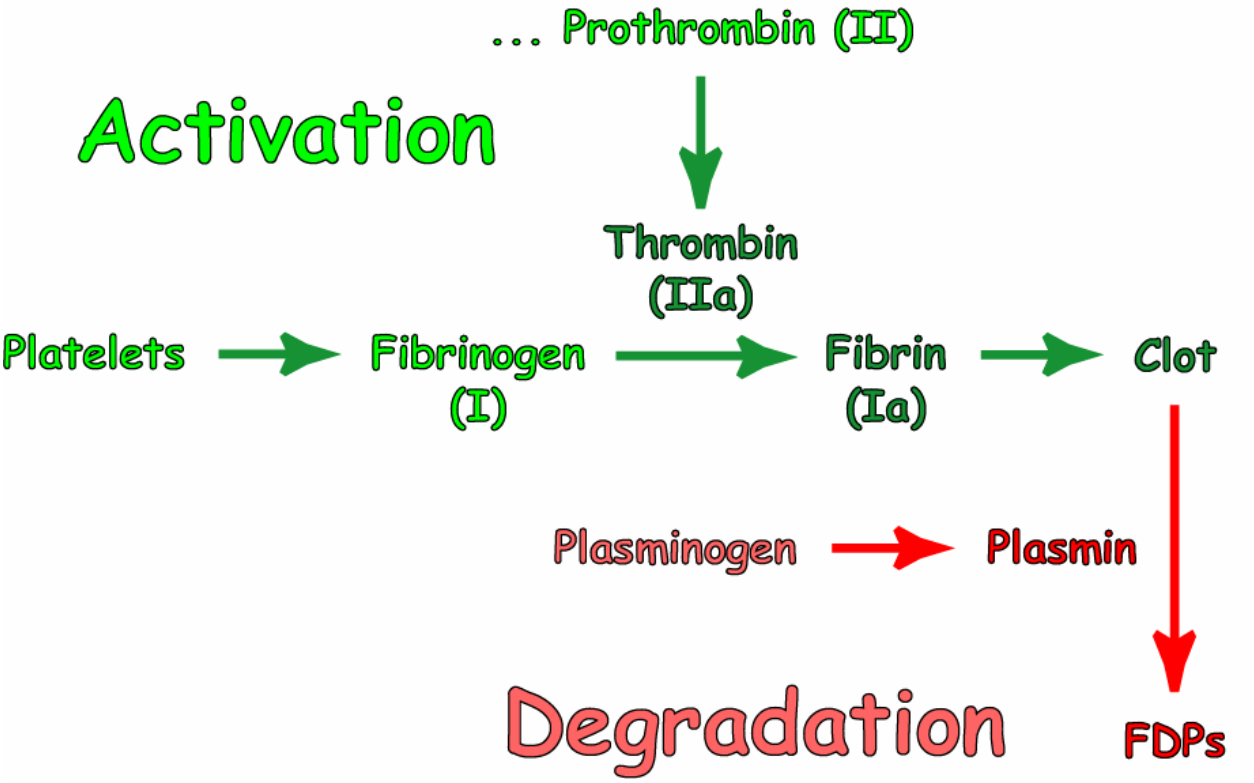
  GOAL: eliminate formed clots

- Inhibit clotting mechanism (anticoagulants)

  GOAL: prevent progression of thrombosis

- Interfere either with platelet adhesion and/or aggregation (antiplatelet drugs)

  GOAL: prevent initial clot formation


... Prothrombin (II)
Activation
Thrombin
(IIa)
Platelets
Fibrinogen
(I)
Fibrin
(Ia)
Clot
Plasminogen
Plasmin
Degradation
FDPs

THROMBOLYTIC DRUGS

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

Common Features

The effectiveness of thrombolytics is inversely related to the time elapsed since the thrombic crisis began → these drugs are most effective within **6 hours of onset of symptoms**

- 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 **tPA**s) 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 **tPA**s)

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

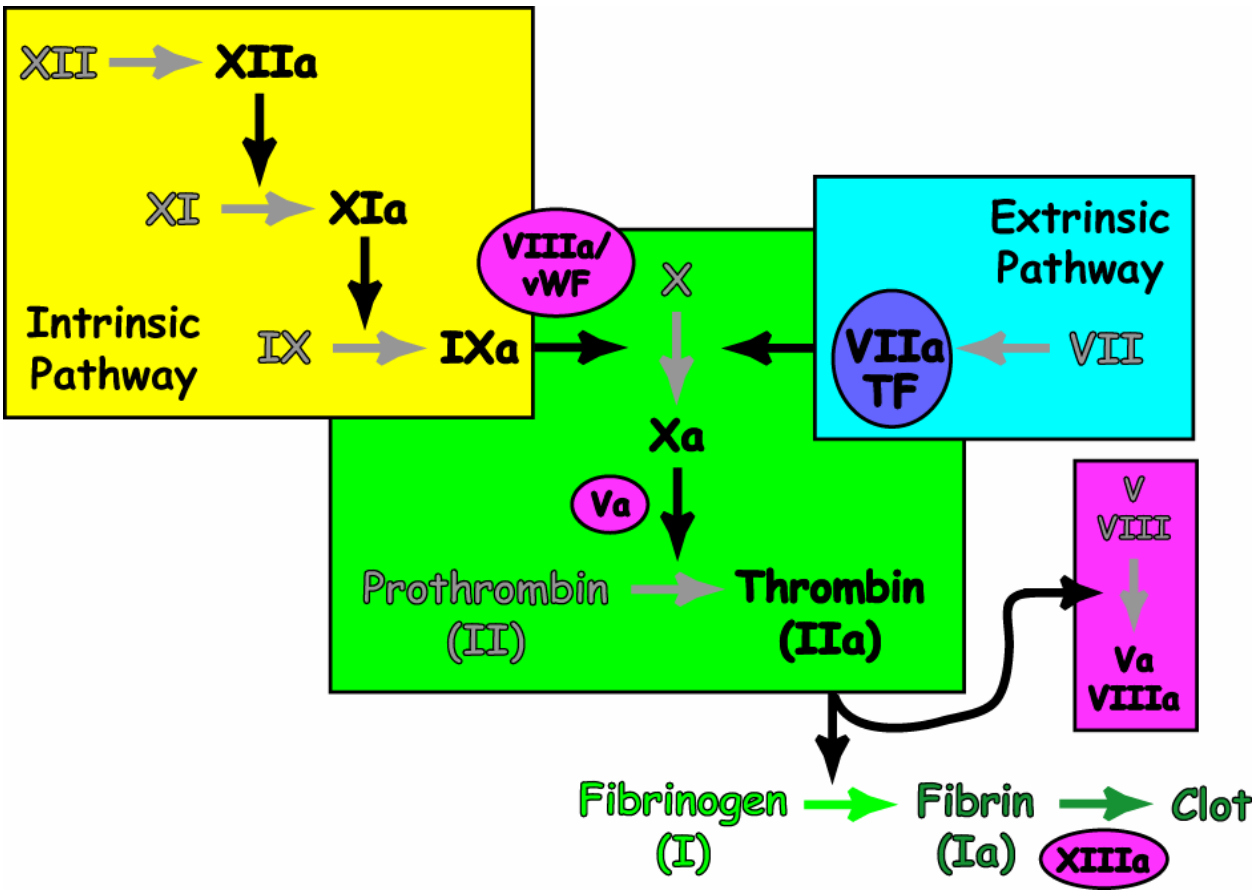
3. TISSUE PLASMINOGEN ACTIVATORS (tPAs): ALTEPLASE, RETEPLASE, TENECTEPLASE

- 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., **DROTRECOGIN 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 hypothrombic response:
  - massive deep-vein thrombosis
  - pulmonary infarct
  - post-operative acute MI (except brain, spinal cord or eye)
  - 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

A unique side effect to the use of heparin is a transient thrombocytopenia (HIT).

  - small % of patients develop antibody-mediated thrombocytopenia that is associated with thrombosis (paradoxical)
  - 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
  - osteoporosis
  - progressive reduction in antithrombin III → decreased effectiveness, increased clotting
  - 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

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

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

- monitored by aPTT – **ARGATROBAN** causes elevated INRs because of test interference, making the transition to warfarin difficult

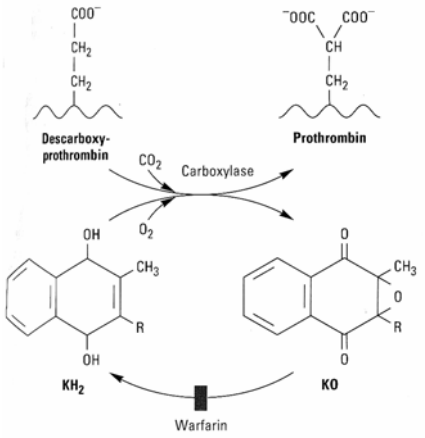
Adverse Effects

- **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



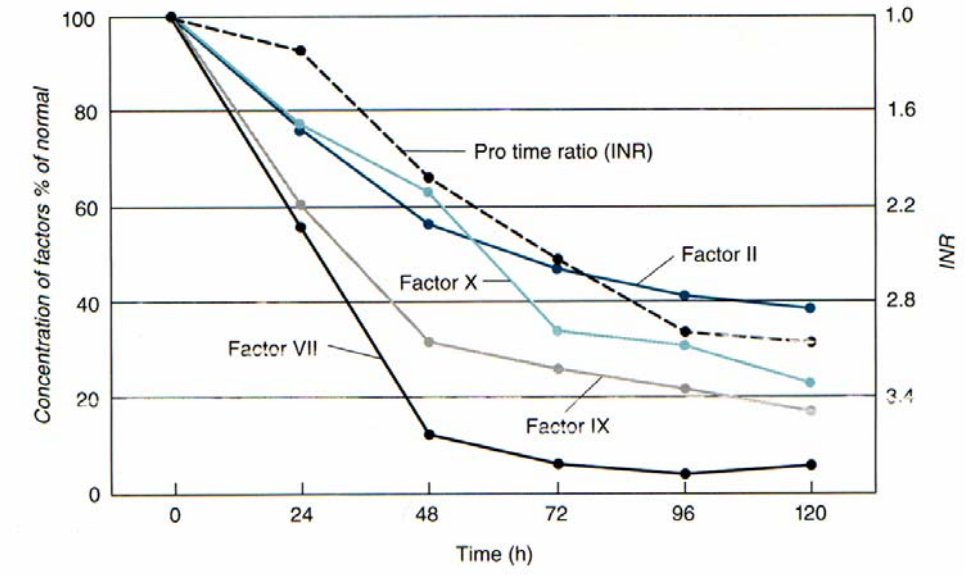
Pharmacokinetics

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!**

- 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); $t_{½}$ 35 hr, biological $t_{½}$ 6-6O hrs
- small daily doses – adjustment of prothrombin time takes ~ 1 week

Therapeutic Indications

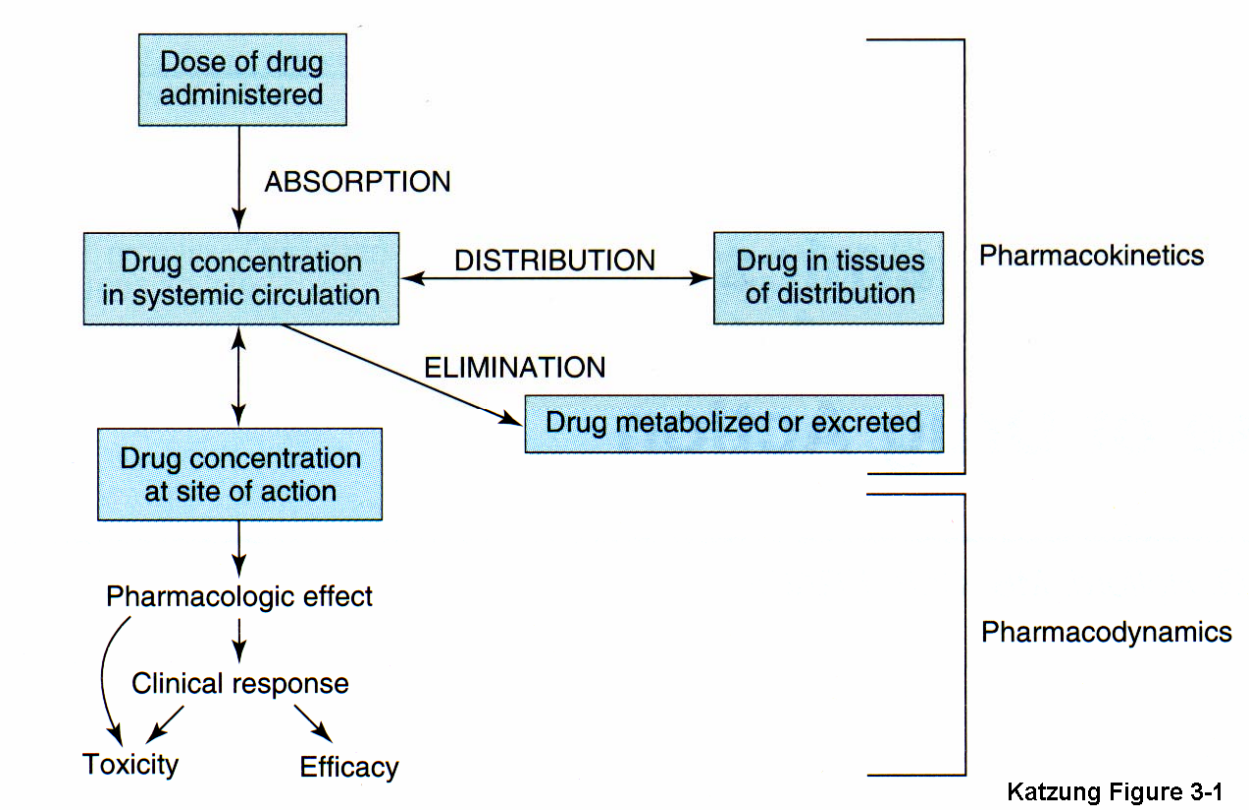
- rodenticides

- 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**



Katzung Figure 3-1

PHARMACOKINETIC

- **ABSORPTION**
  ↑ binding in intestine
- **DISTRIBUTION**
  ↓ plasma protein binding
- **ELIMINATION**
  cytP450 inhibition
  cytP450 induction

PHARMACODYNAMIC

- **SYNERGISM**
  ↓ platelet/clotting factor function
- **ANTAGONISM**
  ↑ concentration of clotting factors
- **ALTERED VITAMIN K**
  ↓ availability of vitamin K

Drug Interactions

Importance of Cytochrome P450 Isozymes

Page 8 **Cytochrome P450 Table** *Pocket 2001*

INHIBITORS, INDUCERS, AND SUBSTRATES OF CYTOCHROME P450 ISOZYMES

Bear in mind that inhibitors and inducers listed on the chart below do not necessarily cause clinically important drug interactions with the substrates listed below. This chart only predicts the *potential* for a drug interaction. Please refer to other resources for more definitive information when a drug interaction is suspected based on the information given in the chart.

CYP 1A2			
Inhibitors	***Inducers***	***Substrates***	
cimetidine	barbiturates	amitriptyline	olanzapine
ciprofloxacin	carbamazepine	caffeine	propranolol
enoxacin	charcoal-broiled foods	clomipramine	riluzole
erythromycin	lansoprazole	clozapine	ropinirole
♦fluvoxamine	omeprazole	cyclobenzaprine	R-warfarin
grepafloxacin	phenytoin	grepafloxacin	tacrine
isoniazid	rifampin	imipramine	theophylline
mexiletine	smoking	mirtazapine	zileuton
norfloxacin			
tacrine			
zileuton			

CYP2C9			
Inhibitors	***Inducers***	***Substrates***	
amiodarone	barbiturates	carvedilol	montelukast
cimetidine	carbamazepine	celecoxib	naproxen
cotrimoxazole	rifampin	diclofenac	phenytoin
fluconazole	rifapentine	flurbiprofen	piroxicam
♦fluvoxamine	St Johns wort	fluvastatin	tolbutamide
isoniazid		glimepiride	torsemide
ketoconazole (weak)		ibuprofen	S-warfarin
metronidazole		irbesartan	zafirlukast
zafirlukast		losartan	

CYP 2C19			
Inhibitors	Inducers	Substrates	
felbamate	None	amitriptyline	lansoprazole
fluoxetine		citalopram	phenytoin
fluvoxamine		clomipramine	omeprazole
modafinil		diazepam	R-warfarin
omeprazole		imipramine	
oxcarbazepine			

CYP2D6			
Inhibitors	***Inducers***	***Substrates***	
amiodarone	None	amitriptyline	metoprolol
chloroquine		carvedilol	mexiletine
cimetidine		chlorpromazine	mirtazapine
clomipramine		clomipramine	nortriptyline
diphenhydramine		clozapine	oxycodone
fluoxetine		codeine*	paroxetine
fluphenazine		desipramine	perphenazine
haloperidol		dextromethorphan	propafenone
paroxetine		dihydrocodeine*	propranolol
perphenazine		donepezil	risperidone
propafenone		flecainide	ritonavir
propoxyphene		fluoxetine	thioridazine
quinacrine		haloperidol	timolol
♦quinidine		hydrocodone*	tolterodine
♦ritonavir		imipramine	tramadol*
sertraline		loratadine	trazodone
terbinafine		maprotiline	venlafaxine
thioridazine		methamphetamine	

Pharmacopoeia Deluxe **Cytochrome P450 Table** **Page 9**

CYP3A4			
Inhibitors	***Inducers***	***Substrates***	
amiodarone	barbiturates	alfentanil	lovastatin
amprenavir	carbamazepine	alprazolam	methadone
clarithromycin	dexamethasone	amlodipine	midazolam
cyclosporine	efavirenz	amprenavir	mirtazapine
danazol	ethosuximide	atorvastatin	montelukast
delavirdine	griseofulvin	bepridil	nefazodone
diltiazem	modafinil	buspirone	nelfinavir
efavirenz	nafcillin	carbamazepine	nicardipine
erythromycin	nevirapine	cerivastatin	nifedipine
ethinyl estradiol	oxcarbazepine	cisapride	nimodipine
fluconazole	phenytoin	citalopram	nisoldipine
fluvoxamine	primidone	clarithromycin	paclitaxel
grapefruit juice	rifabutin	clomipramine	pimozide
indinavir	♣rifampin	corticosteroids	quetiapine
itraconazole	rifapentine	cyclophosphamide	quinidine
ketoconazole	St Johns wort	cyclosporine	quinine
nefazodone		dapsone	repaglinide
nelfinavir		delavirdine	rifabutin
quinine		diazepam	ritonavir
♦ritonavir		diltiazem	saquinavir
saquinavir		disopyramide	sertraline
Synercid		dofetilide	sibutramine
troleandomycin		donepezil	sildenafil
verapamil		doxorubicin	simvastatin
zafirlukast		efavirenz	sirolimus
		erythromycin	sufentanil
		ethinyl estradiol	tacrolimus
		etoposide	tamoxifen
		felodipine	testosterone
		fentanyl	tolterodine
		finasteride	toremifene
		ifosfamide	triazolam
		imipramine	troleandomycin
		indinavir	verapamil
		isradipine	vinblastine
		itraconazole	vincristine
		ketoconazole	R-warfarin
		lansoprazole	zaleplon
		loratadine	zileuton
		losartan	zolpidem
			zonisamide

♦potent inhibitor

♣potent inducer

* Metabolism by CYP2D6 required to convert to active analgesic metabolite; analgesia may be impaired by CYP2D6 inhibitors.

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 drugs that are substrates of that enzyme. If the body lacks other mechanisms for excreting these drugs, they can accumulate and cause toxicity.
- A drug that induces the activity of a specific enzyme can stimulate the metabolism of drugs that are substrates of that enzyme. This can lead to decreased levels of these drugs in the body and could reduce their efficacy.

ILLUSTRATIVE CASE

- A 74-year-old woman with insulin-dependent (type 2) diabetes had been taking **METOPROLOL** and **WARFARIN** for atrial fibrillation and **AMITRIPTYLINE** for diabetic neuropathy for several years. On the death of her husband, she presented with symptoms of depression and **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 found her asleep at 11 am. On awakening, the patient complained of dry mouth and dizziness.
- The ER physician, noting that paroxetine had been added recently, changed the patient to **FLUVOXAMINE**, which he thought would be 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, **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)

Pharmacokinetic INCREASES in Effect	
Inhibition of metabolism	**Decreased Plasma Protein Binding**
Acute alcohol	Clofibrate
Allopurinol	Gemfibrozil
Cimetidine	Phenytoin (initially)
Ciprofloxacin	Sulfonamides
Erythromicin	Trimethoprim-sulfamethoxazole
Fluconazole	
Lovastatin	
Metronidazole	
Sulfonamides	
Trimethoprim-sulfamethoxazole	

Pharmacokinetic DECREASES in Effect	
Enzyme Induction	**Decreased absorption**
Carbamazepine	Cholestyramine
Chronic alcohol	
Phenytoin (ultimately)	

Pharmacodynamic INCREASES in Effect	
Decreased platelet/ clotting factor function	**Decreased availability of vitamin K**
Abciximab	Cephalosporins
ASA	
Heparin, Dalteparin, Enoxaparin	
Hirudin, Lepirudin	

Pharmacodynamic DECREASES in Effect	
Increased concentrations of clotting factors	
Diuretics	Vitamin K

DISEASE STATES	
INCREASE ANTICOAGULANT EFFICACY	**DECREASE ANTICOAGULANT EFFICACY**
Blood dyscrasias[2] (hemophilia, von Willebrand's disease, thrombocytopenia)	Alcoholism (chronic) [4]
Diarrhea[1]	Edema[2]
Elevated temperature[3]	Hyperlipemia[1]
Hepatic disease[2,4]	Hereditary resistance*[2]
Hyperthyroidism[3]	Hypothyroidism[3]
Inadequate diet[1] (esp. vitamin K deficiency)	Nephrotic syndrome[4]
Jaundice[2]	
Small bowel disease[1]	
Steatorrhea[1]	

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)

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.

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

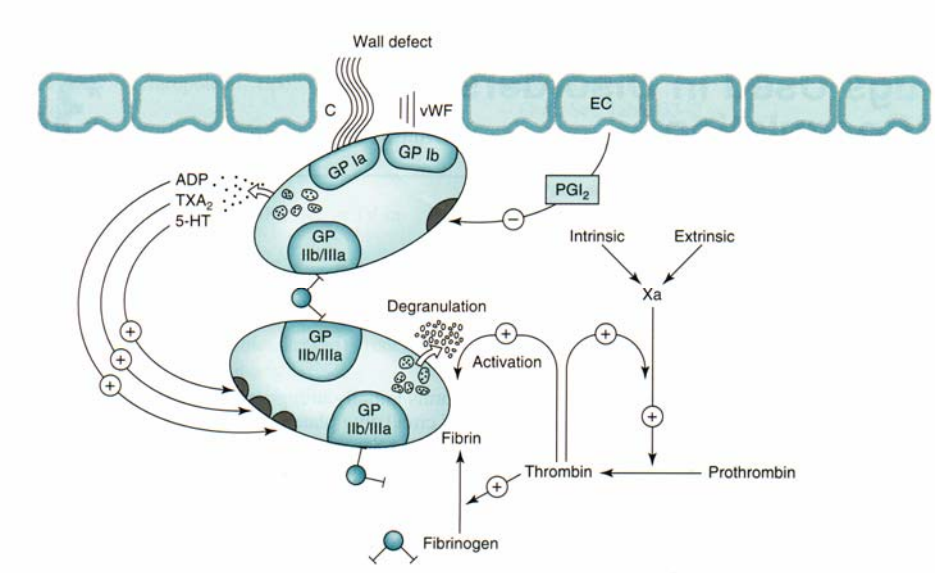
- **HEMORRHAGE:** dose related, no increase in patients with renal or liver insufficiency

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**