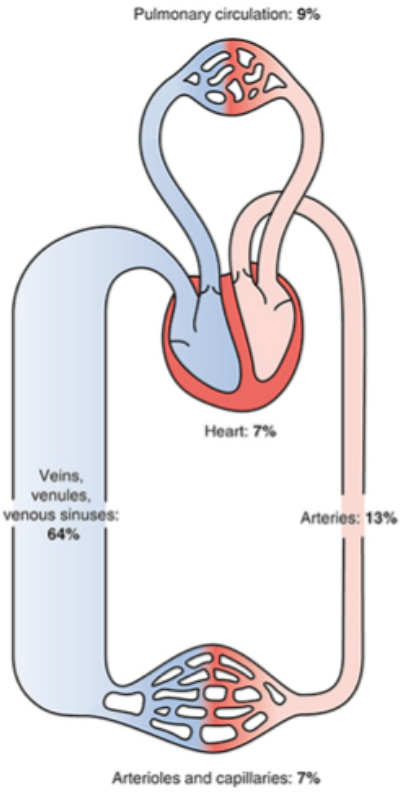
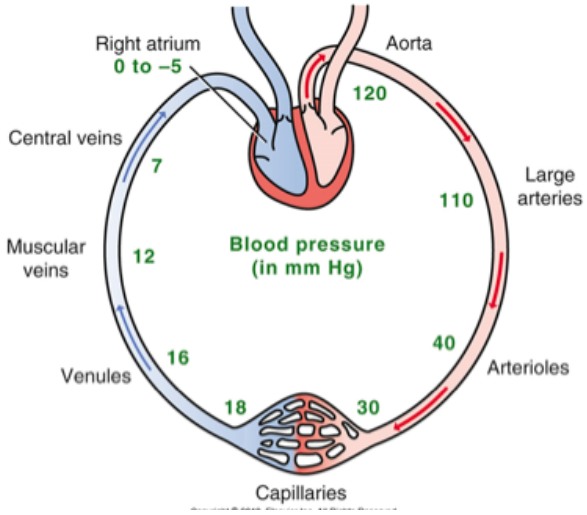
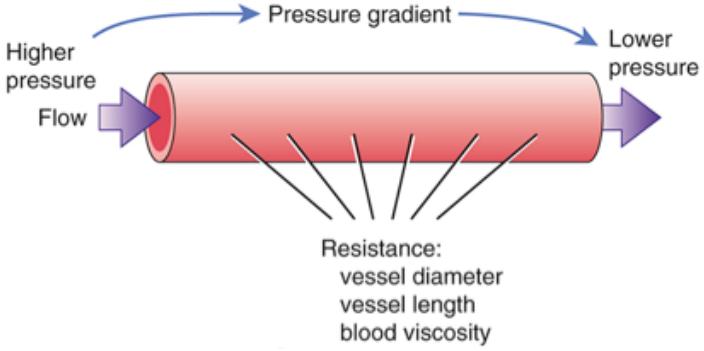
PATHO REVIEW

Hemodynamics Review (Ch. 43)

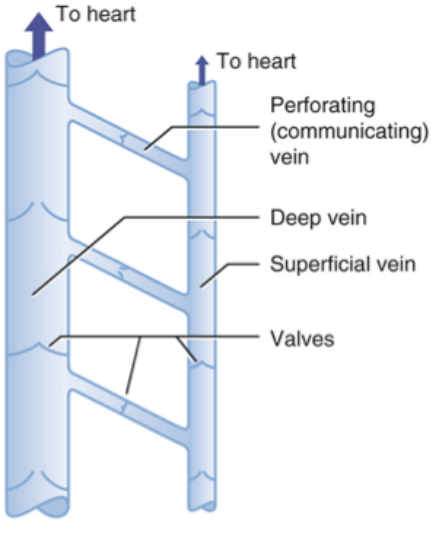
Flow, Pressure & Resistance

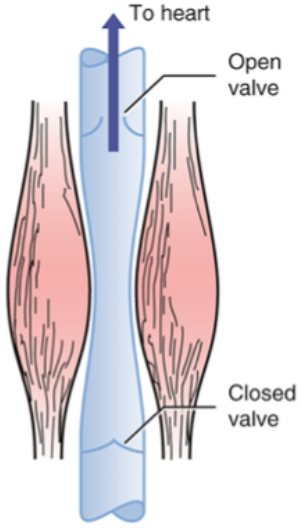






How blood gets back to the heart





Pressure & Resistance

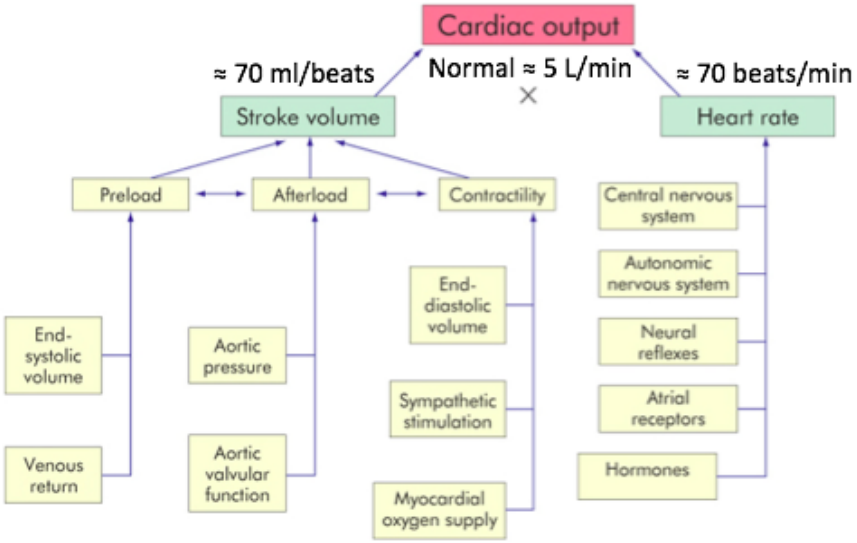
- Flow = pressure (BP) / resistance
  - Increased resistance → decreased flow
  - Increased pressure → increased flow
  - Constant flow: increased resistance → increased pressure
- Resistance = vessel diameter
- Series vs. parallel
- Flow does not equal velocity (riverbed analogy)
- Cross-sectional area ∝ 1/blood velocity

Poiseuille's Law:

$$R = \frac{8vL}{\pi r^4}$$

Cardiac Output (CO)

- Ejection Fraction = SV/EDV
  - Normal ~ 55-65%

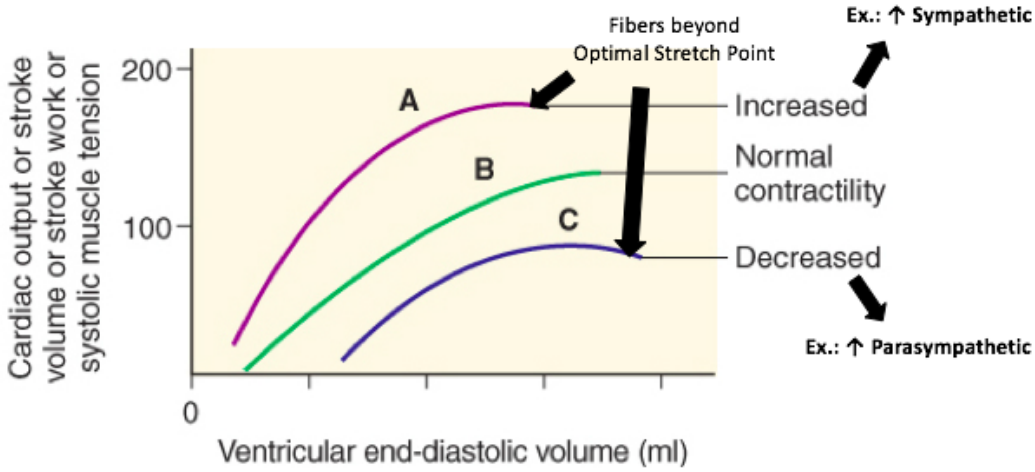


Determinants of Stroke Volume

- Preload = end-diastolic pressure
  - Increased preload (physiologic range) → increased SV
- Afterload = resistance to blood ejection
  - Increased afterload → decreased SV
- Contractility = contraction strength
  - Increased contractility → increased SV
  - Frank-starling Law

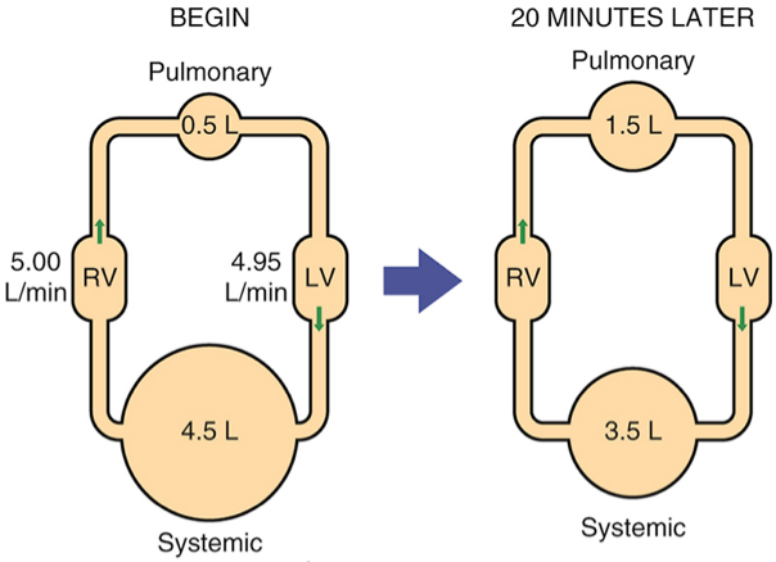
Frank-Starling Law

Increased Muscle tension (increased EDV) → increased contractility (increased SV)

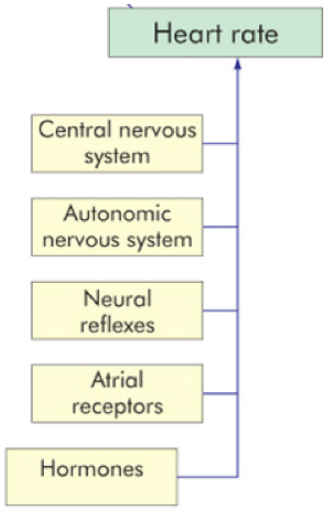


Systemic-Pulmonary Imbalance

Failing heart → systemic pulmonary imbalance → back-flow of blood

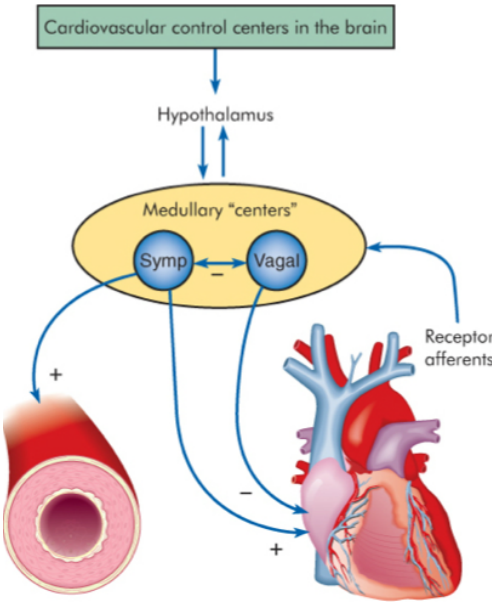


Determinants of Heart Rate



- Cardiovascular control centers = ANS + CNS
  - Medulla (HR & BP), hypothalamus (temperature), amygdala (emotions)
  - Vagal (parasympathetic) tone → resting HR
- Sinus arrhythmia:
  - Inspiration → increased HR
  - Expiration → decreased HR
- Baroreceptor Reflex:
  - Increased BP → decreased HR + vasodilation
  - Decreased BP → increased HR + vasoconstriction
- Hormones
  - Fight-or-flight → adrenal glands → increased NE/epi
  - Thyroid hormone (T3) → increased HR + contractility

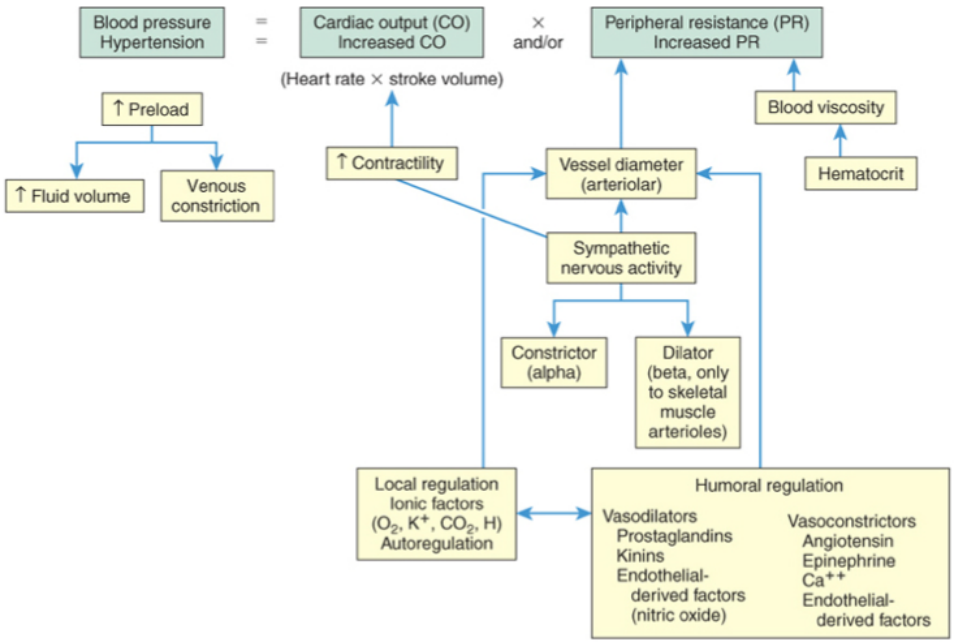
ANS Regulation of the Heart



- Unnecessary for heart beating
- Adjust heart function to the body's needs:
  - Vasodilation vs. vasoconstriction
  - HR (chronotropy)
  - Contractility (inotropy)
- Sympathetic increase in HR & contractility + vasomotor
- Parasympathetic only decreased HR

BP Regulation

- Pressure = flow (CO) x resistance (TPR) (V=IR)
- MAP = P_D + ⅓(Pulse pressure) = 92mmHg
  - Pulse pressure = P_S - P_D
- Hyperemia = increased blood flow
  - Active → exercise
  - Reactive → ischemia reperfusion injury



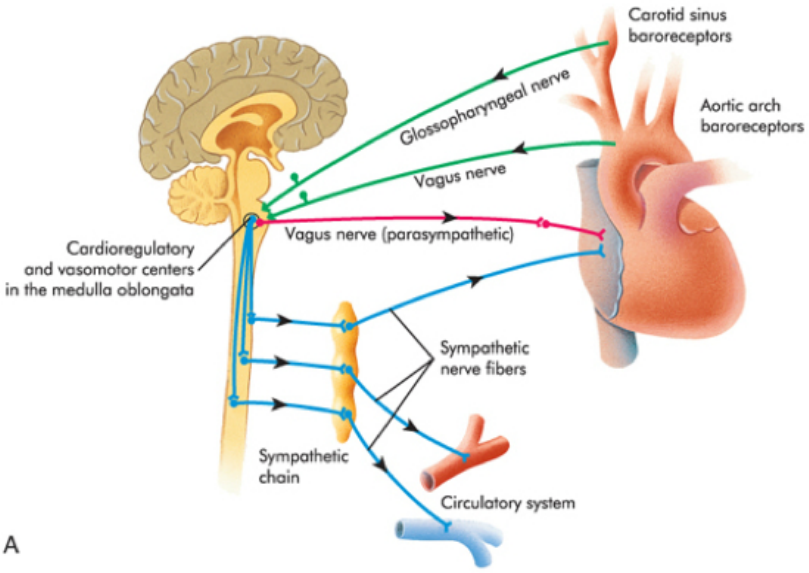
<u>Baroreceptor Reflex</u>

High BP reflex:

- Increased BP → increased stretch
  ↓
- Increased AP firing → increased parasympathetic + decreased sympathetic
  ↓
- Decreased HR & SV + vasodilation → decreased BP

Low BP reflex:

- Decreased BP → decreased stretch
  ↓
- Decreased AP firing → decreased parasympathetic + increased sympathetic
  ↓
- Increased HR & SV + vasoconstriction → increased BP



A

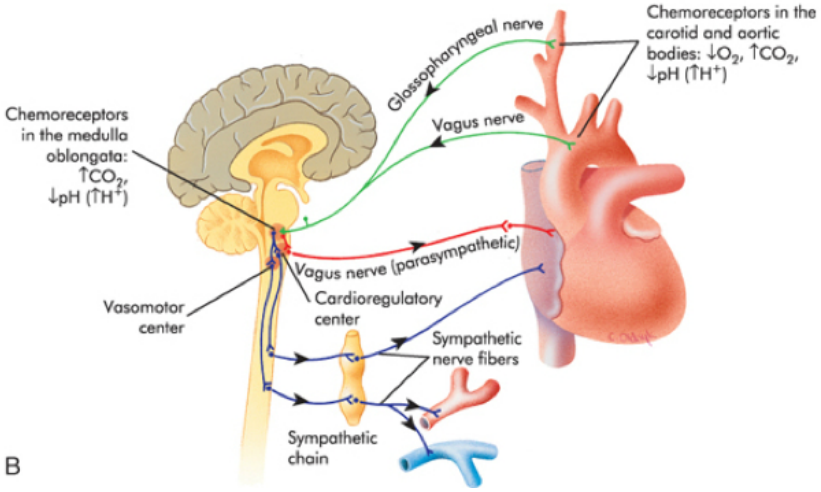
Chemoreceptor Reflex

Alkalosis/High O_2 reflex

- Decreased H+/P_{CO2} or increased P_{O2}
  ↓
- Increased AP firing → increased parasympathetic + decreased sympathetic
  ↓
- Decreased HR & SV + vasodilation → decreased BP

Acidosis/Low O_2 reflex

- Increased H+/P_{CO2} or decreased P_{O2}
  ↓
- Decreased AP firing → Decreased parasympathetic + Increased sympathetic
  ↓
- Increased HR & SV + vasoconstriction → increased BP



**Same chemoreceptors that control ventilation.

**Δ P_{O2} more significant than Δ pH or P_{CO2}

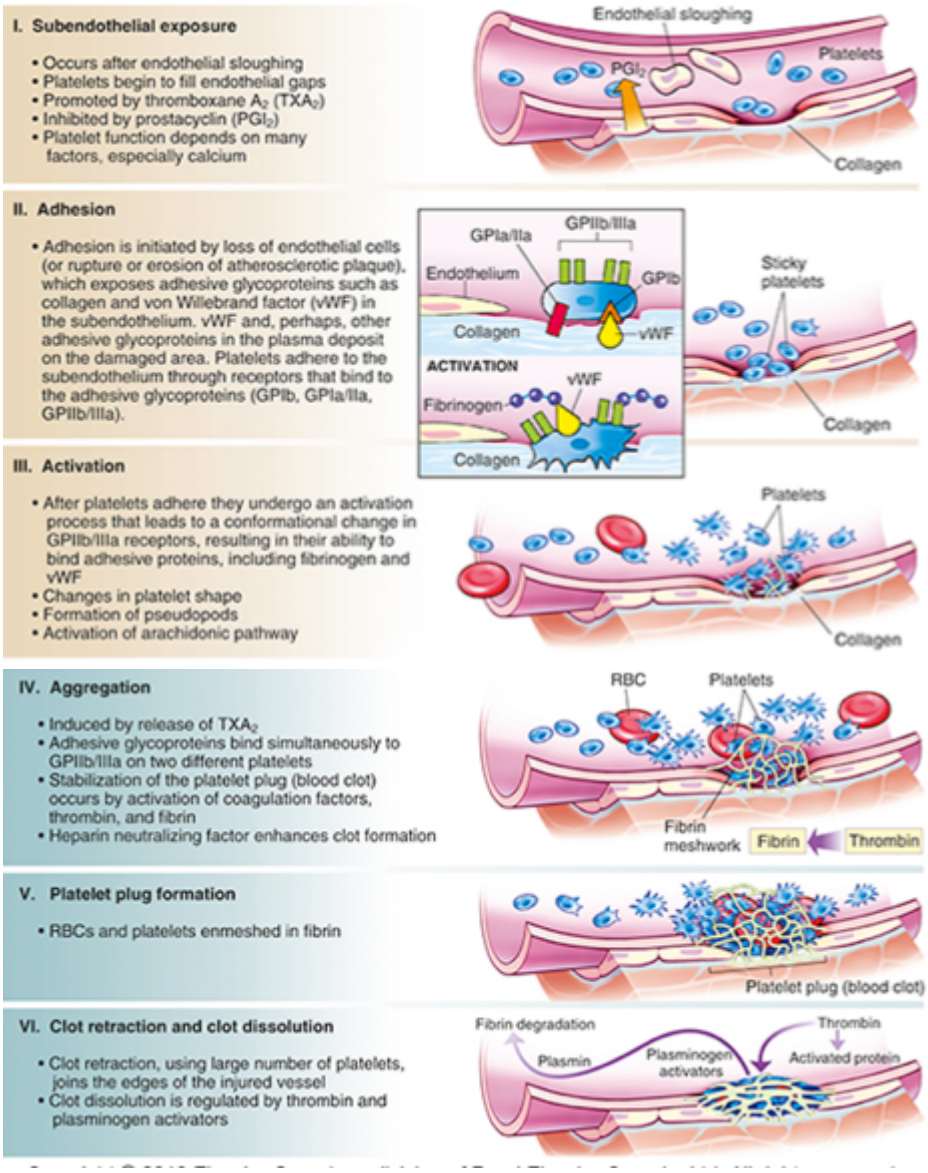
Orthostatic/Postural Hypotension

- Defective Baroreceptor Reflex → decreased BP upon standing up (~20mmHg S or -10mmHG D)
  - Normally: stand up → decreased venous return due to gravity → decreased BP
  - Rapid activation of baroreceptor reflex → increased SNS activity → increased BP
- Acute temporary factors
  - Ex: drugs, massive diuresis, stand up immobile → venous pooling
- Chronic primary or secondary
  - Ex: metabolic syndrome, cardiovascular autonomic neuropathy
- Prevention: raise slowly, calf contraction, vasoconstrictors

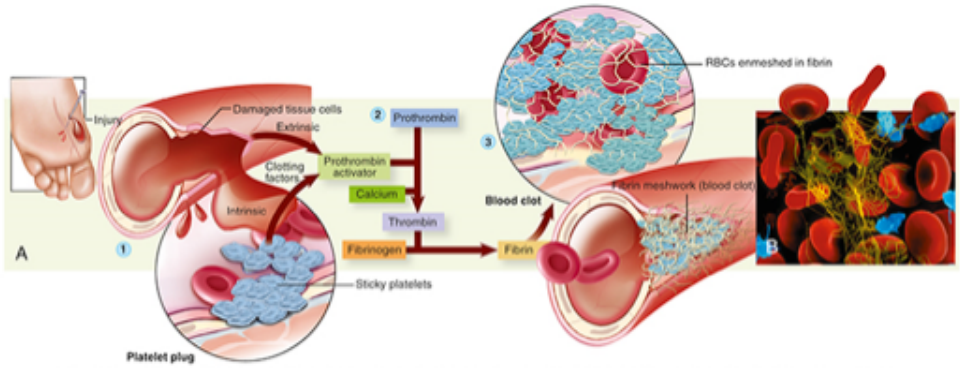
THROMBOEMBOLIC DISORDER DRUGS (Ch. 52)

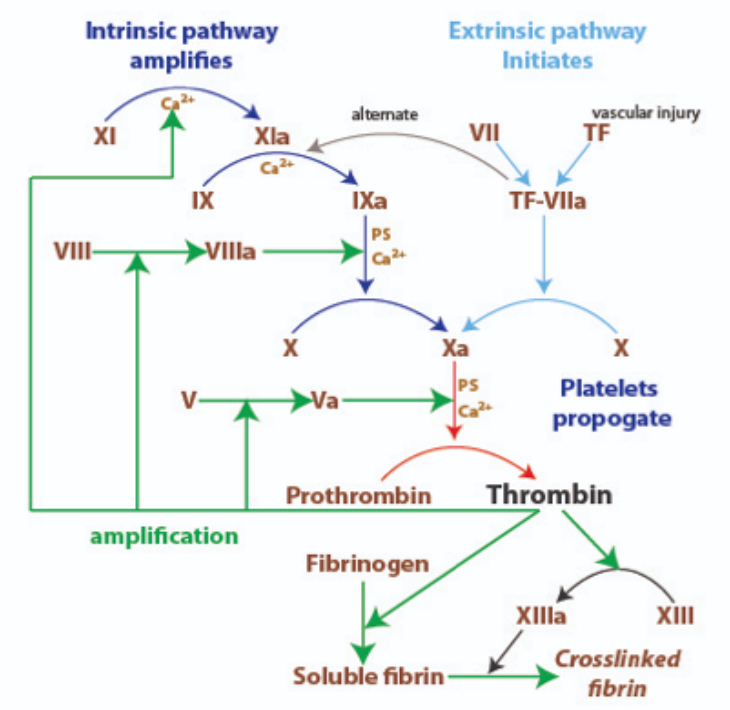
Hemostasis Review

Platelet plug formation

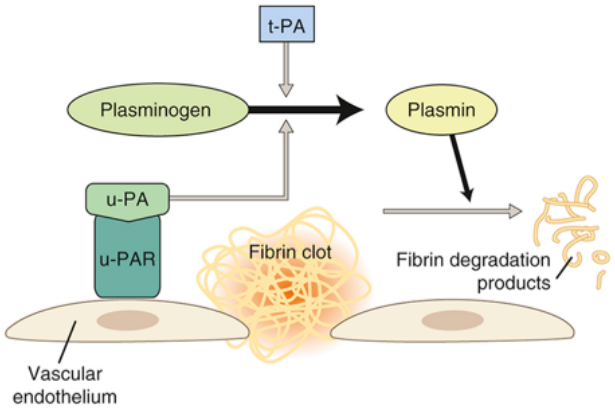


Coagulation Cascade



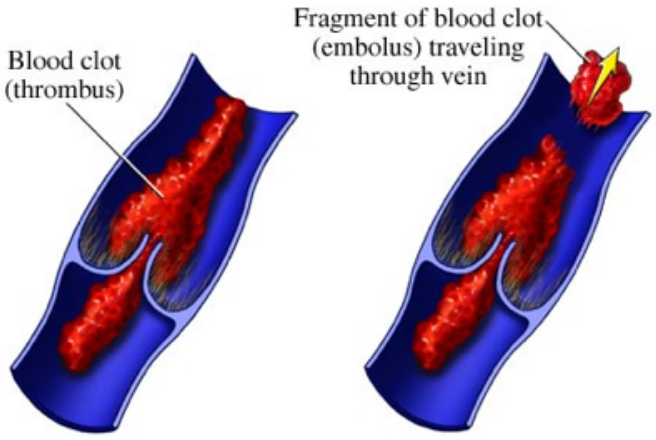


Fibrinolytic System



When a clot has formed, plasmin will help with the degradation of the clot.

Thrombosis



Thrombosis is the formation of the clot.

BACK TO PHARM

Drug Categories Overview

1. Anticoagulant drugs (ex. Warfarin, Heparin)
2. Antiplatelet drugs (ex. Aspirin, Clopidogrel)
3. Thrombolytic (fibrinolytic) drugs (ex. Alteplase)

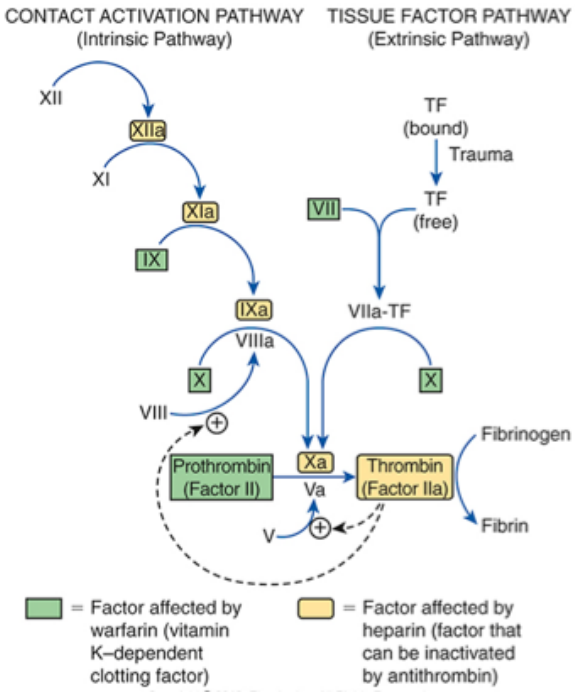
General Safety Alert: they all increase risks of bleeding

- Monitor BP, HR & mucous membrane for internal bleeding signs

Anticoagulants

1. Drugs that activate Antithrombin (ex. heparin)
2. Vitamin K antagonists (ex. warfarin)
3. Direct thrombin inhibitors (ex. dabigatran)
4. Direct factor Xa inhibitors (ex. Apixaban)

Common Action: decreased fibrin formation
Therapeutic Use: venous & arterial thrombosis prevention



Antithrombin Activators: Heparins & Derivatives

Comparison of Drugs That Activate Antithrombin

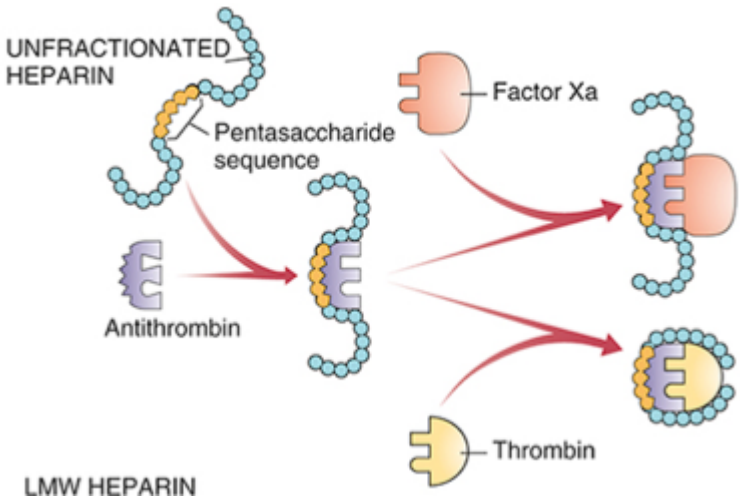
Property	Unfractionated Heparin	Low-Molecular-Weight Heparins	Fondaparinux
Molecular weight range	3000–30,000	1000–9000	1728
Mean molecular weight	12,000–15,000	4000–5000	1728
Mechanism of action	Activation of antithrombin, resulting in the inactivation of factor Xa and thrombin	Activation of antithrombin, resulting in preferential inactivation of factor Xa, plus some inactivation of thrombin	Activation of antithrombin, resulting in selective inactivation of factor Xa
Routes	IV, subQ	SubQ only	SubQ only
Nonspecific binding	Widespread	Minimal	Minimal
Laboratory monitoring	aPTT monitoring is essential	No aPTT monitoring required	No aPTT monitoring required
Dosage	Dosage must be adjusted on the basis of aPTT	Dosage is fixed	Dosage is fixed
Setting for use	Hospital	Hospital or home	Hospital or home

*The mechanism of action differs in selectivity: the unfractionated heparin has more widespread effects vs. others are more selective.

Heparin (unfractionated)

Kinetics

- Large polar molecule → no membrane crossing
- Subcut/IV admin → onset in minutes
- Plasma protein binding → variable activity
- Hepatic metabolism + renal excretion



Mechanism of action:

- The unfractionated heparin will bind & wrap around antithrombin. It can then inhibit factor Xa or thrombin.
- The end result: less fibrin formation

Main therapeutic uses:

- Anticoagulation during pregnancy
- When rapid anticoagulation required: ex. Massive DVT & pulmonary embolism

Main adverse effects:

- Possible hypersensitivity reactions (because it's a protein, and our body can produce an immune response against it)
- Hemorrhage (=10%)
- Spinal/epidural hematoma

    - Monitor neurologic impairment signs/symptoms
- Heparin-induced thrombocytopenia (HIT)
    - Monitor platelet count: < 100,000/mm^3 = discontinue

Nursing Capsule: Heparin Considerations

- High risk patients
    - Hemophilia, peptic ulcers, severe hypertension, threatened abortions
- Contraindications
    - Thrombocytopenia, uncontrollable bleeding & following eye, brain or spinal cord surgery
- Drug interaction: synergistic action with antiplatelet drugs (ex. aspirin)
- Heparin overdose antidote: protamine sulfate IV, 1mg/100 heparin units
- Dosage & administration
    - Dosage in units based on coagulation test results
    - No oral availability (too large and polar for absorption!!)
    - Dosage varies for usage: ex. Small for postoperative prophylaxis vs. large for open heart surgery

Nursing Capsule: Heparin Lab Monitoring

- Therapeutic objective = decrease thrombosis without increased bleeding
- Activated partial thromboplastin time (aPTT)
    - Measures time for blood clot formation
    - Normal value = 40 seconds
    - **Heparin therapy objective** = 60-80 seconds
    - Test every 4-6 hours initially → adjust dosage accordingly
    - Once optimal dosage achieved: test once daily
- Anti-Factor Xa Heparin Assay
    - New test: → increased accuracy
    - Measures Factor Xa activity → inversely proportional to heparin activity
    - Heparin therapy objective = 0.3-0.7 IU/mL
    - Drawback = cost

Low-Molecular Weight Heparins (LMWH)

Action:

- Preferential **inhibition of Factor Xa**
- Less inhibition of thrombin
- Fondaparinux = factor Xa inhibition ONLY

1st Line Tx for Thrombosis Prophylaxis & Therapy:

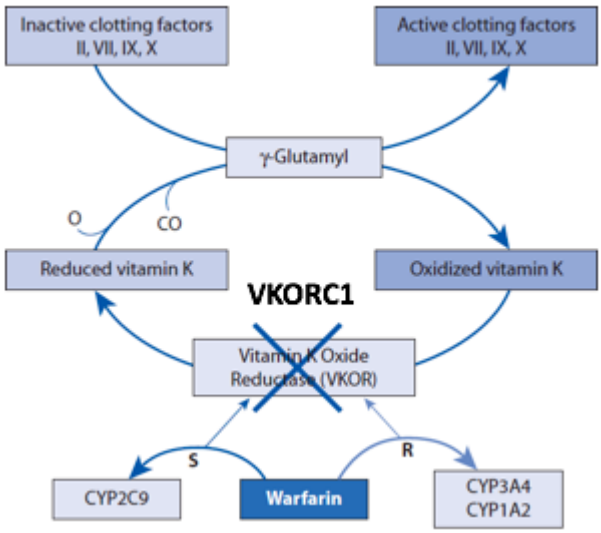
- Efficacy = unfractionated heparin
- Bleeding < heparin
- Other ADRs = heparin
- Less protein binding + longer half-life
- **No aPTT monitoring → allows home use** (huge advantage)

- Fixed dosage / subcutaneous administration

***Superior to Unfractionated Heparin on almost all counts**

Warfarin: Mechanism of Action

- Warfarin is a vitamin K oxidase inhibitor
- Inhibits clotting factor activation: VKORC1 activates vitamin K, which then in turn activates other clotting factors
- No impairment of existing activated factors
- Disadvantage : delayed action (days)
- Advantage: orally available
- Use: long-term thrombosis prophylaxis
- Kinetics:
    - 99% Albumin-bound (high risk of interaction with other protein bound drugs)
    - Mostly CYP2C9 metabolism
    - Urine excretion



History Capsule: Morbid Discovery

- Canadian farmer notices his cattle dying after eating spoiled clover
- Chemical analysis: spoiled clover contained high quantities of a warfarin-like chemical
- Warfarin used as rat poison. Believed to be too dangerous for human medicine
- Failed suicide attempt with warfarin triggered interest in medicinal use
- Clinical trials determined a narrow but safe therapeutic window existed

Warfarin: Toxicity & Interactions

Adverse reactions:

- Severe hemorrhage
    - Discontinue before surgical procedures
- Very teratogenic
    - Fetal hemorrhage & gross malformation
    - Enters breast milk

* The drugs with the most significant number of potential interactions!! Especially likely with other anticoagulant/antiplatelet drugs.

- Interactions = caution not contraindication

Drug Category	Interaction Mechanism	Examples
Increase Warfarin Effect	Albumin Displacement	Aspirin
	Inhibition of Warfarin Degradation	Acetaminophen Ketoconazole
Promote Bleeding	Platelet Aggregation Inhibition	Clopidogrel
	Inihibition of clotting factors/thrombin formation	Heparins Dabigatran
	Ulcer formation promotion	Aspirin
Decrease Warfarin Effect	Induction of Metabolism	Phenytoin
	Increase Clotting Factor Synthesis	Oral Contraceptives
	Decrease Warfarin Absorption	Cholestyramine

*drugs with the most interactions

Nursing Capsule: Warfarin Monitoring

- Prothrombin Time (PT) test:
  - Measures vitamin K-dependent clotting time
  - Normal value = 12 seconds
  - Warfarin objective: see table → adjust dosage accordingly
  - Frequent monitoring throughout therapy
  - Re-test for each drug interaction possibility
  - Home monitoring devices now available
  - Adequate monitoring decreases risks of hemorrhage

Condition Being Treated	INR[b]
Acute myocardial infarction[c]	2–3
Atrial fibrillation[c]	2–3
Valvular heart disease[c]	2–3
Pulmonary embolism	2–3
Venous thrombosis[d]	2–3
Tissue heart valves[c]	2–3
Mechanical heart valves	3–4.5
Systemic embolism	
Prevention	2–3
Recurrent	2–3

Nb. INR: international normalized ratio derived from PT test

Nursing Capsule: Warnings & Dosage

- Warnings/contraindications
  - Contraindications = same as heparins + pregnancy/lactation + liver impairment/alcoholism
  - Extreme caution = severe hypertension, gastric ulcers, hemophilia, threatened abortions
- Warfarin overdose antidote
  - Vitamin K PO or IV
  - If fails, use fresh whole blood, frozen-fresh plasma or other concentrates of vitamin K clotting factors
- Dosage
  - Individualized via trial-error + INR monitoring
  - Genetic considerations: VKORC1 & CYP2C9 polymorphisms
    - Genetic testings are recommended but not required by FDA
    - Can help reduce bleeding risks

Direct Thrombin Inhibitors

Therapeutic Use:

- Prevention & treatment of thromboembolisms/stroke for: atrial fibrillation patients, knee/hip replacements

Kinetics:

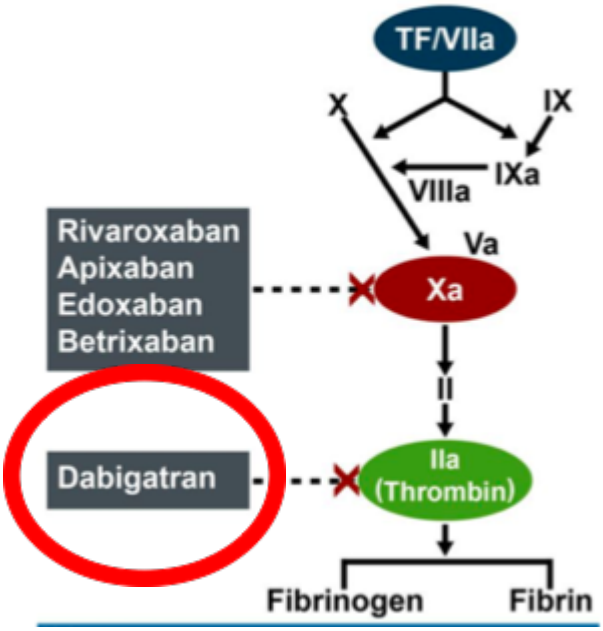
- Good oral absorption
- No plasma protein binding
- No P450 metabolism
- Renal elimination

Main adverse effects:

- Bleeding & GI disturbances
- P-Glycoprotein interactions

Advantages vs. Warfarin:

1. Rapid onset
2. No monitoring
3. Few interactions
4. Lower bleeding risk
5. Fixed dosage



Disadvantages:

1. New drug
2. No antidote
3. Shorter duration

Direct Factor Xa Inhibitors

- Same usage and advantages/disadvantages as Dabigatran
- Main differences = kinetics distribution & metabolism
    - They have protein binding while the thrombin inhibitors do not
- Avoid/caution with renal or hepatic impairments & during pregnancy

Kinetics:

- Good oral absorption
- 92-95% plasma protein binding
- Some CYP3A4 metabolism
- Renal elimination

Main adverse effects:

- Bleeding & spinal hematoma
- CYP2A4 & P-Glycoprotein interactions

Drugs:

- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

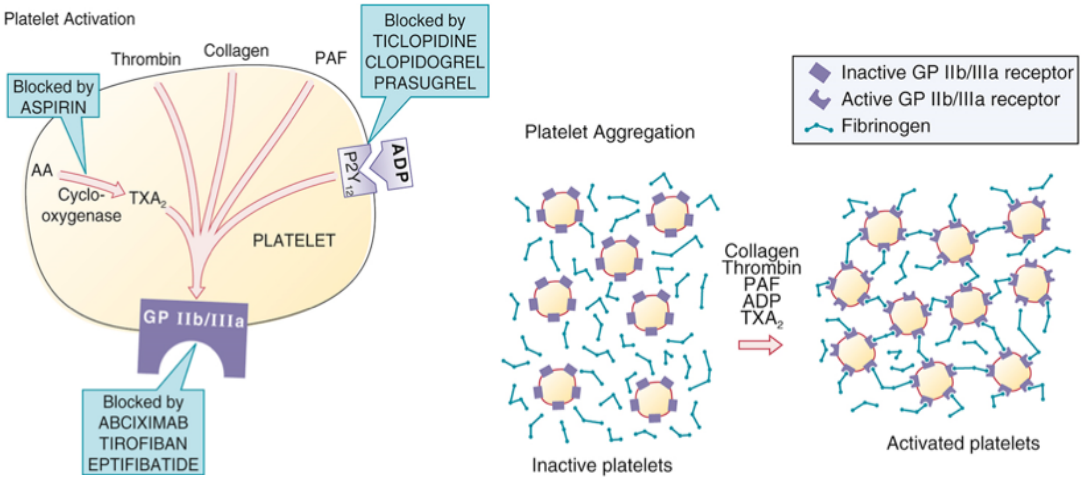
Oral Anticoagulants Summary (Table 52-6, p. 616)

Properties of Oral Anticoagulants

	Warfarin [Coumadin]	Rivaroxaban [Xarelto]	Apixaban [Eliquis]	Edoxaban [Savaysa]	Dabigatran Etexilate [Pradaxa, Pradax ◆]
Mechanism	Decreased synthesis of vitamin K–dependent clotting factors	Inhibition of factor Xa	Inhibition of factor Xa	Inhibition of factor Xa	Direct inhibition of thrombin
Indications					
Atrial fibrillation	Yes	Yes	Yes	Yes	Yes
Heart valve replacement	Yes	No	No	No	No
Knee or hip replacement	Yes	Yes	No	No	Yes
Onset	Delayed (days)	Rapid (hours)	Rapid (hours)	Rapid (hours)	Rapid (hours)
Duration	Prolonged	Short	Short	Short	Short
Antidote available	Yes (oral/parenteral vitamin K)	No	No	No	No
Drug-food interactions	Many	Few	Few	Few	Few
INR testing needed	Yes	No	No	No	No
Dosage	Adjusted based on INR	Fixed	Fixed	Fixed	Fixed
Doses/day	One	One	Two	One	Two
Clinical experience	Extensive	Limited	Limited	Limited	Limited
Advantages, summary	Decades of clinical experience Precise dosage timing not critical, owing to long duration Antidote available for overdose	Rapid onset Fixed dosage No blood tests needed Less bleeding and hemorrhagic stroke Few drug-food interactions	Same as rivaroxaban	Same as rivaroxaban	Same as rivaroxaban
Disadvantages, summary	Delayed onset Blood tests required No fixed dosage Many drug-food interactions	Dosing on time is important, owing to short duration No antidote to overdose Limited clinical experience	Same as rivaroxaban	Same as rivaroxaban	Same as rivaroxaban *plus* GI disturbances are common

Antiplatelet Drugs

- Best against arterial thrombosis
  - (anticoagulants = best against vein thrombosis)
- Diagram below:
  - Aspirin can block COX enzyme inhibiting the formation of TXA2 → inhibiting GP protein activation
  - Directly inhibit the GP protein activation
  - Block the ADP receptor called $P2Y_{12}$ receptor → inhibits platelet aggregation



Antiplatelet Drugs

Properties of the Major Classes of Antiplatelet Drugs

	Aspirin, a Cyclooxygenase Inhibitor	$P2Y_{12}$ Adenosine Diphosphate (ADP) Receptor Blockers	Protease-Activated Receptor-1 (PAR-1) Antagonists	Glycoprotein (GP) IIb/IIIa Receptor Blockers
Representative drug	Aspirin	Clopidogrel [Plavix]	Vorapaxar [Zontivity]	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Irreversibly inhibits cyclooxygenase, and thereby blocks synthesis of TXA_2	Irreversibly blocks receptors for ADP[a]	Reversibly blocks the protease-activated receptor-1 (PAR-1) expressed on platelets	Reversibly blocks receptors for GP IIb/IIIa
Route	PO	PO	PO	IV infusion
Duration of effects	Effects persist 7–10 days after the last dose	Effects persist 7–10 days after the last dose[a]	Effects persist 7–10 days after the last dose	Effects stop within 4 hr of stopping the infusion
Cost	$3/month	$87/month	$320/month	$1000/course

Notice the last column is IV infusion, and the last row about cost.

Aspirin - Antiplatelet Action

Indication:

- *Ischemic stroke* (to reduce the risk of death and nonfatal stroke)
- *TIAs* (to reduce the risk of death and nonfatal stroke)
- *Chronic stable angina* (to reduce the risk of MI and sudden death)
- *Unstable angina* (to reduce the combined risk of death and nonfatal MI)
- *Coronary stenting* (to prevent reocclusion)
- *Acute MI* (to reduce the risk of vascular mortality)
- *Previous MI* (to reduce the combined risk of death and nonfatal MI)
- *Primary prevention of MI* (to prevent a first MI in men and in women age 65 and older)

MI prevention benefit vs. GI bleeding risk analysis to determine if Aspirin should be administered

Optimal Dosage:

- Initial acute MI treatment = 325mg/day
- Maintenance & chronic prevention: 81mg/day

$P2Y_{12}$ ADP Receptor Antagonists

Clopidogrel

- Inhibits ADP-stimulated platelet aggregation by blocking the $P2Y_{12}$ ADP receptor
- Prodrug → CYP2C19 activation
- Poor metabolizers contraindications → switch to other ADP-antagonist
- Main use = coronary artery stent blockage prevention

	$P2Y_{12}$ Adenosine Diphosphate (ADP) Receptor Blockers
Representative drug	Clopidogrel [Plavix]
Mechanism of antiplatelet action	Irreversibly blocks receptors for ADP[a]
Route	PO
Duration of effects	Effects persist 7–10 days after the last dose[a]
Cost	$87/month

Main Adverse Effects

- Bleeding & rare cases of thrombotic thrombocytopenic purpura
- Interactions: CYP2C19 inhibitors
- Proton pump inhibitors consensus statement:
  - PPI + clopidogrel for GI bleeding high risk patients (interaction at the CYP2C19 enzyme)
  - Clopidogrel alone if no particular GI bleeding risk

Glycoprotein IIb/IIIa Antagonists

- "Super Aspirin" → most effective antiplatelet drugs
- Antagonism of GP IIb/IIIa inhibits all pathways
- Short term use only in emergency situations due to cost
- Adverse effects = other antiplatelets
- Bleeding risk >> other antiplatelets
- Decrease ischemic complications in ACS
- Decrease reocclusion risk following balloon or laser angioplasty

Application
Acute coronary syndromes (ACS)
Percutaneous coronary intervention[a] (PCI) following treatment for ACS
PCI without prior treatment for ACS

	Glycoprotein (GP) IIb/IIIa Receptor Blockers
Representative drug	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Reversibly blocks receptors for GP IIb/IIIa
Route	IV infusion
Duration of effects	Effects stop within 4 hr of stopping the infusion
Cost	$1000/course

Thrombolytic Drugs

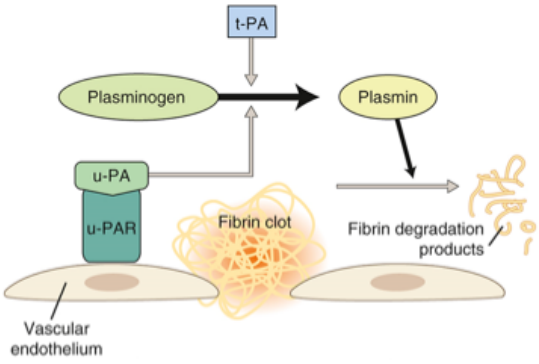
Properties of Thrombolytic (Fibrinolytic) Drugs

	Alteplase (tPA)	Tenecteplase	Reteplase
Brand name	Activase, Cathflo Activase	TNKase	Retavase
Description	A compound identical to human tPA	Modified form of tPA with a prolonged half-life	A compound that contains the active sequence of amino acids present in tPA
Source	All three drugs are made using recombinant DNA technology		
Mechanism	All three drugs promote conversion of plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi		
Indications			
Acute MI	Yes	Yes	Yes
Acute ischemic stroke	Yes	No	No
Acute pulmonary embolism	Yes	No	No
Clearing a blocked central venous catheter	Yes	No	No
Adverse effect: Bleeding	With all three drugs, bleeding is the primary adverse effect		
Half-life (min)	5	20–24	13–16
Dosage and administration for acute MI	*Intravenous:* 15-mg bolus, then 50 mg infused over 30 min, then 35 mg infused over 60 min	*Intravenous:* Single bolus based on body weight (see text)	*Intravenous:* 10-unit bolus 2 times, separated by 30 min

*Note the differences in half-life: alteplase has the shortest half-life.

Alteplase (Recombinant tPA)

- Digest fibrin → thrombolysis
- Degrade fibrinogen & clotting factors → increased bleeding risks



Therapeutic Use:

- Acute MI / acute ischemic stroke / acute PE
- Administration: sooner the better!
- IV infusions only / very short duration

Bleeding = major adverse effects:

- Can destroy clots of recently healed vessels → severe internal bleeding
- Antidote = IV aminocaproic acid + blood replacement
- Super contraindication: patients with a history of intracranial hemorrhage (ICH)

Hemophilia Medications (Ch. 54)

Hemophilia

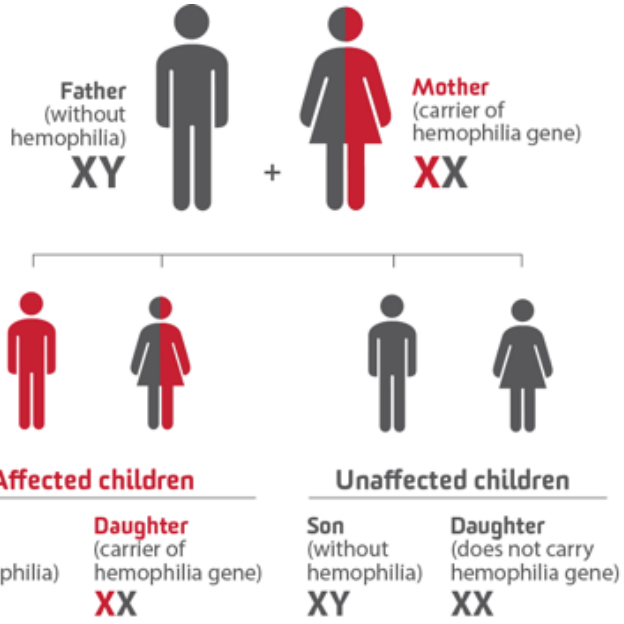
- Hemophilia A: most common type of hemophilia. 8 out of 10 people with hemophilia have hemophilia A > people with hemophilia A do not have enough clotting factor VIII (factor *)
- Hemophilia B: is also known as Christma disease and a less common type of hemophilia. People with hemophilia B do not have enough clotting factor IX (factor 9). It is caused by a deficiency in clotting factor 9.

Clinical Classification of Hemophilia Severity

Disease Parameter	Disease Severity		
	Severe	Moderate	Mild
Clotting factor level (VIII or IX)	Less than 1% of normal	Between 1% and 5% of normal	Between 6% and 49% of normal
Bleeding tendency	Can bleed with very mild injury	Can bleed with moderate injury	Can bleed with severe injury, surgery, or invasive procedures
Bleeding frequency	May bleed once or twice a week	May bleed once a month	May never have a bleeding episode
Occurrence of joint bleeding	Frequent	Less frequent	Infrequent, but can occur in response to severe injury

Hemophilia: Inheritance

- X-linked recessive disease
- Severity of hemophilia depends on mutations



Nursing Capsule: Hemophilia Therapy Overview

Ideal specialist team:

- Hematologist + orthopedist + dietician + psychologist
- Physical & occupational therapist + genetic counselor
- Infectious disease specialist + social worker + nurse coordinator

Cornerstone = replacement therapy

- Factor VIII (hemophilia A) or Factor IX (hemophilia B) or desmopressin (mild)
- Adjunct = antifibrinolytic drugs (ex. Aminocaproic acid)
- Good prognosis but lifelong therapy → treatment = very costly (60-150k/year)

Bleeding-related pain management

- Mild → acetaminophen
- Severe → opioid
- Avoid Aspirin & other NSAIDs

Immunization

- Normal vaccination schedule is recommended in hemophilic children
  - Monitor closely for signs of bleeding
- Hepatitis A & B vaccines for both the patient & family members administering clotting factors

<u>Factor VIII & IX Concentrates</u>

Therapeutic Use:

- Hemophilia A (VIII) & B (IX) treatment
- Plasma-derived (cheaper) or recombinant (safer - less allergic reactions)
- 3rd generation recombinant (ex. Adavate) = treatment of choice

Dosage & Administration

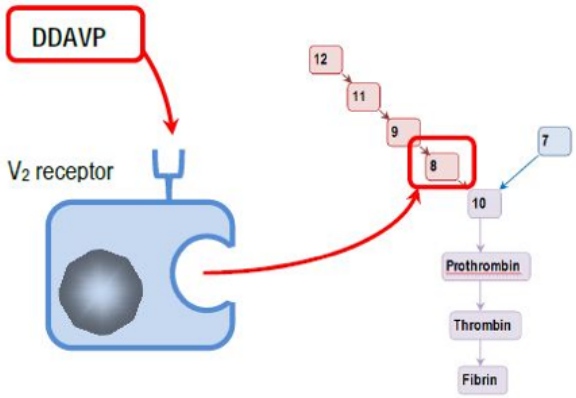
- On demand - to stop a bleeding
  - Slow IV push over 5-10min
  - Dosage depends on site & severity
  - Calculate based on % of activity target & patient body weight
- Prophylactic therapy
  - Mostly for severe hemophilia in kids
  - Goal = maintain % factor VIII above 1%
  - At home infusions 3-4x/week (VIII) or 2x/week (IX)
  - Central venous access devices can be installed

Safety Alert

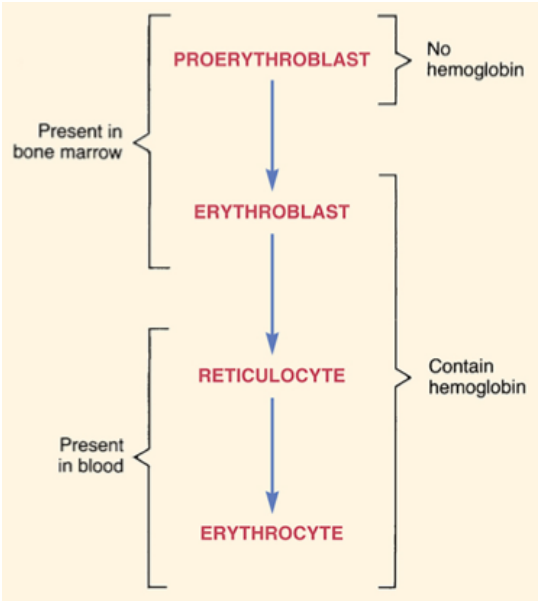
- Mild to severe allergic reactions
  - Mild → antihistamines
  - Severe → subcutaneous epinephrine

<u>Desmopressin (DDAVP)</u>

- Analog of Vasopressin/ADH
- Adverse effects: fluid retention/hyponatremia
- Used only for mild hemophilia A prophylaxis & treatment
- Releases stored Factor VIII
- Cheaper & safer than factor replacement (no risk for allergic reactions)
- Administration = intranasal or IV



DRUGS FOR ANEMIC DEFICIENCIES (Ch. 55)



RBC Development

Necessary ingredients for proper RBC development:

1. Healthy bone marrow
2. Erythropoietin → stimulate RBC maturation
3. Iron → hemoglobin synthesis
4. Vitamin B12 → DNA synthesis
5. Folic acid → DNA synthesis

Anemia = decrease in RBC #, size or hemoglobin

Deficiency in any of the above → anemia

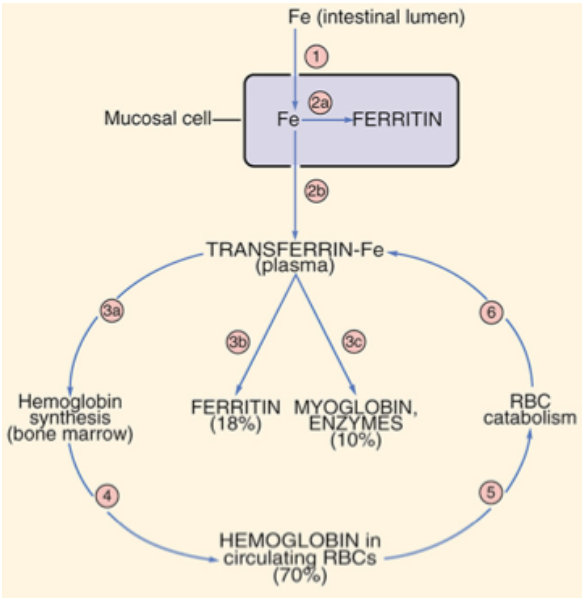
Marrow dysfunction → anemia

- Reticulocyte is the monitoring point.
    - When there is a case of anemia or risk of anemia, we want to look at the reticulocyte count. Why? Because it's a better measure of the development of RBC. If we only look at the amount of erythrocytes (active RBCs), at that precise moment the amount of RBCs might be healthy, but you're amount of reticulocytes might be low, indicating you will have anemia in a few days or months.

*Review hematology pathophysiology lecture if necessary

Iron Physiology

- Most common nutritional deficiency worldwide
- Necessary for hemoglobin, myoglobin & some enzymes
- Intestinal absorption rate varies with need ~2-20%
- Ferritin = storage / transferrin = plasma transport
- Physiologic excretion = very low
- Iron loss → **blood donation, hemorrhage & menses**



Individual Characteristic	Recommended Dietary Allowance (RDA)
Male	11 mg/day
Female	18 mg/day
Pregnant Female	27 mg/day (must use supplements)

Iron deficiency

Causes	Consequences	Diagnosis
1. **Blood volume expansio**n (ex. Pregnancy, puberty) 2. **Chronic blood loss** (ex. GI bleeding, menses) Mostly increased in demand Decreased uptake = very rare	**1. Iron deficiency anemia** a. Microcytic & hypochromic b. Fatigue & skin pallor c. Severe = tachycardia & angina 2. Impaired myoglobin synthesis 3. Impaired enzyme synthesis 4. Impaired child development 5. Impaired cognition	**Hallmarks:** 1. microcytic/hypochromic RBCs 2. Absence of aggregated ferritin **Lab Tests to confirm:** ● Decreased RBCs & reticulocyte count ● Decreased hemoglobin & hematocrit values ● Decreased serum iron content ● Increased serum iron-binding capacity

Ferrous Iron Salts

Indications: Iron deficiency anemia treatment + prevention

- All equivalent efficacy & toxicity
- Ferrous sulfate = preferred choice because cheaper

Main Adverse Effects:

- GI disturbances (dose-dependent) → tolerance & colored stool
    - Ex: nausea, diarrhea/constipation, heartburn
- Teeth staining
- Iron poisoning in children/kids = leading poisoning fatality
    - Main symptoms = acidosis & shock
    - Antidotes = gastric lavage or iron chelating agents can
- Drug interactions: antacids & tetracyclines decreases absorption / vitamin C increases absorption

Parenteral Iron: Iron Dextran

- Indications: patients for whom oral iron is inefficient/impossible
    - Ex: GI diseases or severe blood loss

Nursing Capsule: Iron Deficiency Guidelines

Assessments:

- Determine cause of iron deficiency to optimize intervention
- Monitor reticulocyte & hemoglobin levels for therapeutic success/failure
- Avoid therapeutic combinations with other iron, folic acid or vitamin B12 medications

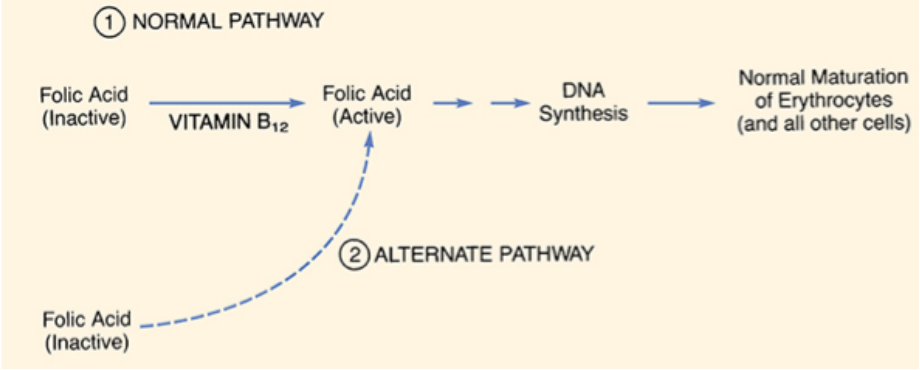
Dosage & administration considerations:

- Oral iron salts = best between meals to maximize absorption
    - With meals only during initiation or with large doses to minimize GI distress
    - Optimal dosage = 65mg 3x/day for a total of 200mg
- Parenteral iron dextran = complex dosage equation with body weight & severity of anemia
- Safety alert: fatal anaphylactic reactions with parenteral
    - Test dose before full-blown administration → monitor for 15min
    - IV administration has lower anaphylaxis risk than IM
    - Epinephrine & reanimation equipment readily available

Therapy duration: until hemoglobin levels are normal ~1-2 months

Vitamin B12 Physiology

- Main utility = folic acid activation
- Absorption at distal ileum requires intrinsic factor → mostly stored in the liver
- Very slow excretion → daily requirements are minuscule
- Deficiency takes years to develop



*Note: alternate pathway when high levels of folic acid. So if you have B12 deficiency, it can be overridden if you have high levels of folic acid via the alternate pathway.

Vitamin B12 Deficiency

Causes:

- Impaired absorption
    - Ex. GI diseases, lack of intrinsic factor
- Insufficient diet = very rare

Diagnosis:

- Megaloblast detection
- Test of plasma B12 levels
- B12 absorption test

Consequences:

→ Affects mostly highly dividing cells

- **Megaloblastic (pernicious) anemia**
  - Pernicious = old connotation when no Tx available
  - Macrocytic (large) RBC
  - Systemic Hypoxia, heart failure & dysrhythmias
- **Nervous System Injuries**
  - Demyelination of neurons
  - Long-term deficiency = permanent damage
  - Unrelated to folic acid or DNA
- GI disturbances
- Decreased WBC & platelets

Cyanocobalamin (B12 supplement)

- Drug of choice for all B12 deficiencies
- May produce hypokalemia: RBC synthesis requires potassium

Dosage and administration:

- Oral
  - Mild to moderate deficiency patients
  - Even if lack of intrinsic factor as ~1% is still absorbed → very high dosage
- Parenteral
  - Best for patients with severe deficiency → neurologic damage
  - IM or subcutaneous only, NEVER IV
- Intranasal
  - Good alternative to parenteral injections

Nursing Capsule: Vitamin B12 Deficiency Guidelines

Moderate B12 deficiency:

- Only manifestation = megaloblasts, NO neuronal damage or WBC decrease
- Manage via B12 supplements

Severe B12 deficiency:

- Disruptions of all blood cells + GI disturbances + neuronal injuries
- **Treatment protocol**: IM B12 + folic acid injection + blood replacement + platelet transfusion
- **Monitor success**: megaloblasts disappear + reticulocyte count increases
  - Need to see both. If you only see megaloblasts disappear with a decrease in reticulocyte count, that means he RBCs are being destroyed.
- Neurologic recovery is proportional to duration of deficiency

Long-term therapy:

- Patients with B12 malabsorption + intrinsic factor deficiency
- Monthly injections or very large oral doses

Folic Acid Physiology

- Necessary for DNA synthesis
- Alternative pathway bypasses need for vitamin B12
- Unlike B12, deficiency develops rapidly due to daily loss
- Extensive enterohepatic recycling decreases folate loss
- RDA for adults = 400 mcg/day; 600 mcg for pregnant women

*N.B. B12 deficiency does not equal folate deficiency

Vitamin B_{12} Deficiency Versus Folic Acid Deficiency

	Vitamin B_{12} Deficiency	Folic Acid Deficiency
Usual cause	Vitamin B_{12} malabsorption from lack of intrinsic factor	Low dietary folic acid
Primary hematologic effect	Megaloblastic anemia	Megaloblastic anemia
Neurologic effect	Damage to brain and spinal cord	None[a]
Diagnosis	Low plasma vitamin B_{12}; low B_{12} absorption (Schilling test)	Low plasma folic acid
Treatment (usual route)	Cyanocobalamin (PO or IM)	Folic acid (PO)
Usual duration of therapy	Lifelong	Short term

[a]Folic acid deficiency early in pregnancy can cause neural tube defects in the fetus.

Folic Acid Deficiency

Causes:

- Alcoholism
  - Poor diet
  - Enterohepatic folate recycling decreases
- Sprue
  - Malabsorption syndrome
- Very rare: drug-induced

Consequences:

- Similar to B12 deficiency except no neuronal injuries
- Potential increase in colorectal cancer & atherosclerosis
- Neural tube defect
  - Deficiency early during pregnancy
  - Avoid this via folate supplements

Diagnosis:

- Megaloblastic anemia with high B12 levels

Folic Acid Supplements

- Pteroylglutamic acid = inactive folic acid → rapidly activated upon absorption
- Already active form are no longer effective and more expensive
- Indications:
  - Folic acid deficiency megaloblastic anemia treatment & prophylaxis
  - Initial severe vitamin B12 megaloblastic anemia therapy

- Adverse effects:
    - None short-term
    - Increased colorectal cancer & atherosclerosis risks long-term

Nursing Capsule: Folic Acid Deficiency Guidelines

- Intervention should match the cause
    - Ex. poor diet → adjust diet, don't take supplements (except pregnancy!)
    - Malabsorption → folate supplementation
- Administration: mostly PO, rarely injected
- Prophylactic supplements: only for soon to be pregnant, pregnant or lactating women
- Severe deficiency management:
    - Initially: IM injection of B12 + folic acid → combination fastens recovery
    - Continue with oral folate only
    - Monitor success: same as with B12

HEMATOPOIETIC AGENTS (Ch. 56)

Hematopoietic Growth Factors (HGF)

HGF = naturally occurring hormones regulating proliferation & differentiation of blood cells
Also called Colony-Stimulating Factors (CSF)

Therapeutic applications:

- Post-chemotherapy platelet & WBC regeneration
- Boost bone marrow transplant recovery
- Boost RBC synthesis in chronic renal failure (CRF) patients

Nursing advice:

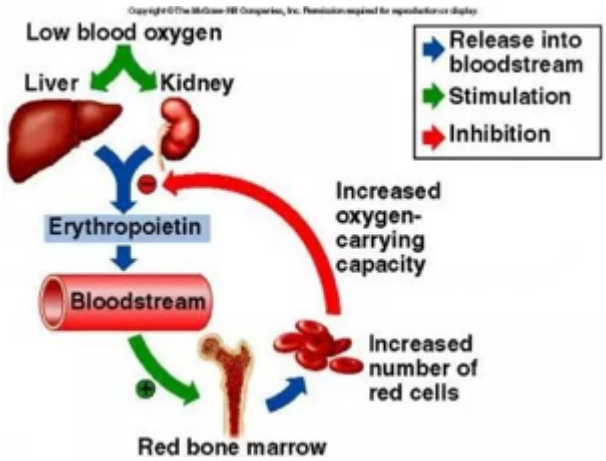
- These agents are usually contraindicated in patients with myeloid (blood) cancer

Nomenclature for Hematopoietic Growth Factors

Biologic Name	Pharmacologic Names	
	Generic Name	Brand Name
ERYTHROPOIETIC GROWTH FACTORS		
Erythropoietin	Darbepoetin alfa	Aranesp
	Epoetin alfa	Epogen, Procrit, Eprex ♣
LEUKOPOIETIC GROWTH FACTORS		
Granulocyte colony-stimulating factor (G-CSF)	Filgrastim	Neupogen
	Pegfilgrastim	Neulasta
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Sargramostim	Leukine
THROMBOPOIETIC GROWTH FACTOR		
Interleukin-11	Oprelvekin	Generic only

Erythropoietin (EPO)

- Primary function: promote RBC maturation
- Alternative to blood transfusions
- Inefficient without vitamin B12 + folate + iron
- Other functions:
  - Angiogenesis modulation
  - Cell-injury apoptosis inhibition → maintain cellular integrity



Epoietin Alfa (EPO)

- Parenteral injections only → decreases transfusion requirements
- Indications:
  - Anemia in chronic renal failure (CRF) → but no quality of life improvement!
  - Chemotherapy-induced anemias: palliative purposes only
  - AIDS patients on zidovudine (AZT)
  - Elevate RBC count prior to surgery: only if anticipate significant hemorrhage
- Adverse effects:
  - No significant allergic reactions or interactions
  - Hypertension in CRF patients due to hematocrit increase
  - Serious cardiovascular events
    - Ex. heart failure, cardiac arrest, stroke, MI
    - Greater risk when hemoglobin rises fast

Darbepoetin Alfa (long-acting EPO)

- Longer half-life (49h vs. 24h) than Epoietin Alfa
- Decreases # of injections
- Efficacy & toxicity profile = Epoietin Alfa
- Indications:
  - Anemia associated with CRF
  - Anemia associated with chemotherapy

Nursing Capsule: EPO Considerations

- Safety-alert - minimizing serious cardiovascular events in CRF patients
  - Dosage should be lowest for effective RBC elevation
  - Decrease dosage if hemoglobin increase > 1g/dL in 2 weeks
  - Temporarily hold treatment if hemoglobin > 11g/dL
- Warnings
  - Contraindicated for all cancer patients on a curative/remission therapy
  - Must be combined with anticoagulant for preoperative RBC elevation
- Monitoring
  - Measure hemoglobin levels at baseline + 2x/week until achieved target
  - Blood chemistry, iron levels & complete blood count should be done routinely

Leukopoietic Growth Factors (LGF)

- LGFs stimulate white blood cell (leukocytes) production
- Monitor blood count 2x/week during therapy to avoid leukocytosis & thrombocytosis

	Filgrastim (G-CSF)	Sargramostim (GM-CSF)
Physiology	• Released in response to inflammation • ↑ Neutrophil synthesis + Phagocytic & Cytotoxic	Same as Filgrastim but for macrophages, neutrophil & eosinophil
Therapeutic Use	• ↓ infection risk during chemotherapy • ↓ neutropenia in bone marrow transplant (BMT) patients • ↑ Pre-BMT hematopoietic stem cell (HSC) harvest • Congenital neutropenia therapy (↓ infection)	• Accelerate BMT recovery • ↑ failed BMT survival time • ↑ neutrophil recovery + ↓ infections in acute myeloid leukemia patients
Administration	Degraded in GIT → **Parenteral administration only.**	
Adverse Effects	• Short term: Almost none & no interactions • **Bone Pain**: usually mild, treatable with NSAIDs • **Leukocytosis**: Excessive WBC ↑ with high dosage	Similar to Filgrastim Possible **Leukocytosis & Thrombocytosis**