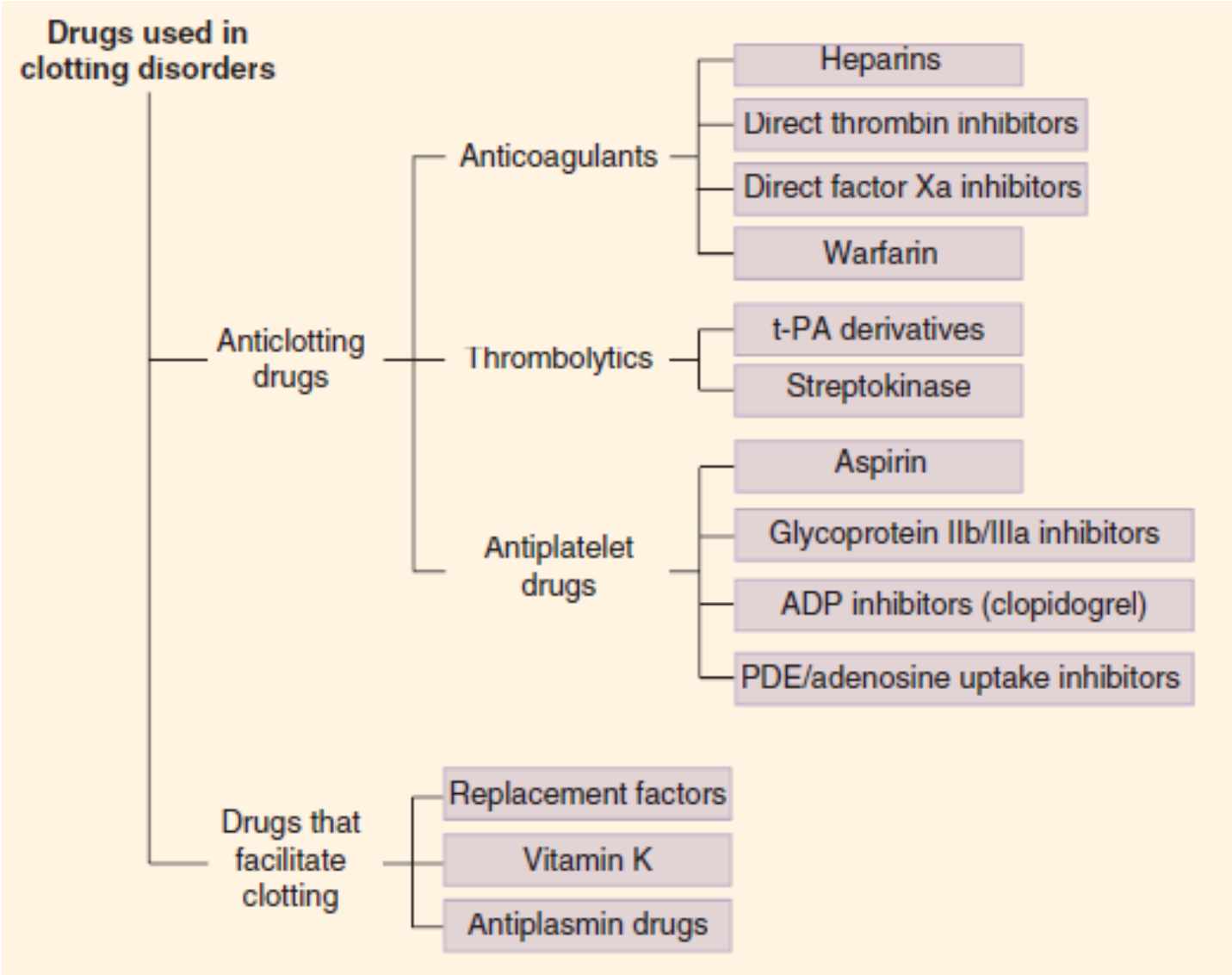
Drugs Used in Coagulation Disorders


Drugs used in clotting disorders
Anticlotting drugs
Anticoagulants
Heparins
Direct thrombin inhibitors
Direct factor Xa inhibitors
Warfarin
Thrombolytics
t-PA derivatives
Streptokinase
Antiplatelet drugs
Aspirin
Glycoprotein IIb/IIIa inhibitors
ADP inhibitors (clopidogrel)
PDE/adenosine uptake inhibitors
Drugs that facilitate clotting
Replacement factors
Vitamin K
Antiplasmin drugs

Thrombosis

- Blood hemostasis refers to the finely regulated dynamic process of maintaining fluidity of the blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs.
- Either extreme—excessive bleeding or thrombosis—represents a breakdown of the hemostatic mechanism.
- Thrombosis, the formation of an unwanted clot within a blood vessel.
- It is important to distinguish between thrombi and emboli:
  - A clot that adheres to a vessel wall is called a “thrombus,”
  - An intravascular clot that floats in the blood is termed an “embolus.”
- Thus, a detached thrombus becomes an embolus.
- Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients.
- Thrombotic disorders include acute myocardial infarction, deep vein thrombosis (DVT), pulmonary embolism, and acute ischemic stroke.

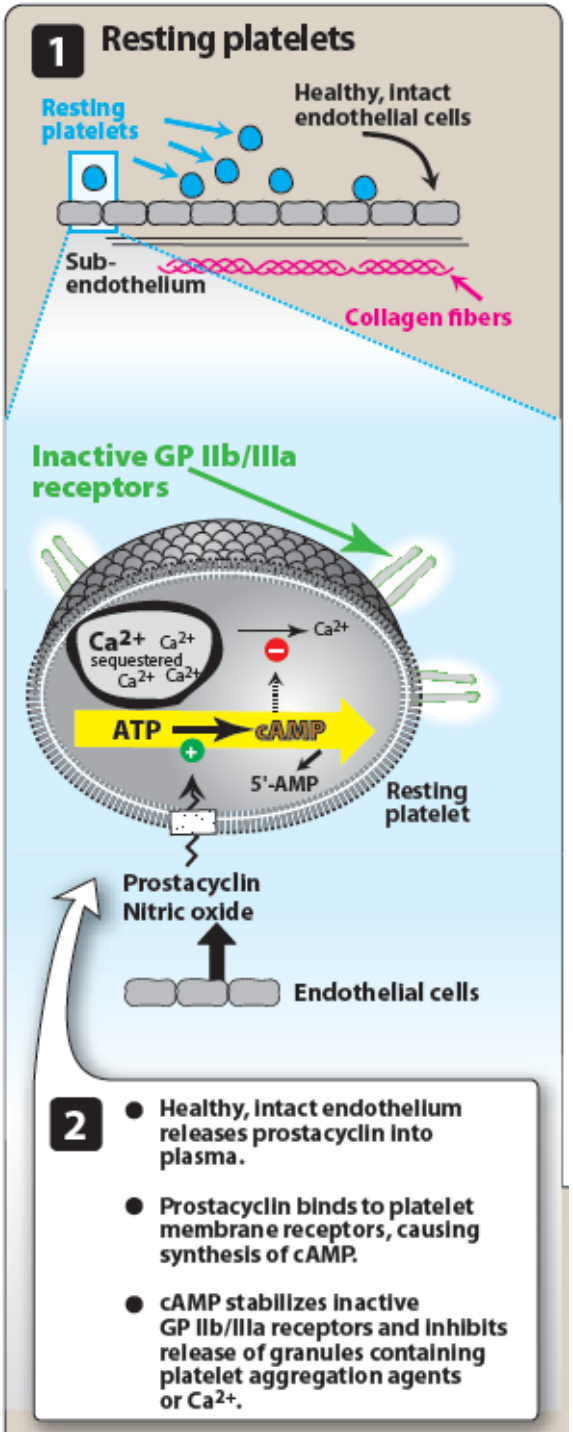
Mechanisms of blood coagulation

A. Resting platelets

- In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged.

1. Roles of prostacyclin and nitric oxide:

- Chemical mediators, such as prostacyclin and nitric oxide, are synthesized by intact endothelial cells and act as inhibitors of platelet aggregation.
- Prostacyclin (prostaglandin I_2) acts by binding to platelet membrane receptors that are coupled to the synthesis of cAMP, an intracellular messenger.
- Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. This prevents platelet activation and the subsequent release of platelet aggregation agents.



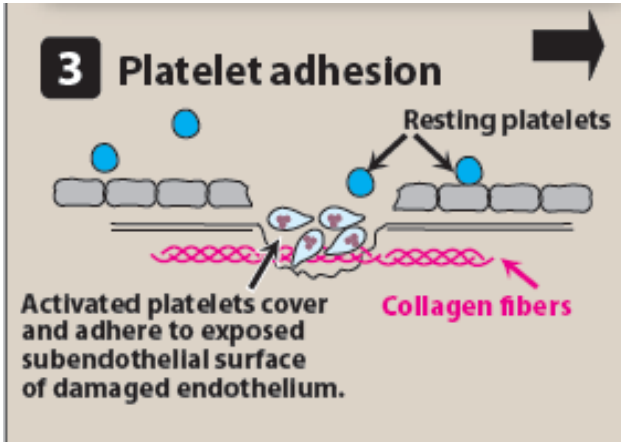
Mechanisms of blood coagulation

2. Roles of thrombin, thromboxanes, and collagen:

- The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen.
- In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the subendothelial layers. The corresponding platelet receptors are, thus, unoccupied and remain inactive. As a result, platelet activation and aggregation are not initiated.
- However, when occupied, each of these receptor types triggers a series of reactions leading to the release of intracellular granules by the platelets into the circulation. This ultimately stimulates platelet aggregation.

B. Platelet adhesion

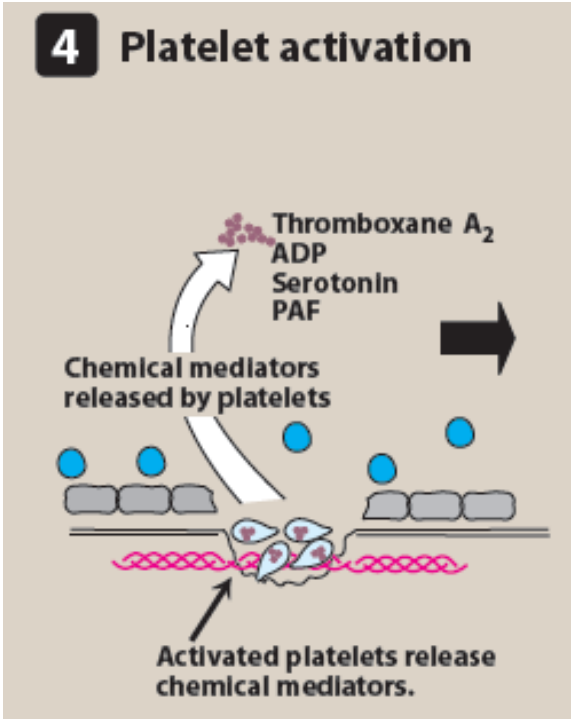
- When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium.
- This triggers a complex series of chemical reactions, resulting in platelet activation.



Mechanisms of blood coagulation

C. Platelet activation

- Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue.
- This causes morphologic changes in platelets and the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A_2, serotonin, platelet-activation factor (PAF), and thrombin.
- These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. The previously dormant platelets become activated and start to aggregate.
- These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.



Mechanisms of blood coagulation

D. Platelet aggregation

- The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet. This leads to:

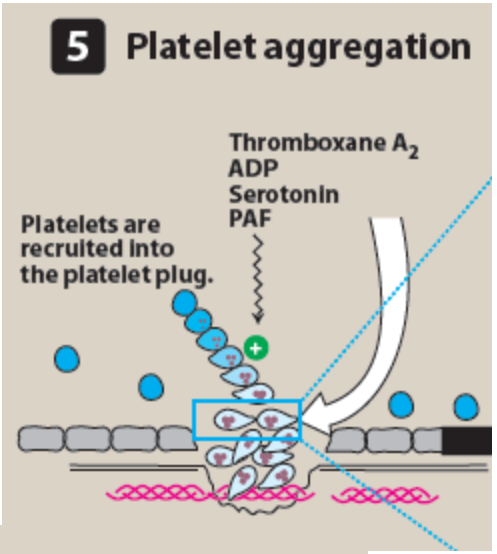
1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets
2) activation of thromboxane A_2 synthesis
3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen

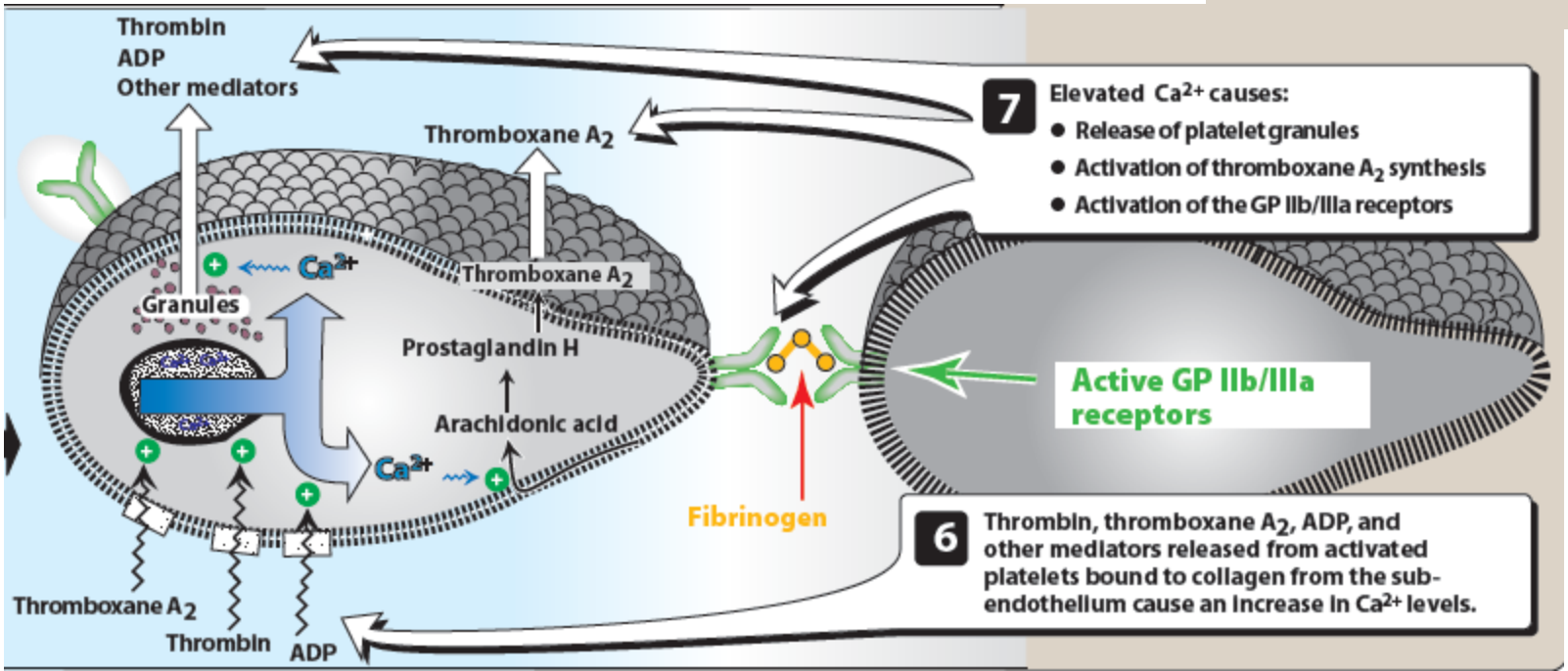
and, ultimately, regulate platelet-platelet interaction and thrombus formation.

- Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation.
- This leads to a large amount of platelet aggregation, because each activated platelet can recruit other platelets

Mechanisms of blood coagulation

D. Platelet aggregation

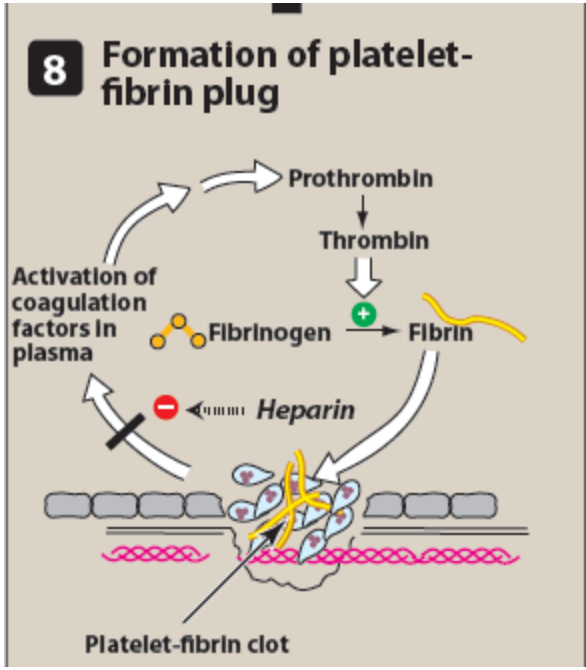




Mechanisms of blood coagulation

E. Formation of a clot

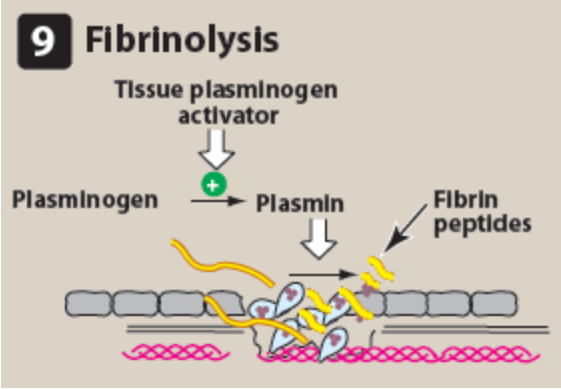
- Local stimulation of the coagulation cascade by tissue factors (TF) released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (Factor IIa).
- In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the plug.
- Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet-fibrin plug.



Mechanisms of blood coagulation

F. Fibrinolysis

- Fibrinolysis refers to the process of fibrin digestion by the fibrin specific protease, plasmin.
- During plug formation, the fibrinolytic pathway is locally activated.
- In response to injury, endothelial cells synthesize and release tissue plasminogen activator (t-PA), which converts plasminogen (an inactive serine protease) to plasmin (active enzyme).
- Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.
- At present, a number of fibrinolytic enzymes are available for treatment of myocardial infarctions, pulmonary emboli, and ischemic stroke.



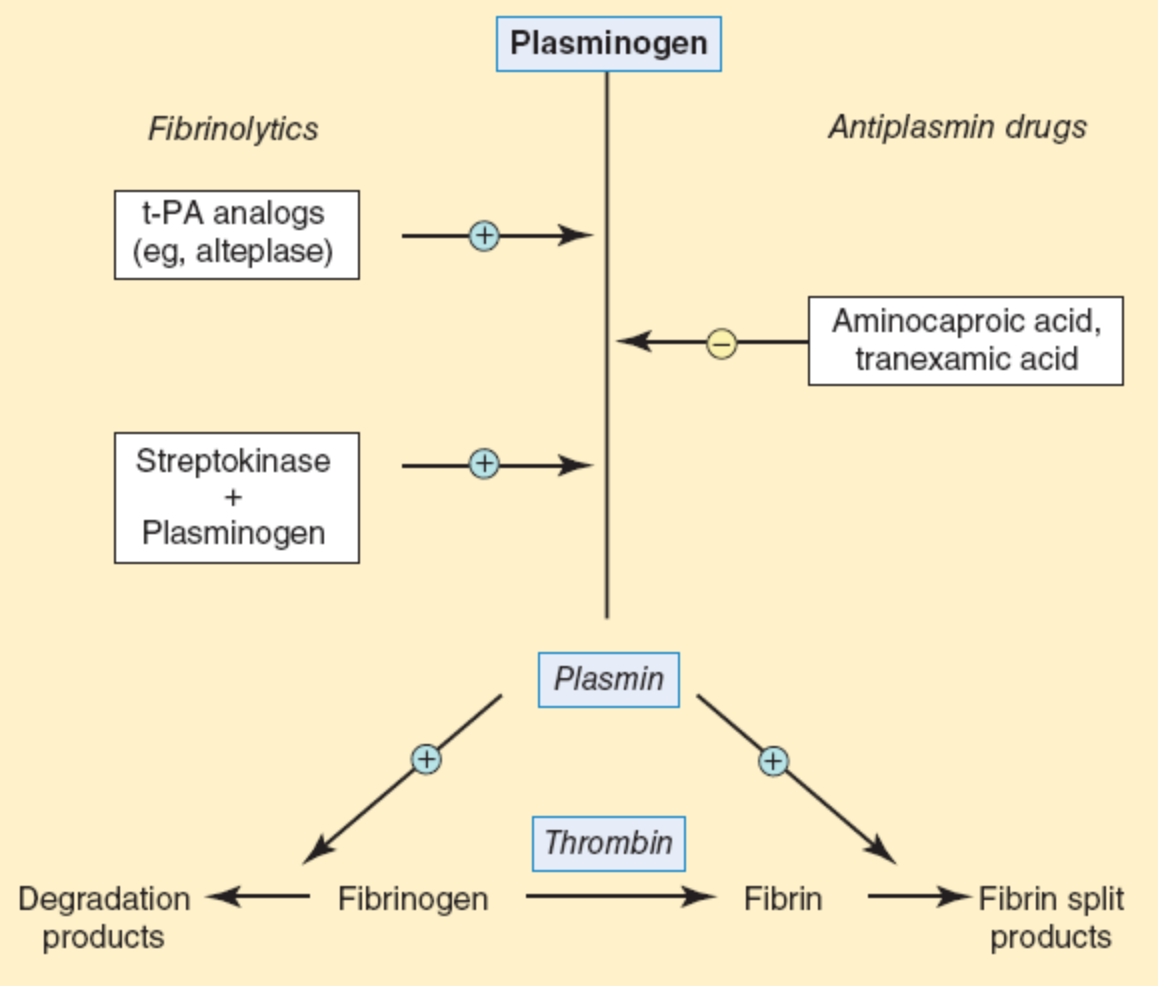
Thrombolytic Drugs

- Thrombolytic (fibrinolytic) drugs rapidly lyse thrombi by catalyzing the formation of the serine protease **plasmin** from its precursor, **plasminogen.**
- The thrombolytic drugs used most commonly are either forms of the endogenous **tissue plasminogen activator (t-PA; eg, alteplase, tenecteplase, and reteplase)** or a protein synthesized by streptococci **(streptokinase).**
- All are given intravenously.

Mechanism of Action

- Plasmin is an endogenous fibrinolytic enzyme that degrades clots by splitting fibrin into fragments. The thrombolytic drugs catalyze the conversion of the inactive precursor, **plasminogen,** to **plasmin.**

Thrombolytic Drugs



Thrombolytic Drugs

Clinical Uses

- The major application of the thrombolytic agents is as an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis. Under ideal conditions (ie, treatment within 6 h), these agents can promptly recanalize the occluded coronary vessel.
- Administration of fibrinolytic drugs by the intravenous route is also indicated in cases of severe pulmonary embolism and severe deep venous thrombosis.

Thrombolytic Drugs

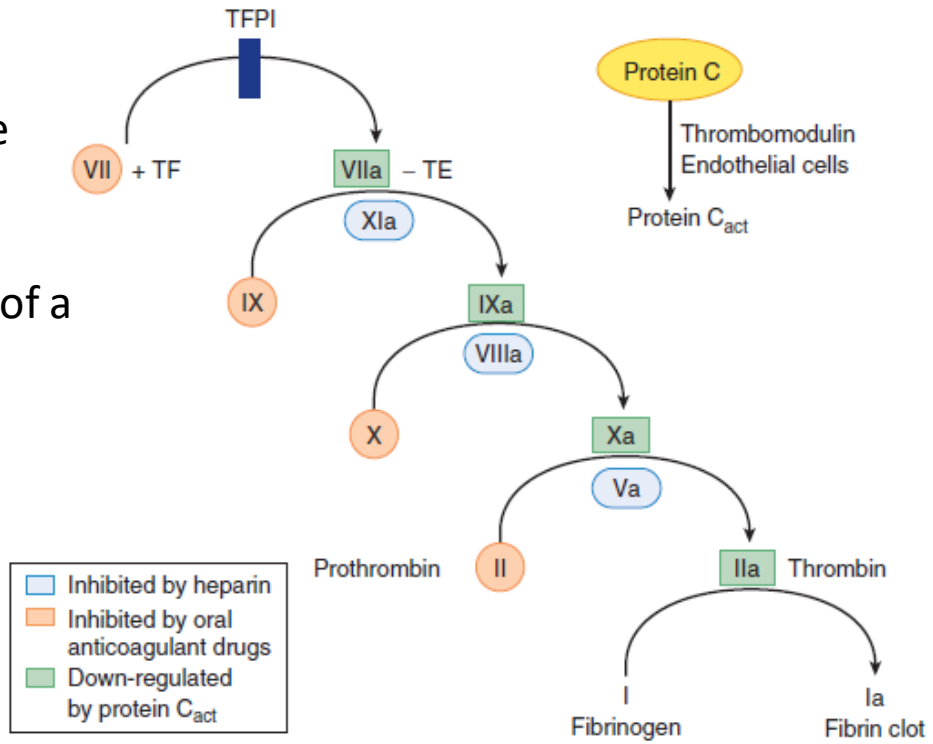
Toxicity

- Bleeding is the most important hazard and has about the same frequency with all the thrombolytic drugs.
- Cerebral hemorrhage is the most serious manifestation.
- Streptokinase, a bacterial protein, an evoke the production of antibodies that cause it to lose its effectiveness or induce severe allergic reactions on subsequent therapy. Patients who have had streptococcal infections may have preformed antibodies to the drug.
- Because they are human proteins, the recombinant forms of t-PA are not subject to this problem. However, they are much more expensive than streptokinase and not much more effective.

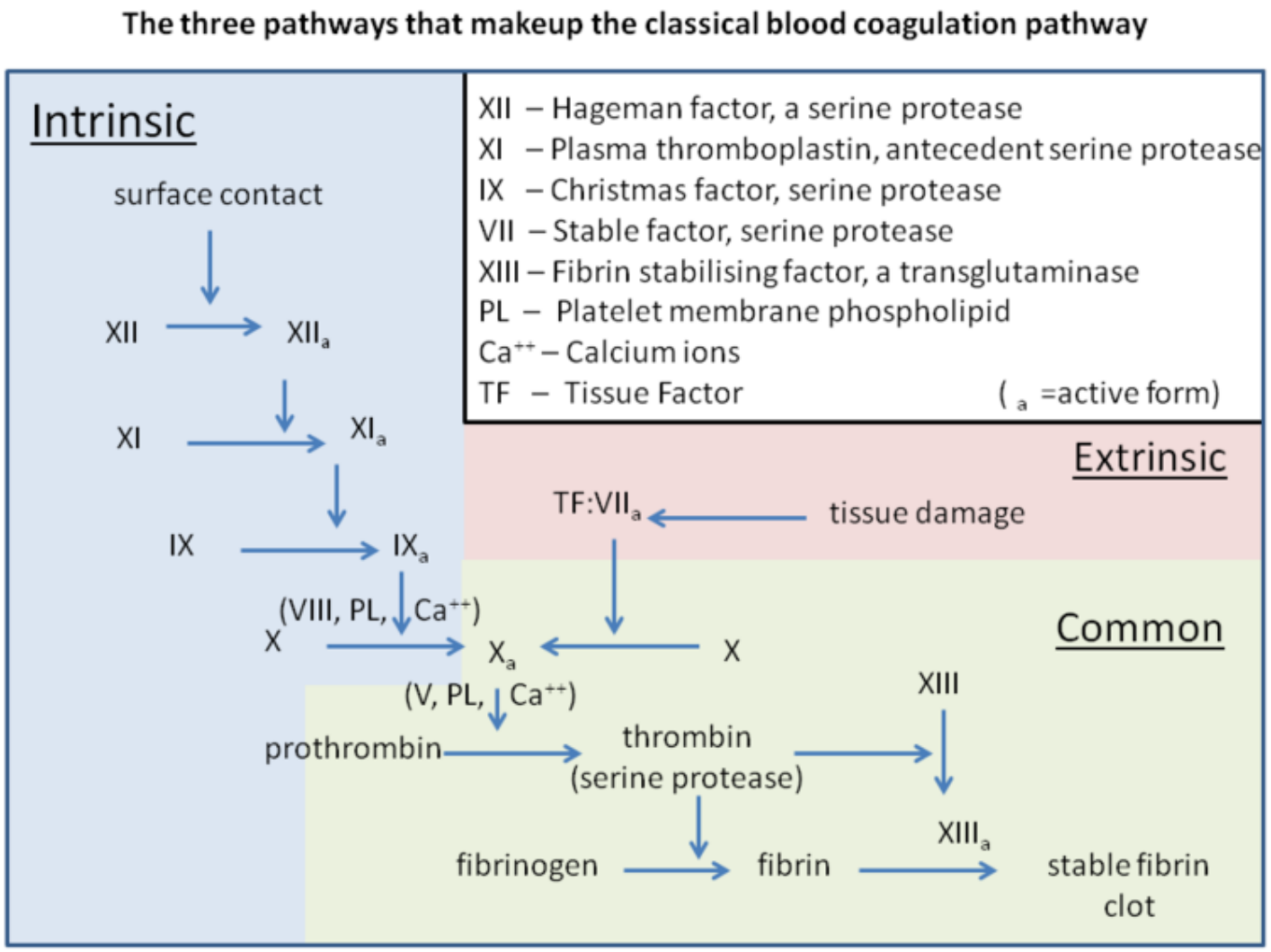
Blood Coagulation Cascade

Number	Roman Numeral
1	I
2	II
3	III
4	IV
5	V
6	VI
7	VII
8	VIII
9	IX
10	X

- The main initiator of blood coagulation in vivo is the tissue factor (TF)-factor VIIa pathway.
- **Tissue factor** is a transmembrane protein ubiquitously expressed outside the vasculature, but not normally expressed in an active form within vessels.
- Several circulating proteins (clotting factors) interact in a cascading series. Each protease factor activates the next clotting factor in the sequence, culminating in the formation of **thrombin (factor IIa),** which in turn convert fibrinogen to fibrin, an essential component of a functional clot.
- Several of these factors are targets for drug therapy.



Intrinsic and extrinsic pathways



Thrombin

- Thrombin has a central role in blood hemostasis and has many functions.
- In clotting, thrombin:

1. proteolytically cleaves small peptides from fibrinogen, allowing fibrinogen to polymerize and form a fibrin clot.
2. Thrombin also activates many upstream clotting factors, leading to more thrombin generation.
3. It activates factor XIII, a transaminase that cross-links the fibrin polymer and stabilizes the clot.
4. Thrombin also exerts anti coagulant effects by activating the protein C pathway, which attenuates the clotting response.

- It should therefore be apparent that the response to vascular injury is a complex and precisely modulated process that ensures that under normal circumstances, repair of vascular injury occurs without thrombosis and downstream ischemia; that is, the response is proportionate and reversible.

Endogenous Anticoagulants

- **Antithrombin** is an endogenous anticoagulant and a member of the serine protease inhibitor family; it inactivates the serine proteases IIa, IXa, Xa, XIa, and XIIa.
- The endogenous anticoagulants **protein C** and **protein S** attenuate the blood clotting cascade by proteolysis of the two cofactors Va and VIIIa.

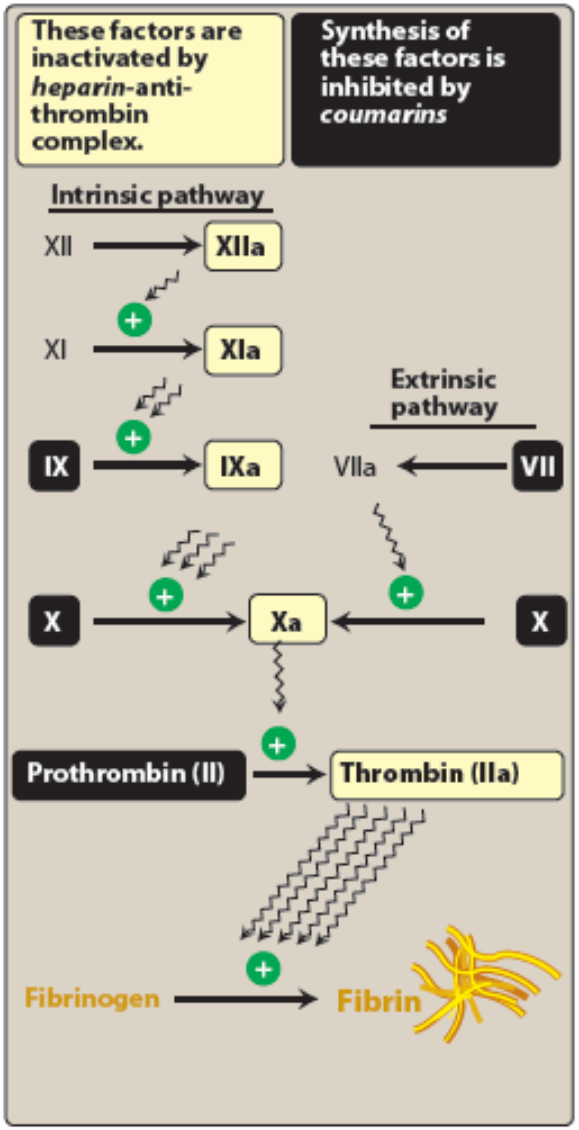
Anticoagulants

- Anticoagulants inhibit the formation of fibrin clots.
- The anticoagulant drugs inhibit either the action of the coagulation factors (such as heparin and heparin-related agents) or interfere with the synthesis of the coagulation factors (such as warfarin).
- Three major types of anticoagulants are available:

1. Heparin and related products, which must be used parenterally.
2. Direct thrombin and factor X inhibitors, which are used parenterally or orally.
3. The orally active coumarin derivatives (eg, warfarin).

TABLE 34–1 Blood clotting factors and drugs that affect them.[1]

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, amino-caproic acid

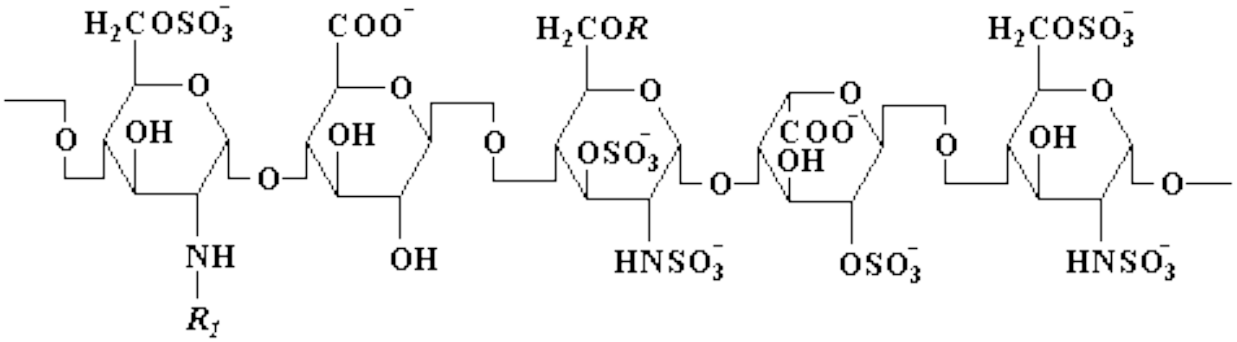


Heparin and related products

Chemistry

- Heparin is a large sulfated polysaccharide polymer obtained from animal sources. Each batch contains molecules of varying size, with an average molecular weight of 15,000–20,000.
- Heparin is given intravenously or subcutaneously to avoid the risk of hematoma associated with intramuscular injection.
  - A **hematoma** is a localized collection of blood outside the blood vessels,usually in liquid form within the tissue.

Heparin

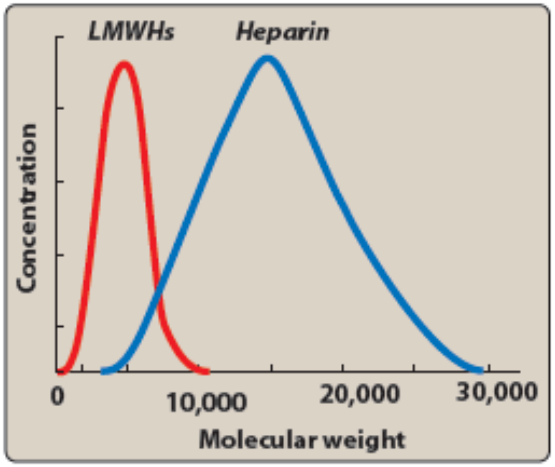


$R_1 = SO_3^-$ or $COCH_3$ $R = H$ or SO_3^-

Heparin and related products

Chemistry

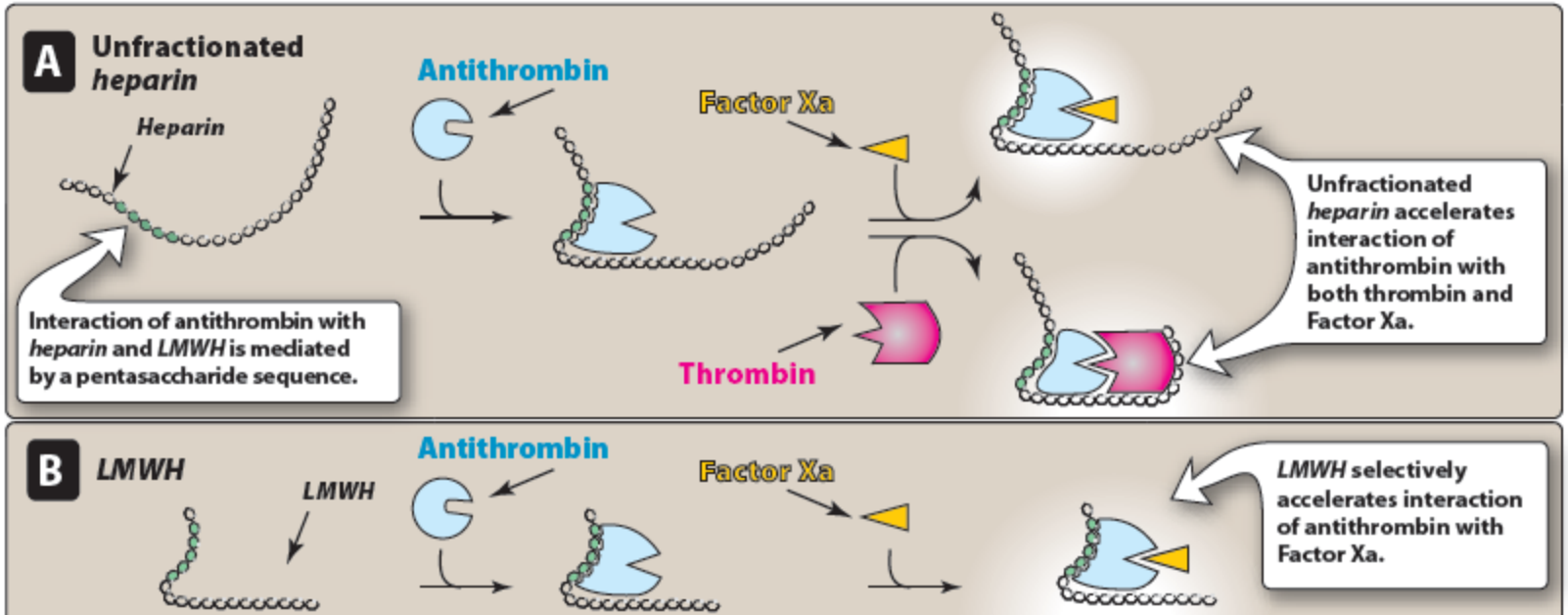
- Low-molecular-weight fractions of heparin (**LMWH**; eg, **enoxaparin)** have molecular weights of 2000–6000. LMW heparins have greater bioavailability and longer durations of action than unfractionated heparin; thus, doses can be given less frequently (eg, once or twice a day). They are given subcutaneously.
- **Fondaparinux** is a small synthetic drug that contains the biologically active pentasaccharide present in unfractionated and LMW heparins. It is administered subcutaneously once daily.



Heparin and related products

Mechanism of action:

- Unfractionated heparin binds to endogenous **antithrombin III (ATIII)** via a key pentasaccharide sequence. The heparin–ATIII complex combines with and irreversibly inactivates thrombin and several other factors, particularly factor Xa. In the presence of heparin, ATIII proteolyzes thrombin and factor Xa approximately 1000-fold faster than in its absence.
- LMW heparins and fondaparinux, like unfractionated heparin, bind ATIII. These complexes have the same inhibitory effect on factor Xa as the unfractionated heparin–ATIII complex. However, they fail to affect thrombin.



Heparin and related products

Clinical Uses:

- Because heparin acts on preformed blood components, it provides anticoagulation immediately after administration.
- Because of its rapid effect, heparin is used when anticoagulation is needed immediately (eg, when starting). Common uses include treatment of DVT, pulmonary embolism, and acute myocardial infarction.
- Because it does not cross the placental barrier, heparin is the drug of choice when an anticoagulant must be used in pregnancy.
- LMW heparins and fondaparinux have similar clinical applications.

Heparin and related products

Toxicity:

- **Increased bleeding** is the most common adverse effect of heparin and related molecules; the bleeding may result in hemorrhagic stroke.
- If bleeding occurs, administration of a specific antagonist such as **protamine sulfate** is indicated.
- Protamine only partially reverses the effects of LMW heparins and does not affect the action of fondaparinux.
- Unfractionated heparin causes moderate transient **thrombocytopenia** in many patients and severe thrombocytopenia (heparin-induced thrombocytopenia or HIT) in a small percentage of patients who produce an antibody that binds to a complex of heparin and platelet factor 4.
- LMW heparins and fondaparinux are less likely to cause this immune-mediated thrombocytopenia.
- Prolonged use of unfractionated heparin is associated with **osteoporosis**.

Heparin and related products

- Close monitoring of the **activated partial thromboplastin time (aPTT or PTT)** is necessary in patients receiving unfractionated heparin.
- Weight-based dosing of the LMW heparins results in predictable pharmacokinetics and plasma levels in patients with normal renal function. Therefore, LMW heparin levels are not generally measured except in the setting of renal insufficiency, obesity, and pregnancy.
- The aPTT test does not reliably measure the anticoagulant effect of the LMW heparins and fondaparinux.

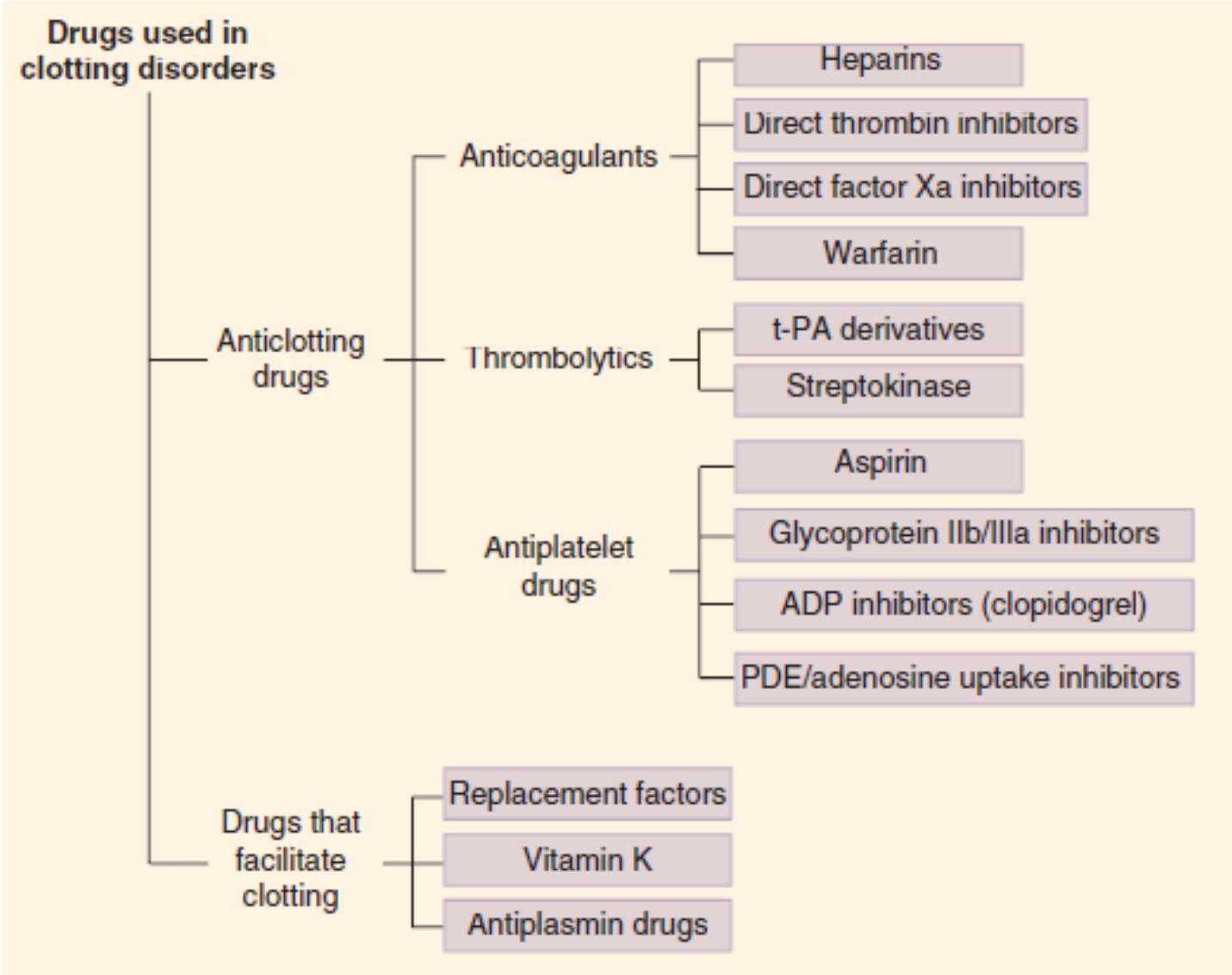
Direct Thrombin and Factor Xa Inhibitors

Direct thrombin inhibitors

- **Lepirudin** (administered parentrally (I.V)) and **dabigatran** is an orally active direct thrombin inhibitor.
- Direct thrombin inhibitors are used as alternatives to heparin primarily in patients with heparin-induced thrombocytopenia.
- The action of these drugs is monitored with the aPTT laboratory test.
- Like other anticoagulants, the direct thrombin inhibitors can cause bleeding. No reversal agents exist.

Direct oral Factor Xa inhibitors

- Oral Xa inhibitors, including the small molecules **rivaroxaban** and **apixaban**, have a rapid onset of action and shorter half-lives than warfarin.
- Rivaroxaban is approved for prevention of venous thromboembolism following hip or knee surgery and for prevention of thromboembolic complications in patients with atrial fibrillation.
- Like other anticoagulants, the factor Xa inhibitors can cause bleeding. No reversal agents exist.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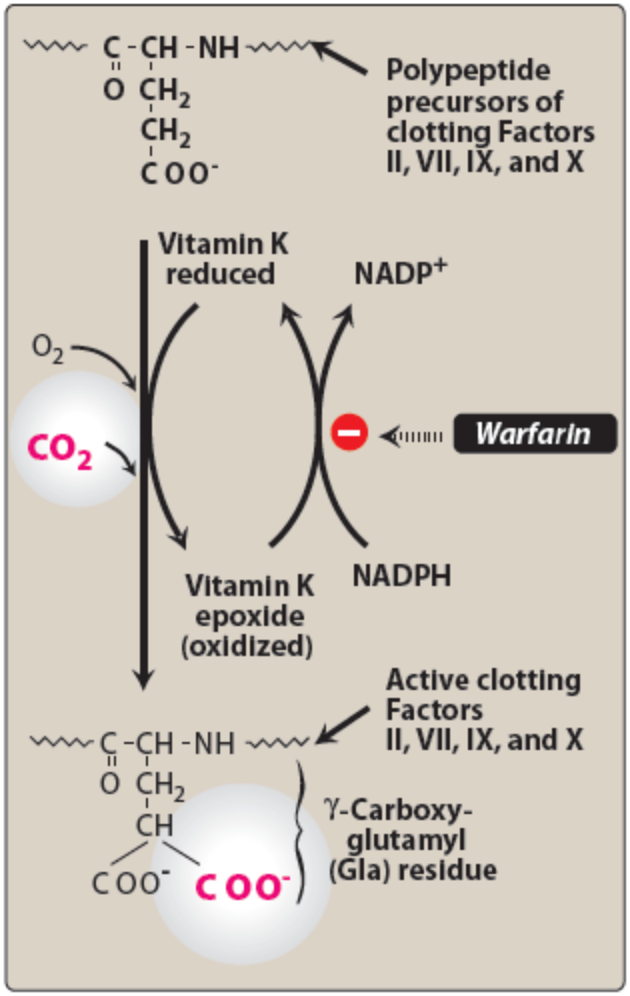
Glycoprotein IIb/IIIa inhibitors
ADP inhibitors (clopidogrel)
PDE/adenosine uptake inhibitors
Drugs that facilitate clotting
Replacement factors
Vitamin K
Antiplasmin drugs

Warfarin

The clinical use of the coumarin anticoagulants began with the discovery of an anticoagulant substance formed in spoiled sweet clover silage which caused hemorrhagic disease in cattle. At the behest of local farmers, a chemist at the University of Wisconsin identified the toxic agent as bishydroxycoumarin. A synthesized derivative, dicumarol and its congeners, most notably warfarin (**W**isconsin **A**lumni **R**esearch **F**oundation, with "arin" from coumarin added; Figure 34–5), were initially used as rodenticides. In the 1950s warfarin (under the brand name Coumadin) was introduced as an antithrombotic agent in humans. Warfarin is one of the most commonly prescribed drugs, used by approximately 1.5 million individuals, and several studies have indicated that the drug is significantly underused in clinical situations where it has proven benefit.

Warfarin

- **Chemistry and pharmacokinetics:**
- **Warfarin** and other coumarin anticoagulants are small, lipid-soluble molecules that are readily absorbed after oral administration.
- Warfarin is highly bound to plasma proteins (>99%), and its elimination depends on metabolism by cytochrome P450 enzymes.
- **Mechanism and effects:**
- Warfarin and other coumarins interfere with the normal post-translational modification of clotting factors in the liver, a process that depends on an adequate supply of reduced vitamin K.
- The drugs inhibit vitamin K epoxide reductase, which normally converts vitamin K epoxide to reduced vitamin K. The vitamin K-dependent factors include thrombin and factors VII, IX, and X.



Warfarin

- Because the clotting factors have half-lives of 8–60 h in the plasma, an anticoagulant effect is observed only after sufficient time has passed for elimination of the normal preformed factors.
- The action of warfarin can be reversed with vitamin K, but recovery requires the synthesis of new normal clotting factors and is, therefore, slow (6–24 h). More rapid reversal can be achieved by transfusion with fresh or frozen plasma that contains normal clotting factors.
- The effect of warfarin is monitored by the **prothrombin time (PT) test.**

Clinical use:

- Warfarin is used for chronic anticoagulation in all of the clinical situations described previously for heparin after initial heparin treatment, <u>except in pregnant women.</u>
- Treatment with warfarin should be initiated with standard doses of 5–10 mg.
- The initial adjustment of the prothrombin time takes about 1 week, which usually results in a maintenance dose of 5–7 mg/d.

H.W: PT method and interpretation?

Warfarin

Toxicity:

- **Bleeding** is the most important adverse effect of warfarin.
- Warfarin can cause bone defects and hemorrhage in the developing fetus and, therefore, is **contraindicated in pregnancy**.
- Because warfarin has a narrow therapeutic window, its involvement in drug interactions is of major concern.
  - Cytochrome P450-inducing drugs (eg, carbamazepine, phenytoin, barbiturates) increase warfarin's clearance and reduce the anticoagulant effect of a given dose.
  - Cytochrome P450 inhibitors (eg, amiodarone, selective serotonin reuptake inhibitors, cimetidine) reduce warfarin's clearance and increase the anticoagulant effect of a given dose.
- Excessive anticoagulant effect and bleeding from warfarin can be reversed by stopping the drug and administering oral or parenteral **vitamin K 1 (phytonadione),** fresh-frozen plasma, prothrombin complex concentrates such as Bebulin and Proplex T, and recombinant factor VIIa (rFVIIa).

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	***Pharmacodynamic***	***Pharmacokinetic***	***Pharmacodynamic***
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

TABLE 34–1 Properties of heparins and warfarin.

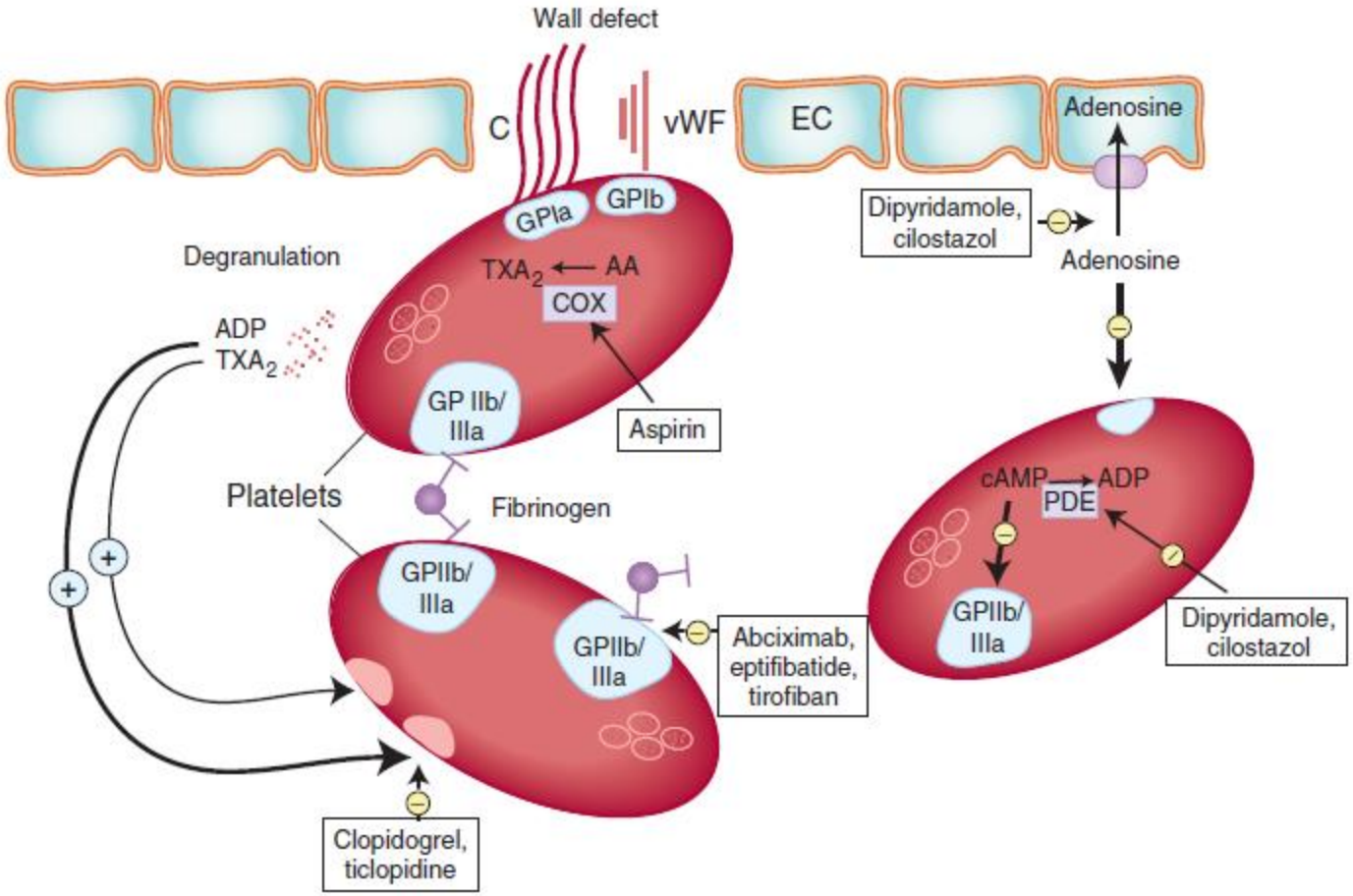
Property	Heparins	Warfarin
Structure	Large acidic polysaccharide polymers	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (minutes)	Slow (days); limited by half-lives of preexisting normal factors
Mechanism of action	Activates antithrombin III, which proteolyzes coagulation factors including thrombin and factor Xa	Impairs post-translational modification of factors II, VII, IX and X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	Prothrombin time
Antidote	Protamine for unfractionated heparin; protamine reversal of LMW heparins is incomplete	Vitamin K_1, plasma, prothrombin complex concentrates
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No

aPTT, activated partial thromboplastin time; LMW, low molecular weight.

Antiplatelet Drugs

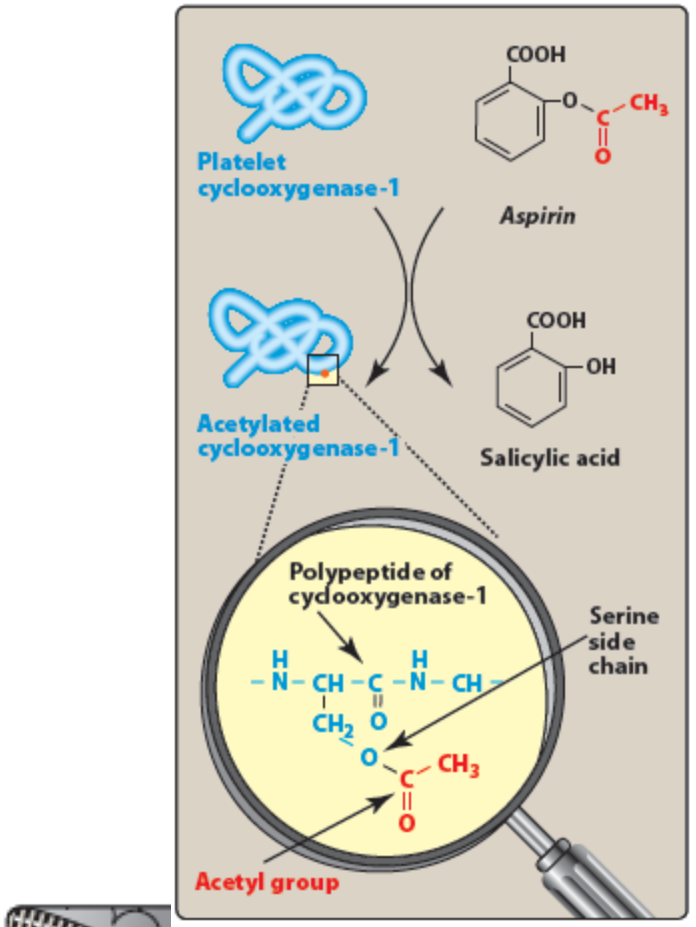
- Antiplatelet drugs include:
  1. **Aspirin** (also known as acetylsalicylic acid; ASA)
  2. Glycoprotein IIb/IIIa receptor inhibitors (**abciximab, tirofiban,** and **eptifibatide),**
  3. Antagonists of ADP receptors (**clopidogrel and ticlopidine)**
  4. **Dipyridamole** and **cilostazol.**

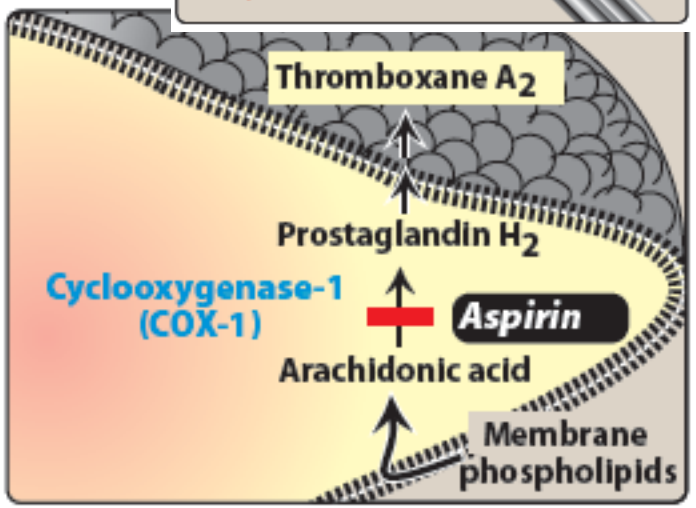
Antiplatelet Drugs



Aspirin

- Aspirin is part of a group of medications called nonsteroidal anti-inflammatory drugs (NSAIDs), but differs from other NSAIDs in the mechanism of action. Aspirin (but not the other NSAIDs) inhibits COX-1 in an irreversible manner.
- The **thromboxane A_2** is an arachidonate product that causes platelets to change shape, release their granules, and aggregate.
- Aspirin inhibits thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation of a serine in COX-1, preventing arachidonate from binding to the active site, thus, inhibition of COX-1.



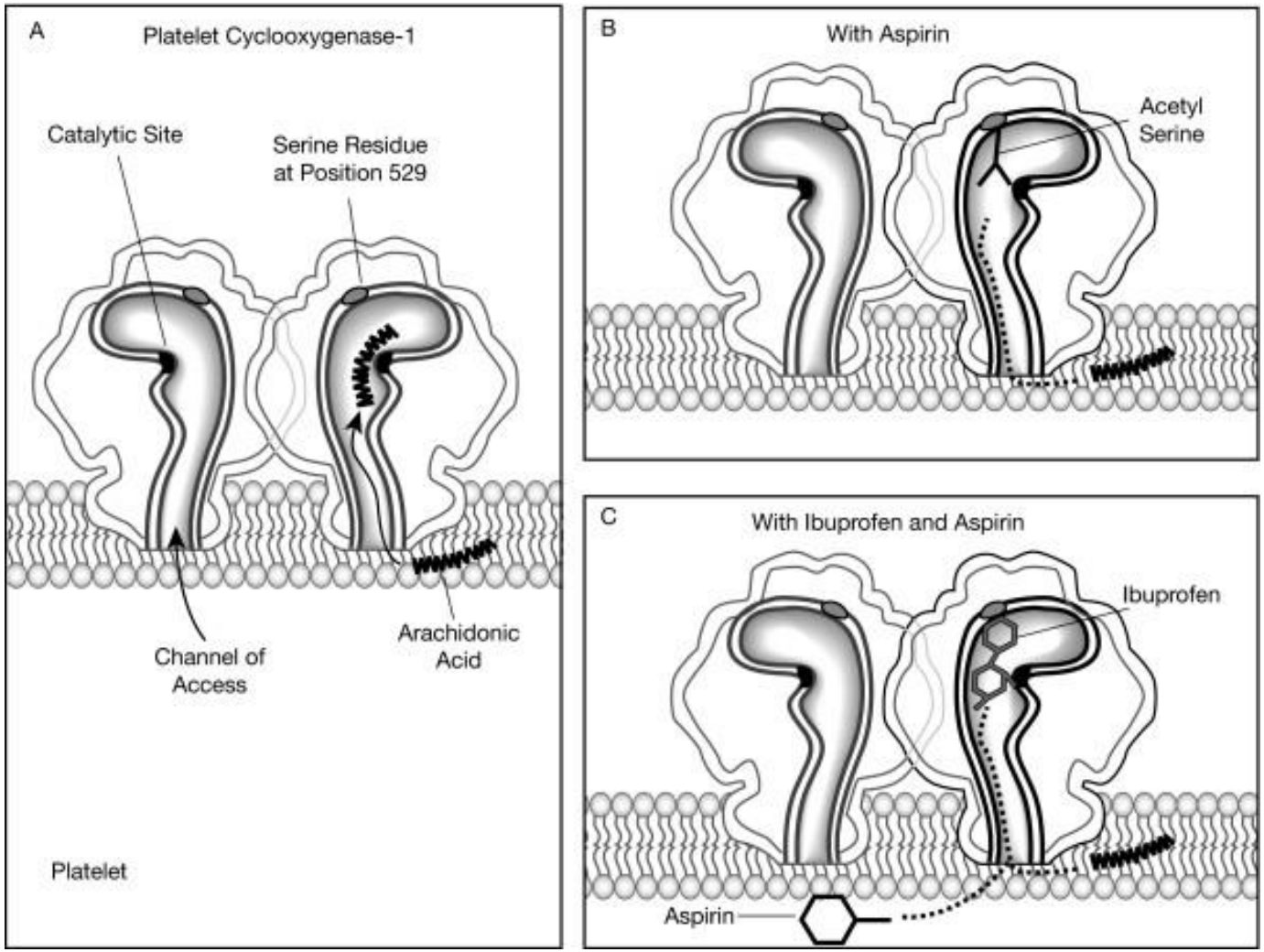


Aspirin

- Aspirin is currently used in the prophylactic treatment to prevent heart attacks, strokes (brain attack), and blood clot formation in people at high risk of developing blood clots.
- Complete inactivation of platelets occurs with 160 mg of aspirin given daily. The recommended dose of aspirin ranges from 50 to 325 mg, with side effects determining the dose chosen.
- Formerly known as “baby aspirin,” 81-mg aspirin is most commonly used.
- Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke as well as GI bleeding, especially at higher doses of the drug.
- Aspirin is frequently used in combination with other drugs having anticlotting properties, such as heparin or clopidogrel.

Aspirin

- NSAIDs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken concomitantly with, or 2 hours prior to aspirin can obstruct the access of aspirin to the serine residue and, thereby, antagonize the platelet inhibition by aspirin.
- Therefore, aspirin should be taken at least 30 minutes before ibuprofen or at least 8 hours after ibuprofen.
- Aspirin as other NSAIDs has antipyretic, anti-inflammatory and analgesic action, but it is the only NSAID that irreversibly exhibits antithrombotic action.

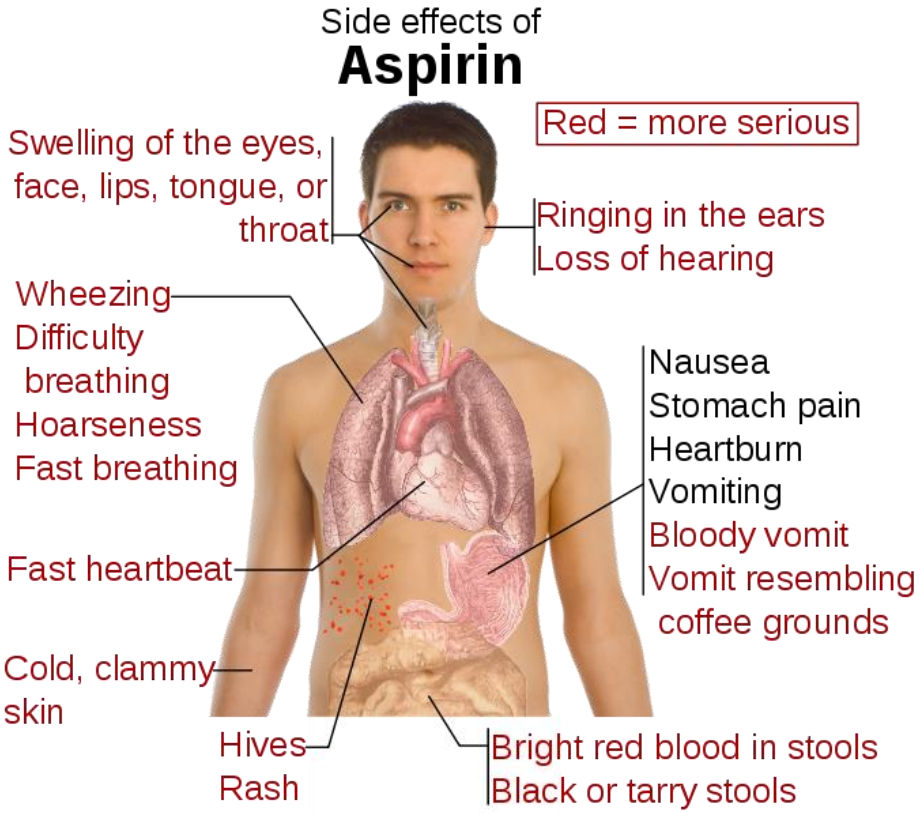

A
Platelet Cyclooxygenase-1
Catalytic Site
Serine Residue
at Position 529
Channel of
Access
Arachidonic
Acid
Platelet
B
With Aspirin
Acetyl
Serine
C
With Ibuprofen and Aspirin
Ibuprofen
Aspirin

Aspirin

Adverse effects:

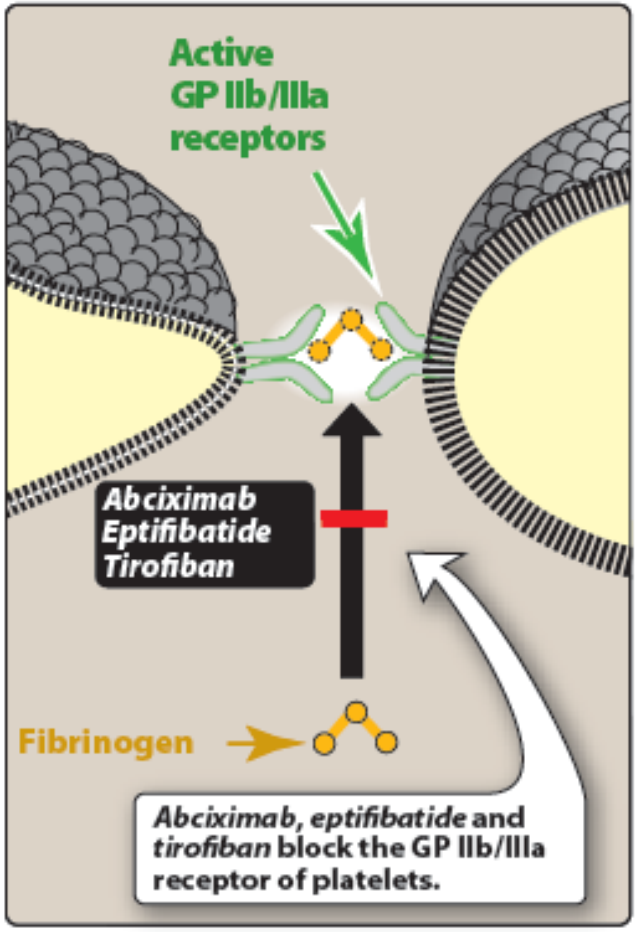
- Gastrointestinal ulcers, stomach bleeding, and tinnitus, especially in higher doses.
- In children and adolescents,

aspirin is no longer indicated to control flu-like symptoms or the symptoms of chickenpox or other viral illnesses, because of the risk of Reye's syndrome.



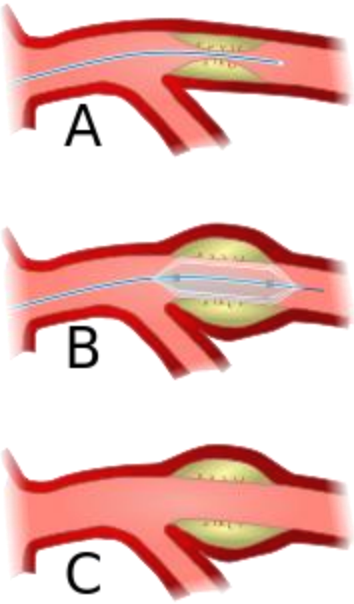
Glycoprotein IIb/IIIa Receptor Inhibitors

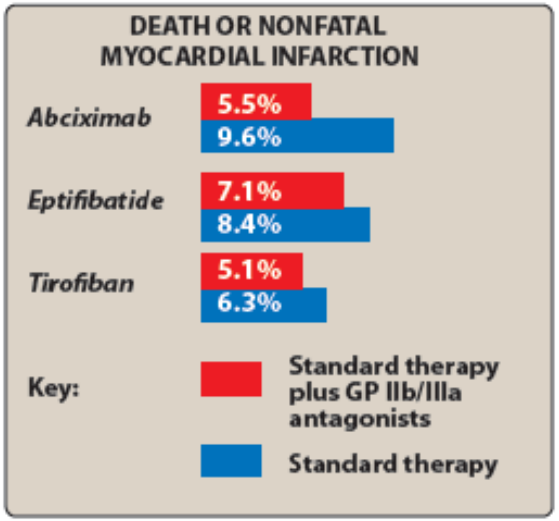
- **Abciximab** is a monoclonal antibody that reversibly inhibits the binding of fibrin and other ligands to the platelet glycoprotein IIb/IIIa receptor, a cell surface protein involved in platelet cross-linking.
- **Eptifibatide** and **tirofiban** also reversibly block the glycoprotein IIb/IIIa receptor.



Glycoprotein IIb/IIIa Receptor Inhibitors

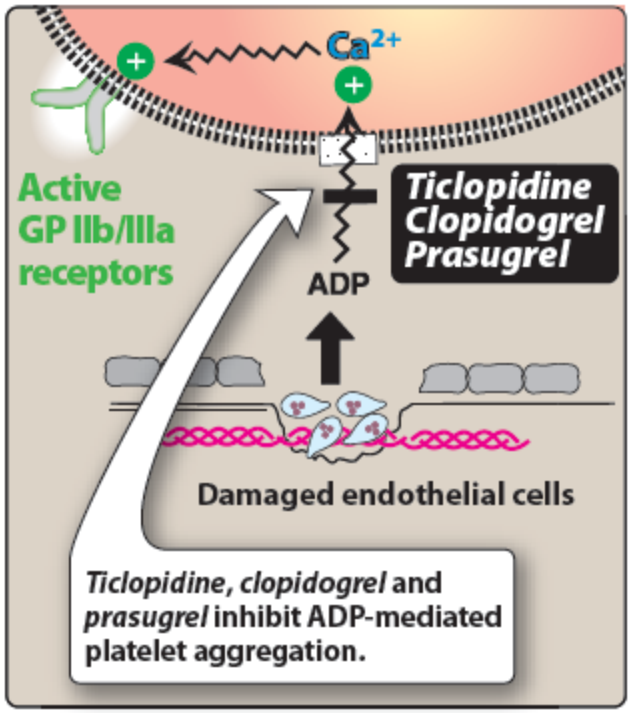
- Abciximab is given intravenously along with either heparin or aspirin as an adjunct to percutaneous coronary intervention (angioplasty) for the prevention of cardiac ischemic complications. It is also approved for unresponsive unstable angina and for prophylactic use in myocardial infarction.
- Eptifibatide and tirofiban, like abciximab, can decrease the incidence of thrombotic complications associated with acute coronary syndromes.





ADP Receptor Antagonists

- **Clopidogrel**, **prasugrel**, and the older drug **ticlopidine** are converted in the liver to active metabolites that irreversibly inhibit the platelet ADP receptor and thereby prevent ADP-mediated platelet aggregation.
- Use of ticlopidine, clopidogrel, or prasugrel to prevent thrombosis is now considered standard practice in patients undergoing placement of a coronary stent.



ADP Receptor Antagonists

- Due to **ticlopidine'**s life-threatening hematologic adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia, ticlopidine is generally reserved for patients who are intolerant to other therapies.
- Therapy with ticlopidine require frequent blood monitoring, especially during the first 3 months of treatment.
- Compared to ticlopidine, **clopidogrel** is the preferred agent in ischemic heart disease events, because there is more data to support use of clopidogrel in these cardiac patients. Furthermore, clopidogrel has a better overall side-effect profile, although TTP may also occur with this agent.
- **Prasugrel** is the newest ADP receptor antagonist. In clinical trials, prasugrel was more effective than clopidogrel in reducing cardiovascular death, nonfatal heart attack, and nonfatal stroke.

ADP Receptor Antagonists

Pharmacokinetics:

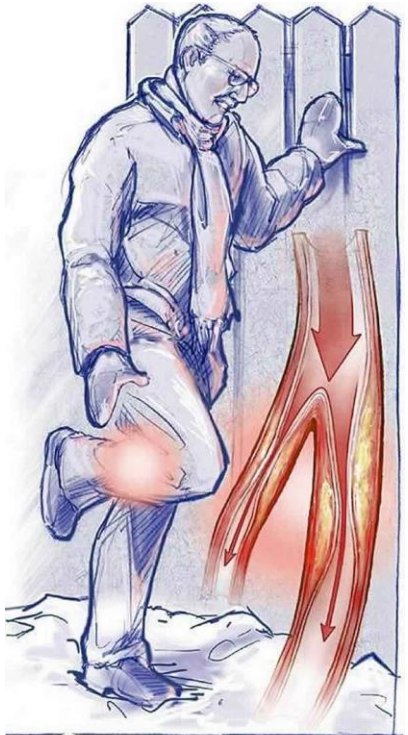
- Food interferes with the absorption of ticlopidine, but not with clopidogrel or prasugrel.
- After oral ingestion, all three of these drugs are extensively bound to plasma proteins.
- They undergo hepatic metabolism by the cytochrome P450 (CYP450) system to active metabolites.
- “Poor metabolizers” and clopidogrel:
- Genetic polymorphism of CYP450 2C19, that primarily biotransforms clopidogrel, leads to less active metabolite, variable pharmacokinetic properties and reduced clinical response in patients who are poor metabolizers.
- Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelets or different strategies be used.

Dipyrimadol and Cilostazol

- Dipyridamole and the newer cilostazol appear to have a dual mechanism of action:
  - They prolong the platelet-inhibiting action of intracellular cAMP by inhibiting phosphodiesterase enzymes that degrade cyclic nucleotides, including cAMP, an inhibitor of platelet aggregation, and cyclic guanosine monophosphate (cGMP), a vasodilator.
  - They also inhibit the uptake of adenosine by endothelial cells and erythrocytes and thereby increase the plasma concentration of adenosine. Adenosine acts through platelet adenosine A2 receptors to increase platelet cAMP and inhibit aggregation.

Dipyrimadol and Cilostazol

- Dipyridamole is approved as an adjunct to warfarin in the prevention of thrombosis in those with cardiac valve replacement and has been used in combination with aspirin for secondary prevention of ischemic stroke.
- Cilostazol is used to treat intermittent claudication, a manifestation of peripheral arterial disease.
- The most common adverse effects of dipyridamole and cilostazol are headaches and GI problems.



Drugs Used in Bleeding Disorders

- Inadequate blood clotting can result from:
  - vitamin K deficiency
  - genetically determined errors of clotting factor synthesis (eg, hemophilia)
  - a variety of drug-induced conditions
  - thrombocytopenia
- Treatment involves administration of:
  1. vitamin K
  2. preformed clotting factors
  3. Fibrinolytic inhibitors
- Thrombocytopenia can be treated by administration of platelets or oprelvekin, the recombinant form of the megakaryocyte growth factor interleukin-11

Vitamin K

- Deficiency of vitamin K, a fat-soluble vitamin, is most common in older persons with abnormalities of fat absorption and in newborns, who are at risk of vitamin K deficiency bleeding.
- The deficiency is readily treated with oral or parenteral **phytonadione (vitamin K1).**
- Large doses of vitamin K1 are used to reverse the anticoagulant effect of excess warfarin.
- The response to vitamin K is slow, requiring about 24 hours (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh-frozen plasma should be infused.

Clotting Factors

- The most important agents used to treat hemophilia are fresh plasma and purified human blood clotting factors, especially **factor VIII (for hemophilia A)** and **factor IX (for hemophilia B)**, which are either purified from blood products or produced by recombinant DNA technology.
- These products are expensive and carry a risk of immunologic reactions.

- Hemophilia is a group of hereditary genetic disorders that impair the body's ability to control coagulation. Haemophilia A (clotting factor VIII deficiency) is the most common form of the disorder. Haemophilia B (factor IX deficiency).

Fibrinolytic Inhibitors

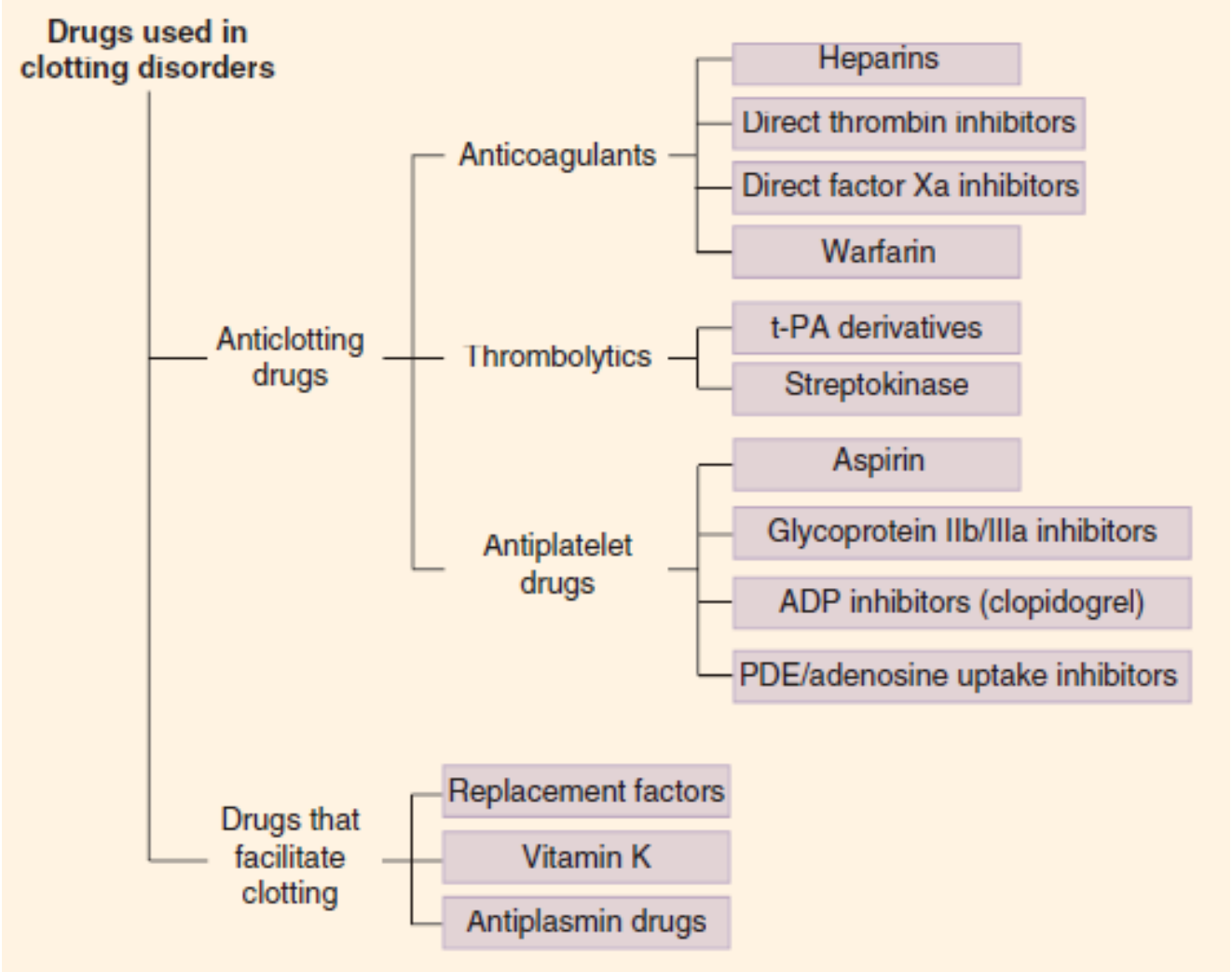
- Antiplasmin agents are valuable for the prevention or management of acute bleeding episodes in patients with hemophilia and others with a high risk of bleeding disorders.
- **Aminocaproic acid** and **tranexamic acid** are orally active agents that inhibit fibrinolysis by inhibiting plasminogen activation.
- Adverse effects include thrombosis, hypotension, myopathy, and diarrhea.

20.3 A 54-year-old male with a prosthetic aortic valve replacement complained to his family physician of black and tarry stools. Physical examination and vital signs were unremarkable except for subconjunctival hemorrhages and bleeding gums. Stools tested positive for heme, and hematuria was observed. The patient has been receiving oral warfarin since his valve replacement 1 year earlier. Prothrombin time was found to be significantly elevated. Which one of the following therapies would provide the most rapid recovery from the observed bleeding secondary to warfarin treatment?

A. Intravenous vitamin K.
B. Transfusion of fresh-frozen plasma.
C. Intravenous protamine sulfate.
D. Immediate withdrawal of warfarin treatment.
E. Intravenous administration of anti-warfarin antibodies.

Correct answer = B. Whole blood, frozen plasma, or plasma concentrates of the blood factors may be employed to rapidly arrest hemorrhaging. Minor bleeding may be treated by withdrawal of the drug and administration of oral vitamin K_1, but severe bleeding requires greater doses of the vitamin given intravenously. However, reversal following administration of vitamin K takes approximately 24 hours. Protamine sulfate is used to neutralize an overdose of heparin, not an overdose of warfarin. Immediate withdrawal of warfarin treatment will not have an immediate effect, because the anticoagulant effects of warfarin last between 5 and 7 days.

Questions??


Drugs used in clotting disorders
Anticlotting drugs
Anticoagulants
Heparins
Direct thrombin inhibitors
Direct factor Xa inhibitors
Warfarin
Thrombolytics
t-PA derivatives
Streptokinase
Antiplatelet drugs
Aspirin
Glycoprotein IIb/IIIa inhibitors
ADP inhibitors (clopidogrel)
PDE/adenosine uptake inhibitors
Drugs that facilitate clotting
Replacement factors
Vitamin K
Antiplasmin drugs