severe effects, including fever, arthralgias, and capillary damage with edema. Allergic reactions are rare. **Pegfilgrastim,** a covalent conjugation product of filgrastim and a form of polyethylene glycol, has a much longer serum half-life than recombinant G-CSF. Lenograstim, used widely in Europe, is a glycosylated form of recombinant G-CSF.

C. Megakaryocyte Growth Factors

Oprelvekin (interleukin-11 [**IL-11**]) stimulates the growth of primitive megakaryocytic progenitors and increases the number of peripheral platelets. IL-11 is used for the treatment of patients who have had a prior episode of thrombocytopenia after a cycle of cancer chemotherapy. In such patients, it reduces the need for platelet transfusions. The most common adverse effects of IL-11 are fatigue, headache, dizziness, and fluid retention.

Romiplostim, a thrombopoietin receptor agonist with a novel peptide structure, is used subcutaneously in patients with chronic idiopathic thrombocytopenia who have failed to respond to conventional treatment. **Eltrombopag** is an oral agonist of the thrombopoietin receptor that is also used for patients with chronic idiopathic thrombocytopenia that is refractory to other agents. The risk of hepatotoxicity and hemorrhage has restricted eltrombopag use to registered physicians and patients.

QUESTIONS

Questions 1–4. A 23-year-old pregnant woman is referred by her obstetrician for evaluation of anemia. She is in her fourth month of pregnancy and has no history of anemia; her grandfather had pernicious anemia. Her hemoglobin is 10 g/dL (normal, 12–16 g/dL).

1. If this woman has macrocytic anemia, an increased serum concentration of transferrin, and a normal serum concentration of vitamin B_{12}, the most likely cause of her anemia is deficiency of which of the following?
(A) Cobalamin
(B) Erythropoietin
(C) Folic acid
(D) Intrinsic factor
(E) Iron

2. The laboratory data for your pregnant patient indicate that she does not have macrocytic anemia but rather microcytic anemia. Optimal treatment of normocytic or mild microcytic anemia associated with pregnancy uses which of the following?
(A) A high-fiber diet
(B) Erythropoietin injections
(C) Ferrous sulfate tablets
(D) Folic acid supplements
(E) Hydroxocobalamin injections

3. If this patient has a young child at home and is taking iron-containing prenatal supplements, she should be warned that they are a common source of accidental poisoning in young children and advised to make a special effort to keep these pills out of her child's reach. Toxicity associated with acute iron poisoning usually includes which of the following?
(A) Dizziness, hypertension, and cerebral hemorrhage
(B) Hyperthermia, delirium, and coma
(C) Hypotension, cardiac arrhythmias, and seizures
(D) Necrotizing gastroenteritis, shock, and metabolic acidosis
(E) Severe hepatic injury, encephalitis, and coma

4. The child in the previous question did ingest the iron-containing supplements. What immediate treatment is necessary? Correction of acid-base and electrolyte abnormalities and
(A) Activated charcoal
(B) Oral deferasirox
(C) Parenteral deferoxamine
(D) Parenteral dantrolene

5. A 45-year-old male stomach cancer patient underwent tumor removal surgery. After surgery, he developed megaloblastic anemia. His anemia is caused by a deficiency of X and can be treated with Y.
(A) X = intrinsic factor; Y = folic acid.
(B) X = intrinsic factor; Y = vitamin B_{12}
(C) X = extrinsic factor; Y = parenteral iron
(D) X = extrinsic factor; Y = sargramostim

6. Which of the following is *most* likely to be required by a 5-year-old boy with chronic renal insufficiency?
(A) Cyanocobalamin
(B) Deferoxamine
(C) Erythropoietin
(D) Filgrastim (G-CSF)
(E) Oprelvekin (IL-11)

7. In a patient who requires filgrastim (G-CSF) after being treated with anticancer drugs, the therapeutic objective is to prevent which of the following?
(A) Allergic reactions
(B) Cancer recurrence
(C) Excessive bleeding
(D) Hypoxia
(E) Systemic infection

8. The megaloblastic anemia that results from vitamin B_{12} deficiency is due to inadequate supplies of which of the following?
(A) Cobalamin
(B) dTMP
(C) Folic acid
(D) Homocysteine
(E) N^5-methyltetrahydrofolate

Questions 9 and 10. After undergoing surgery for breast cancer, a 53-year-old woman is scheduled to receive 4 cycles of cancer chemotherapy. The cycles are to be administered every 3–5 wk. Her first cycle was complicated by severe chemotherapy-induced thrombocytopenia.

9. During the second cycle of chemotherapy, it would be appropriate to consider treating this patient with which of the following?
(A) Darbepoetin alpha
(B) Filgrastim (G-CSF)
(C) Iron dextran
(D) Oprelvekin (IL-11)
(E) Vitamin B_{12}

10. Twenty months after finishing her chemotherapy, the woman had a relapse of breast cancer. The cancer was now unresponsive to standard doses of chemotherapy. The decision was made to treat the patient with high-dose chemotherapy followed by autologous stem cell transplantation. Which of the following drugs is most likely to be used to mobilize the peripheral blood stem cells needed for the patient's autologous stem cell transplantation?
(A) Erythropoietin
(B) Filgrastim (G-CSF)
(C) Folic acid
(D) Intrinsic factor
(E) Oprelvekin (interleukin-11)

ANSWERS

1. Deficiencies of folic acid or vitamin B_{12} are the most common causes of megaloblastic anemia. If a patient with this type of anemia has a normal serum vitamin B_{12} concentration, folate deficiency is the most likely cause of the anemia. The answer is **C.**

2. Iron deficiency microcytic anemia is the anemia that is most commonly associated with pregnancy. In this condition, oral iron supplementation is indicated. The answer is **C.**

3. Acute iron poisoning often causes severe gastrointestinal damage resulting from direct corrosive effects, shock from fluid loss in the gastrointestinal tract, and metabolic acidosis from cellular dysfunction. The answer is **D.**

4. Activated charcoal does ***not*** bind iron and thus is ineffective. Oral deferasirox is effective for chronic iron toxicity. Dantrolene inhibits Ca^{2+} release from the sarcoplasmic reticulum and is an antidote for malignant hyperthermia induced by inhaled anesthetics. The answer is **C.**

5. Resection of the stomach does lead to loss of intrinsic factor and the patient will be deficient in vitamin B_{12}. Prevention or treatment of iron deficiency anemia (microcytic cell size) is the *only* indication for iron administration. Sargramostim is a GM-CSF and is used to stimulate the production of neutrophils and other myeloid and megakaryocyte progenitors. The answer is **B.**

6. The kidney produces erythropoietin; patients with chronic renal insufficiency often require exogenous erythropoietin to avoid chronic anemia. The answer is **C.**

7. Filgrastim (G-CSF) stimulates the production and function of neutrophils, important cellular mediators of the innate immune system that serve as the first line of defense against infection. The answer is **E.**

8. Deficiency of vitamin B_{12} (cobalamin) leads to a deficiency in tetrahydrofolate and subsequently a deficiency of the dTMP required for DNA synthesis. Homocysteine and N^5-methyltetrahydrofolate accumulate. The answer is **B.**

9. Oprelvekin (IL-11) stimulates platelet production and decreases the number of platelet transfusions required by patients undergoing bone marrow suppression therapy for cancer. The answer is **D.**

10. The success of transplantation with peripheral blood stem cells depends on infusion of adequate numbers of hematopoietic stem cells. Administration of G-CSF to the donor (in the case of autologous transplantation, the patient who also will be the recipient of the transplantation) greatly increases the number of hematopoietic stem cells harvested from the donor's blood. The answer is **B.**

SKILL KEEPER ANSWERS: ROUTES OF ADMINISTRATION (SEE CHAPTER 1)

All of the hematopoietic growth factors are proteins with molecular weights greater than 15,000. Like other proteinaceous drugs, the growth factors cannot be administered orally because they have very poor bioavailability. Their peptide bonds are destroyed by stomach acid and digestive enzymes.

Injections are required for intravenous, intramuscular, and subcutaneous administration. The intravenous route offers the fastest onset of drug action and shortest duration of drug action. Because intravenous administration can produce high blood levels, this route of administration has the greatest risk of producing concentration-dependent drug toxicity. Intramuscular injection has a quicker onset of action than subcutaneous injection, and larger volumes of injected fluid can be given. Because protective barriers can be breached by the needle or tubing used for drug injection, all 3 of these routes of administration carry a greater risk of infection than does oral drug administration.

transient ischemic attacks (TIAs), ischemic stroke, and other thrombotic events.

The glycoprotein IIb/IIIa inhibitors prevent restenosis after coronary angioplasty and are used in acute coronary syndromes (eg, unstable angina and non-Q-wave acute myocardial infarction).

Clopidogrel and ticlopidine are effective in preventing TIAs and ischemic strokes, especially in patients who cannot tolerate aspirin. Clopidogrel is routinely used to prevent thrombosis in patients who have received a coronary artery stent.

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.

D. Toxicity

Aspirin and other NSAIDs cause gastrointestinal and CNS effects (Chapter 36). All antiplatelet drugs significantly enhance the effects of other anticlotting agents. The major toxicities of the glycoprotein IIb/IIIa receptor-blocking drugs are bleeding and, with chronic use, thrombocytopenia. Ticlopidine is used rarely because it causes bleeding in up to 5% of patients, severe neutropenia in about 1%, and very rarely **thrombotic thrombocytopenic purpura (TTP)**, a syndrome characterized by the disseminated formation of small thrombi, platelet consumption, and thrombocytopenia. Clopidogrel is less hematotoxic. The most common adverse effects of dipyridamole and cilostazol are headaches and palpitations. Cilostazol is contraindicated in patients with congestive heart failure because of evidence of reduced survival.

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, and thrombocytopenia. Treatment involves administration of vitamin K, preformed clotting factors, or antiplasmin drugs. Thrombocytopenia can be treated by administration of platelets or oprelvekin, the recombinant form of the megakaryocyte growth factor interleukin-11 (see Chapter 33).

A. 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 bleeding due to vitamin K deficiency. The deficiency is readily treated with oral or parenteral **phytonadione (vitamin K_1)**. In the United States, all newborns receive an injection of phytonadione. Large doses of vitamin K_1 are used to reverse the anticoagulant effect of excess warfarin.

B. Clotting Factors and Desmopressin

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 and, in the case of factors purified from blood products, infection (although most known blood-borne pathogens are removed by chemical treatment of the plasma extracts.)

The vasopressin V_2 receptor agonist **desmopressin acetate** (see Chapter 37) increases the plasma concentration of von Willebrand factor and factor VIII. It is used to prepare patients with mild hemophilia A or von Willebrand disease for elective surgery.

C. Antiplasmin Agents

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 (Figure 34–2). Adverse effects include thrombosis, hypotension, myopathy, and diarrhea.

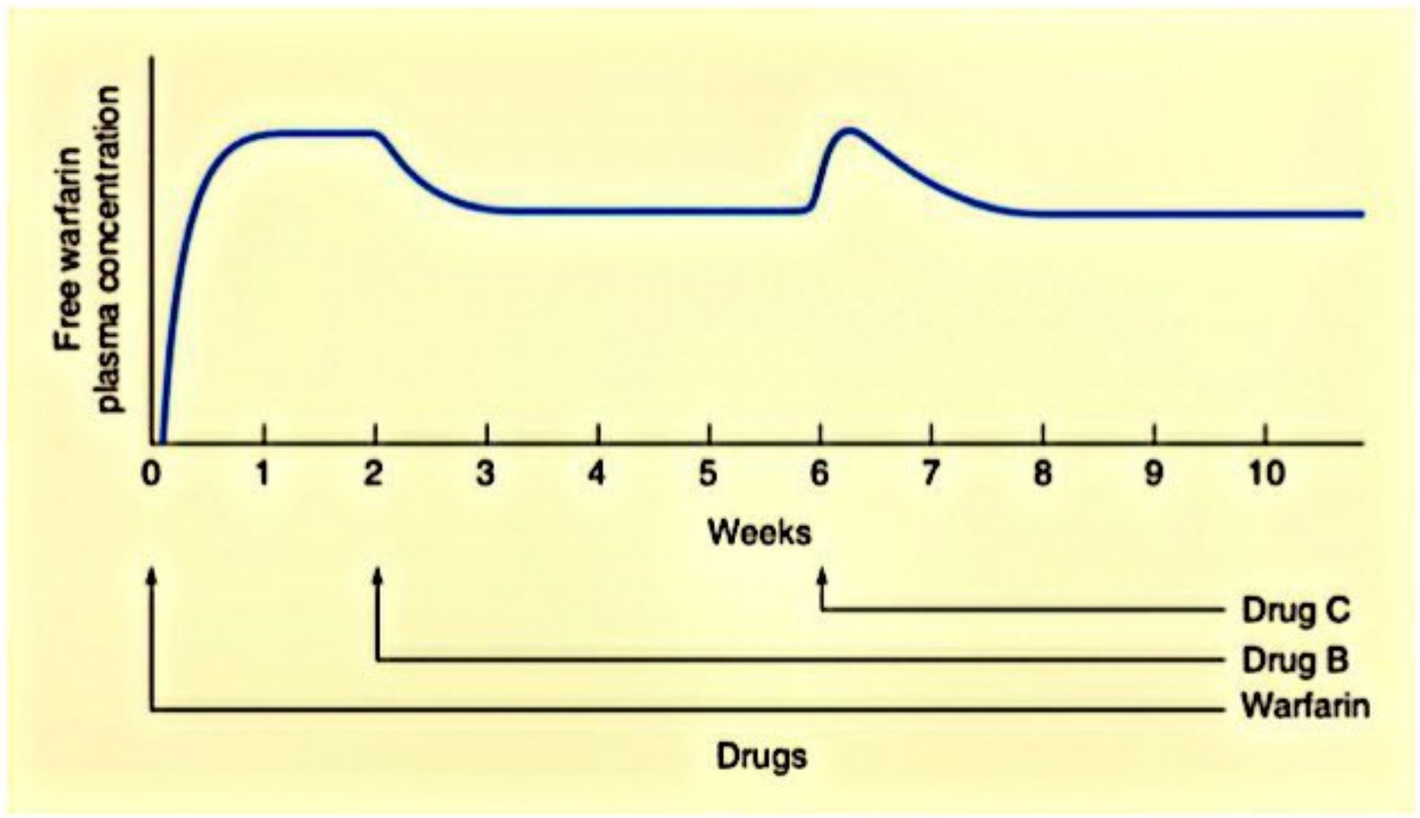
QUESTIONS

Questions 1–3. A 55-year-old lawyer is brought to the emergency department 2 h after the onset of severe chest pain during a stressful meeting. He has a history of poorly controlled mild hypertension and elevated blood cholesterol but does not smoke. ECG changes (ST elevation) and cardiac enzymes confirm the diagnosis of myocardial infarction. The decision is made to attempt to open his occluded artery.

1. Which of the following drugs accelerates the conversion of plasminogen to plasmin?
   (A) Aminocaproic acid
   (B) Heparin
   (C) Argatroban
   (D) Reteplase
   (E) Warfarin

2. If a fibrinolytic drug is used for treatment of this man's acute myocardial infarction, which of the following adverse drug effects is most likely to occur?
   (A) Acute renal failure
   (B) Development of antiplatelet antibodies
   (C) Encephalitis secondary to liver dysfunction
   (D) Hemorrhagic stroke
   (E) Neutropenia

3. If this patient undergoes a percutaneous coronary angiography procedure and placement of a stent in a coronary blood vessel, he will need to be on dual antiplatelet therapy. eg, aspirin and clopidogrel for at least a year. Which of the following most accurately describes the mechanism of action of clopidogrel?
   (A) Clopidogrel directly binds to the platelet ADP receptors
   (B) Clopidogrel irreversibly inhibits cyclooxygenase
   (C) Clopidogrel facilitates the action of antithrombin III
   (D) The active metabolite of clopidogrel binds to the platelet ADP receptors
   (E) The active metabolite of clopidogrel binds to the platelet glycoprotein IIb/IIIa receptors



4. The above graph shows the plasma concentration of free warfarin as a function of time for a patient who was treated with 2 other agents, drugs B and C, on a daily basis at constant dosage starting at the times shown. Which of the following is the most likely explanation for the observed changes in warfarin concentration?
   (A) Drug B displaces warfarin from plasma proteins; drug C displaces warfarin from tissue-binding sites
   (B) Drug B inhibits hepatic metabolism of warfarin; drug C displaces drug B from tissue-binding sites
   (C) Drug B stimulates hepatic metabolism of warfarin; drug C displaces warfarin from plasma protein
   (D) Drug B increases renal clearance of warfarin; drug C inhibits hepatic metabolism of drug B

Questions 5–7. A 58-year-old woman with chronic hypertension and diabetes mellitus was recently admitted to the hospital for congestive heart failure and new onset atrial fibrillation. She is now seeing you after discharge and, though feeling better, is still in atrial fibrillation. An echocardiogram shows an ejection fraction of 40%; there are no valvular abnormalities. An ECG reveals only atrial fibrillation. You calculate her risk using the CHADS(2) system and the score indicates that she requires anticoagulation rather than antiplatelet therapy.

5. You are discussing the risks and benefits of anticoagulation therapy with her, including the option of using direct thrombin inhibitors. Which of the following anticoagulants is a direct inhibitor of thrombin?
   (A) Abciximab
   (B) Dabigatran
   (C) Rivaroxaban
   (D) Warfarin

6. She tells you that her main reason for not wanting oral anticoagulation is that she does not want to come to clinic for frequent blood draws. You agree on an oral alternative and start her on apixaban. You counsel her extensively on the importance of taking the medication each day, as suddenly stopping can lead to
   (A) Anaphylaxis
   (B) Excess bleeding
   (C) Increase in INR
   (D) Stroke
   (E) Thrombocytopenia

7. She is excited about not having to come in for blood tests but wonders if there is a test, just in case the doctors need to know. Which of the following tests would provide accurate information about the coagulation status of a patient taking apixaban?
   (A) aPTT
   (B) Factor X test
   (C) INR
   (D) PT test

Questions 8 and 9. A 67-year-old woman presents with pain in her left thigh muscle. Duplex ultrasonography indicates the presence of deep vein thrombosis (DVT) in the affected limb.

8. The decision was made to treat this woman with enoxaparin. Relative to unfractionated heparin, enoxaparin
   (A) Can be used without monitoring the patient's aPTT
   (B) Has a shorter duration of action
   (C) Is less likely to have a teratogenic effect
   (D) Is more likely to be given intravenously
   (E) Is more likely to cause thrombosis and thrombocytopenia

9. During the next week, the patient was started on warfarin and her enoxaparin was discontinued. Two months later, she returned after a severe nosebleed. Laboratory analysis revealed an INR (international normalized ratio) of 7.0 (INR value in such a warfarin-treated patient should be 2.0–3.0). To prevent severe hemorrhage, the warfarin should be discontinued and this patient should be treated immediately with which of the following?
   (A) Aminocaproic acid
   (B) Desmopressin
   (C) Factor VIII
   (D) Protamine
   (E) Vitamin K_1

10. A patient develops severe thrombocytopenia in response to treatment with unfractionated heparin and still requires parenteral anticoagulation. The patient is most likely to be treated with which of the following?
   (A) Abciximab
   (B) Bivalirudin
   (C) Tirofiban
   (D) Plasminogen
   (E) Vitamin K_1

ANSWERS

1. Reteplase is the only thrombolytic drug listed. Heparin and warfarin are anticoagulants. Argatroban is a direct inhibitor of thrombin, and aminocaproic acid is an inhibitor, not an activator, of the conversion of plasminogen to plasmin. The answer is **D**.

2. The most common serious adverse effect of the fibrinolytics is bleeding, especially in the cerebral circulation. The fibrinolytics do not usually have serious effects on the renal, hepatic, or hematologic systems. Unlike heparin, they do not induce antiplatelet antibodies. The answer is **D**.

3. Clopidogrel is a prodrug that is activated by CYP2C9 and CYP2C19. It irreversibly binds to the ADP receptor on the surface of platelets that serves as a key role in platelet aggregation. Aspirin and clopidogrel help prevent platelet-induced occlusion of coronary stents. The answer is **D**.

4. A drug that increases metabolism (clearance) of the anticoagulant lowers the steady-state plasma concentration (both free and bound forms), whereas one that displaces the anticoagulant increases the plasma level of the free form only until elimination of the drug has again lowered it to the steady-state level. The answer is **C**.

5. Abciximab is an antiplatelet agent that binds to and inhibits GPIIb/IIIa. Rivaroxaban is an oral factor X inhibitor and warfarin inhibits vitamin K epoxide reductase (VKOR). The answer is **B**.

6. Due to the shorter half-life of the oral factor X and thrombin inhibitors, the anticoagulant status of the patient changes rapidly. Sudden cessation of short-acting oral anticoagulants can lead to stroke. Excess bleeding is associated with taking any of the anticoagulants not with stopping them. An increase in INR reflects increased anticoagulation by warfarin. Thrombocytopenia is a risk associated with heparin. The answer is **D**.

7. INR (measured as PT test) reflects changes due to warfarin and to some extent the thrombin inhibitors. Factor X inhibition is not reliably measured by the aPTT (used for unfractionated heparin) or PT test. The answer is **B**.

8. Enoxaparin is an LMW heparin. LMW heparins have a longer half-life than standard heparin and a more consistent relationship between dose and therapeutic effect. Enoxaparin is given subcutaneously, not intravenously. It is less, not more, likely to cause thrombosis and thrombocytopenia. Neither LMW heparins nor standard heparin are teratogenic. The aPTT is not useful for monitoring the effects of LMW heparins. The answer is **A**.

9. The elevated INR indicates excessive anticoagulation with a high risk of hemorrhage. Warfarin should be discontinued and vitamin K_1 administered to accelerate formation of vitamin K-dependent factors. The answer is **E**.

10. Direct thrombin inhibitors such as bivalirudin and argatroban provide parenteral anticoagulation similar to that achieved with heparin, but the direct thrombin inhibitors do not induce formation of antiplatelet antibodies. The answer is **B**.

SKILL KEEPER ANSWERS: TREATMENT OF ATRIAL FIBRILLATION (SEE CHAPTERS 13 AND 14)

1. *The β-adrenoceptor-blocking drugs (class II; eg, propranolol, acebutolol) and calcium channel-blocking drugs (class IV; eg, verapamil, diltiazem) are useful for atrial fibrillation because they slow atrioventricular (AV) nodal conduction and thereby help control ventricular rate. Though rarely used, digoxin can be effective by increasing the effective refractory period in AV nodal tissue and decreasing AV nodal conduction velocity. If symptoms persist in spite of effective rate control, ablation therapy or class I or class III antiarrhythmic drugs (eg, amiodarone, procainamide, sotalol) can be used in an attempt to provide rhythm control.*

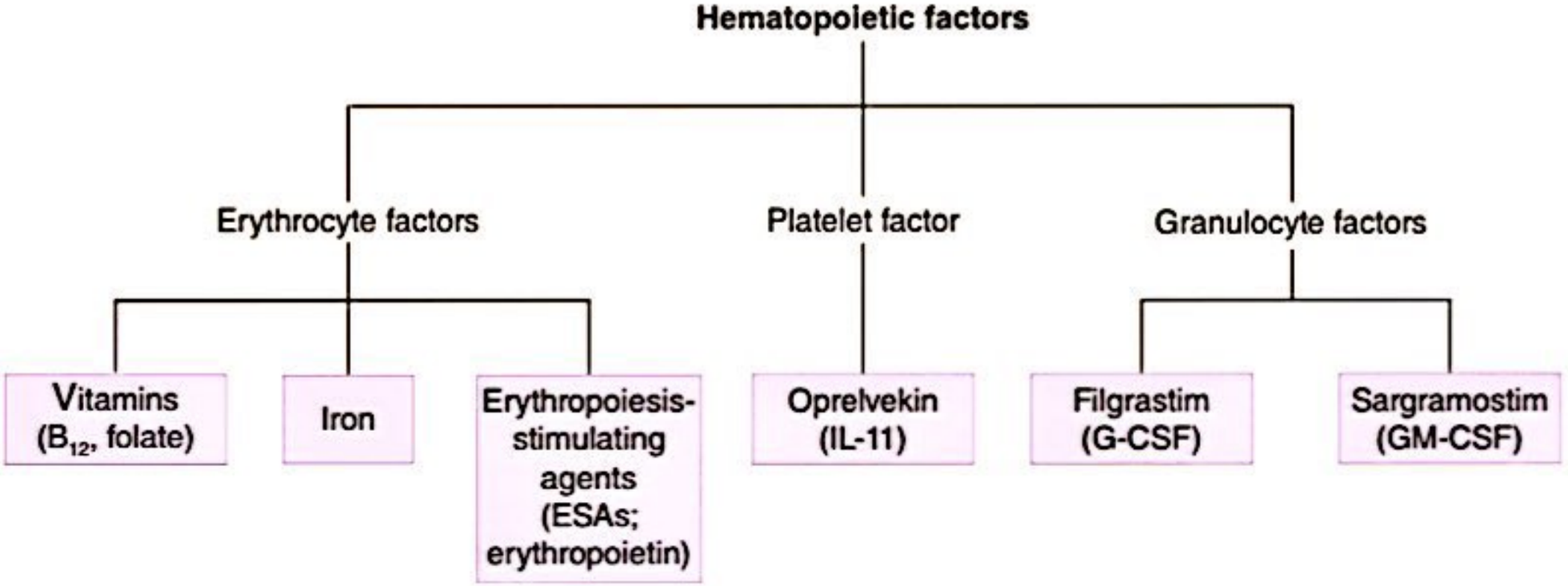
2. *With warfarin, one is always concerned about pharmacodynamic and pharmacokinetic drug interactions. A metabolite of amiodarone inhibits the metabolism of warfarin and can increase the anticoagulant effect of warfarin. None of the other antiarrhythmic drugs mentioned appears to have significant interactions with warfarin.*

CHECKLIST

When you complete this chapter, you should be able to:

- ❑ List the 3 major classes of anticlotting drugs and compare their usefulness in venous and arterial thromboses.
- ❑ Name 3 types of anticoagulants and describe their mechanisms of action.
- ❑ Explain why the onset of warfarin's action is relatively slow.
- ❑ Compare the oral anticoagulants, standard heparin, and LMW heparins with respect to pharmacokinetics, mechanisms, and toxicity.
- ❑ Give several examples of warfarin's role in pharmacokinetic and pharmacodynamic drug interactions.
- ❑ Diagram the role of activated platelets at the site of a damaged blood vessel wall and show where the 4 major classes of antiplatelet drugs act.
- ❑ Compare the pharmacokinetics, clinical uses, and toxicities of the major antiplatelet drugs.
- ❑ List 3 drugs used to treat disorders of excessive bleeding.

Blood cells play essential roles in oxygenation of tissues, coagulation, protection against infectious agents, and tissue repair. Blood cell deficiency is a relatively common occurrence that can have profound repercussions. The most common cause of erythrocyte deficiency, or anemia, is insufficient supply of iron, vitamin B_{12} or folic acid substances required for normal production of erythrocytes. Pharmacologic treatment of these types of anemia usually involves replacement of the missing substance. An alternative therapy for certain types of anemia and for deficiency in other types of blood cells is administration of recombinant hematopoietic growth factors, which stimulate the production of various lineages of blood cells and regulate blood cell function.



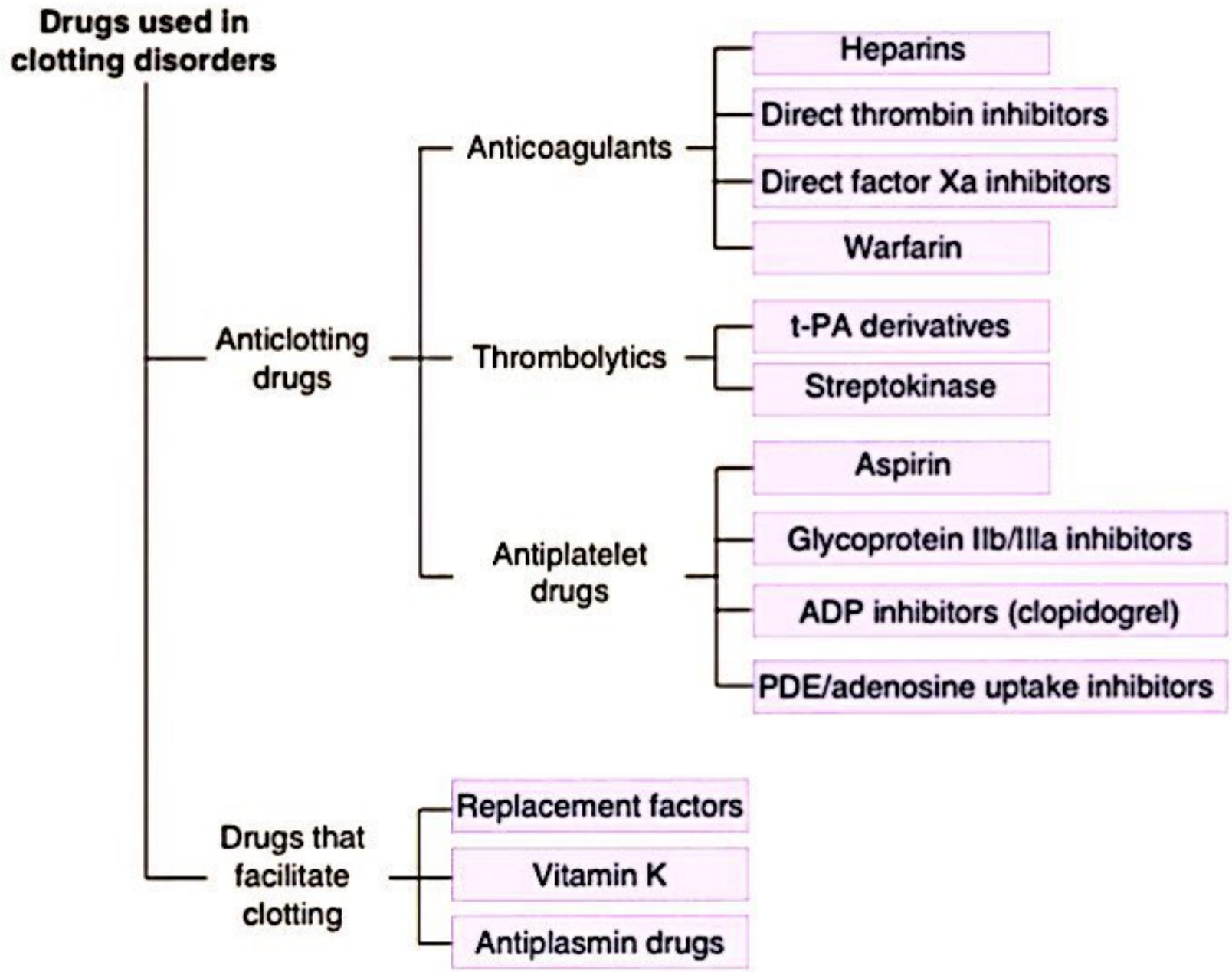
DRUG SUMMARY TABLE: Drugs for Cytopenias; Hematopoietic Growth Factors

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Iron				
Ferrous sulfate	Required for biosynthesis of heme and heme-containing proteins, including hemoglobin and myoglobin	Iron deficiency, which manifests as microcytic anemia	Complicated endogenous system for absorbing, storing, and transporting iron • no mechanism for iron excretion other than cell and blood loss	Acute overdose results in necrotizing gastroenteritis, abdominal pain, bloody diarrhea, shock, lethargy, and dyspnea • chronic iron overload results in hemochromatosis, with damage to the heart, liver, and pancreas
Ferrous gluconate and ferrous fumarate: oral iron preparations				
Iron dextran, iron sucrose complex, sodium ferric gluconate complex and ferumoxytol: parenteral preparations; can cause pain, hypersensitivity reactions. Ferumoxytol may interfere with MRI studies.				
Iron chelators (see also Chapters 57 and 58)				
Deferoxamine	Chelates excess iron	Acute iron poisoning • inherited or acquired hemochromatosis	Preferred routes of administration: intramuscular or subcutaneous	Rapid IV administration may cause hypotension • neurotoxicity and increased susceptibility to certain infections has occurred with long-term use
Deferasirox: oral iron chelator for treatment of hemochromatosis				

DRUG SUMMARY TABLE: Drugs for Cytopenias; Hematopoietic Growth Factors (*Continued*)

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Vitamin B_{12}				
Cyanocobalamin, hydroxocobalamin	Cofactor required for essential enzymatic reactions that form tetrahydrofolate, convert homocysteine to methionine, and metabolize L-methylmalonyl-CoA	Vitamin B_{12} deficiency, which manifests as megaloblastic anemia and is the basis of pernicious anemia	Parenteral vitamin B_{12} is required for pernicious anemia and other malabsorption syndromes	No toxicity associated with excess vitamin B_{12}
Folic acid				
Folacin (pteroylglutamic acid)	Precursor of an essential donor of methyl groups used for synthesis of amino acids, purines, and deoxynucleotides	Folic acid deficiency, which manifests as megaloblastic anemia • prevention of congenital neural tube defects	Oral is well absorbed; need for parenteral administration is rare	Not toxic in overdose, but large amounts can mask vitamin B_{12} deficiency
Erythropoiesis-stimulating agents (ESAs)				
Epoetin alfa	Agonist of erythropoietin receptors expressed by red cell progenitors	Anemia, especially associated with chronic renal failure, HIV infection, cancer, and prematurity • prevention of need for transfusion in patients undergoing certain types of elective surgery	Intravenous or subcutaneous administration 1–3 × per week	Hypertension, thrombotic complications, and, very rarely, pure red cell aplasia • to reduce the risk of serious cardiovascular events, hemoglobin levels should be maintained <12 g/dL
Darbepoetin alfa: long-acting glycosylated form administered weekly				
Methoxy polyethylene glycol-epoetin beta: long-acting form administered 1–2 × per month				
Myeloid growth factors				
G-CSF (filgrastim)	Stimulates G-CSF receptors expressed on mature neutrophils and their progenitors	Neutropenia associated with congenital neutropenia, cyclic neutropenia, myelodysplasia, and aplastic anemia • secondary prevention of neutropenia in patients undergoing cytotoxic chemotherapy • mobilization of peripheral blood cells in preparation for autologous and allogenic stem cell transplantation	Daily subcutaneous administration	Bone pain • rarely, splenic rupture
Pegfilgrastim: long-acting form of filgrastim that is covalently linked to a type of polyethylene glycol				
GM-CSF (sargramostim): myeloid growth factor that acts through a distinct GM-CSF receptor to stimulate proliferation and differentiation of early and late granulocytic progenitor cells, and erythroid and megakaryocyte progenitors. Clinical uses are similar to those of G-CSF, although it is more likely than G-CSF to cause fever, arthralgia, myalgia, and a capillary leak syndrome				
Plerixafor: antagonist of CXCR4 receptor used in combination with G-CSF for mobilization of peripheral blood cells prior to autologous transplantation in patients with multiple myeloma or non-Hodgkin's lymphoma who responded suboptimally to G-CSF alone				
Megakaryocyte growth factors				
Oprelvekin (interleukin-11; IL-11)	Recombinant form of an endogenous cytokine • activates IL-11 receptors	Secondary prevention of thrombocytopenia in patients undergoing cytotoxic chemotherapy for nonmyeloid cancers	Daily subcutaneous administration	Fatigue, headache, dizziness, anemia, fluid accumulation in the lungs, and transient atrial arrhythmias
Romiplostim: genetically engineered protein in which the F_c components of a human antibody are fused to multiple copies of a peptide that stimulates the thrombopoietin receptors; approved for treatment of idiopathic thrombocytopenic purpura (ITP)				
Eltrombopag: orally active agonist of thrombopoietin receptor; restricted use because of risk of hepatotoxicity and hemorrhage				

The drugs used in clotting and bleeding disorders fall into 2 major groups: (1) drugs used to decrease clotting or dissolve clots already present in patients at risk for vascular occlusion and (2) drugs used to increase clotting in patients with clotting deficiencies. The first group, the anticlotting drugs, includes some of the most commonly used drugs in the United States. Anticlotting drugs are used in the treatment and prevention of myocardial infarction and other acute coronary syndromes, atrial fibrillation, ischemic stroke, and deep vein thrombosis (DVT). Within the anticlotting group, the anticoagulant and thrombolytic drugs are effective in treatment of both venous and arterial thrombosis, whereas antiplatelet drugs are used primarily for treatment of arterial disease.



DRUG SUMMARY TABLE: Drugs Used for Anticoagulation & for Bleeding Disorders

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Drug Interactions
Anticoagulants				
Heparins				
Unfractionated heparin	Complexes with antithrombin III • irreversibly inactivates the coagulation factors thrombin and factor Xa	Venous thrombosis, pulmonary embolism, myocardial infarction, unstable angina, adjuvant to percutaneous coronary intervention (PCI) and thrombolytics	Parenteral administration	Bleeding (monitor with aPTT, protamine is reversal agent) • thrombocytopenia • osteoporosis with chronic use
LMW heparins (enoxaparin, dalteparin, tinzaparin): more selective anti-factor X activity, more reliable pharmacokinetics with renal elimination, protamine reversal only partially effective, less risk of thrombocytopenia				
Fondaparinux: effects similar to those of LMW heparins				
Direct factor X inhibitors				
Rivaroxaban	Binds to the active site of factor Xa and inhibits its enzymatic action	Venous thrombosis, pulmonary embolism, prevention of stroke in patients with nonvalvular atrial fibrillation	Oral administration • fixed dose, no routine monitoring (factor Xa test)	Bleeding • no specific reversal agent
Apixaban and edoxaban: similar to rivaroxaban				
Direct thrombin inhibitors				
Buvalirudin, argatroban, and dabigatran	Bind to thrombin's active site and inhibit its enzymatic action	Anticoagulation in patients with heparin-induced thrombocytopenia (HIT)	Bivalirudin and argatroban: IV administration Dabigatran: oral administration	Both: Bleeding (monitor with aPTT)
Coumadin anticoagulant				
Warfarin	Inhibits vitamin K epoxide reductase and thereby interferes with production of functional vitamin K-dependent clotting and anticlotting factors	Venous thrombosis, pulmonary embolism, prevention of thromboembolic complications of atrial fibrillation or cardiac valve replacement	Oral administration • delayed onset and offset of anticoagulant activity • many drug interactions	Bleeding (monitor with PT, vitamin K_1 is a reversal agent) • thrombosis early in therapy due to protein C deficiency • teratogen
Thrombolytic drugs				
Alteplase, recombinant human tissue plasminogen activator (t-PA)	Converts plasminogen to plasmin, which degrades the fibrin in thrombi	Coronary artery thrombosis, ischemic stroke, pulmonary embolism	Parenteral administration	Bleeding, especially cerebral hemorrhage
Reteplase, tenecteplase: similar to alteplase but with a longer half-life				
Streptokinase: bacterial protein that forms a complex with plasminogen that rapidly converts plasminogen to plasmin. Subject to inactivating antibodies and allergic reactions				

DRUG SUMMARY TABLE: Drugs Used for Anticoagulation & for Bleeding Disorders (*Continued*)

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Drug Interactions
Antiplatelet drugs				
COX inhibitor				
Aspirin	Nonselective, irreversible COX inhibitor • reduces platelet production of thromboxane A_2, a potent stimulator of platelet aggregation	Prevention and treatment of arterial thrombosis	Dose required for antithrombotic effect is lower than anti-inflammatory dose (see Chapter 36) • duration of activity is longer than pharmacokinetic half-life due to irreversible action	Gastrointestinal toxicity, nephrotoxicity • hypersensitivity reaction due to increased leukotrienes; tinnitus, hyperventilation metabolic acidosis, hyperthermia, coma in overdose
Glycoprotein IIb/IIIa inhibitor (GP IIb/IIIa)				
Abciximab	Inhibits platelet aggregation by interfering with GPIIb/IIIa binding to fibrinogen and other ligands	Used during PCI to prevent restenosis • acute coronary syndrome	Parenteral administration	Bleeding, thrombocytopenia with prolonged use
Eptifibatide, tirofiban: Reversible GP IIb/IIIa inhibitors of smaller size than abciximab				
ADP receptor antagonists				
Clopidogrel	Prodrug: active metabolite by CYP2C9 and CYP2C19 irreversibly inhibits platelet ADP receptor	Acute coronary syndrome, prevention of restenosis after PCI, prevention and treatment of arterial thrombosis	Oral administration	Bleeding, gastrointestinal disturbances, hematologic abnormalities
Ticlopidine: older ADP receptor antagonist with more toxicity, particularly leukopenia and thrombotic thrombocytopenic purpura				
Prasugrel: newer drug, similar to clopidogrel with less variable kinetics, activation primarily by CYP3A4				
Ticagrelor: reversible ADP receptor antagonist that does not require activation				
Dipyridamole				
Dipyridamole	Inhibits adenosine uptake and inhibits phosphodiesterase enzymes that degrade cyclic nucleotides (cAMP, cGMP)	Prevention of thromboembolic complications of cardiac valve replacement • combined with aspirin for secondary prevention of ischemic stroke	Oral administration	Headache, palpitations, contraindicated in congestive heart failure
Cilostazol: similar to dipyridamole				
Drugs used in bleeding disorders				
Reversal agents				
Vitamin K_1 (phytonadione)	Increases supply of reduced vitamin K, which is required for synthesis of functional vitamin K-dependent clotting and anticlotting factors	Vitamin K deficiency, reversal of excessive warfarin anticlotting activity	Oral or parenteral administration	Severe infusion reaction when given IV or IM
Protamine: Cationic form is acidic protein administered parenterally to reverse excessive anticlotting activity of unfractionated heparin				

DRUG SUMMARY TABLE: Drugs Used for Anticoagulation & for Bleeding Disorders (*Continued*)

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Drug Interactions
Clotting factors				
Factor VIII	Key factor in the clotting cascade	Hemophilia A	Parenteral administration	Infusion reaction, hypersensitivity reaction
Plasma and purified human clotting factors: available to treat other forms of hemophilia				
Desmopressin: vasopressin V_2 receptor agonist increases concentrations of von Willebrand factor and factor VIII (see Chapter 37)				
Antiplasmin drugs				
Aminocaproic acid	Competitively inhibits plasminogen activation	Excessive fibrinolysis	Oral or parenteral administration	Thrombosis, hypotension, myopathy, diarrhea
Tranexamic acid: analog of aminocaproic acid				

aPTT, activated partial thromboplastin time; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; GP, glycoprotein; PCI, percutaneous coronary intervention.

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	Activate antithrombin III, which inactivates 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.