Anticoagulants and Antiplatelet agents

- Blood dysfunctions
  - Thrombosis
  - Bleeding
  - Circulation problems
  - Anemia

- Thrombosis: Formation of unwanted clot in a blood vessel
- Thrombotic disorders
  - Acute myocardial infarction
  - Deep vein thrombosis
  - Pulmonary embolism
  - Acute ischemic stroke
- Treatment of thrombotic disorders
  - Anticoagulants
  - Fibrinolytics

- Thrombus: a clot that adheres to a vessel wall
- Embolus: an intravenous clot that floats in the blood
- Thrombi and emboli are dangerous, they occlude blood vessels and deprive tissues of oxygen and nutrients

- Arterial thrombosis is caused by atherosclerosis and usually consists of platelet-rich clot

- Venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade and usually involves a clot that is rich in fibrin with fewer platelet than in arterial clots

- Platelets response to vascular injury
  - Physical trauma to vascular system such as a cut triggers a series of interactions between platelets, endothelial cells and coagulation cascade that stop the blood loss from a damaged blood vessel
  - Initially there is a vasospasm of the damaged blood vessel to prevent further blood loss
  - Next platelet-fibrin plug is formed at the site of puncture

- The creation of an unwanted thrombus involves similar steps caused by pathologic conditions in the vascular system

- Nitric oxide and prostacyclin are synthesized by the endothelium, they inhibit platelet aggregation
  - Damage to the endothelium decreases prostacyclin levels leading to platelet aggregation
- Platelet membranes contain receptors for prostacyclin, thrombin, thromboxanes and exposed collagen
- When thrombin, thromboxanes or collagen receptors on the platelets are occupied, platelet aggregation is stimulated

- When endothelium is injured, platelets adhere to the uncovered collagen leading to platelet activation and release of platelet granules which contain ADP, serotonin, thromboxane A_2, platelet activation factors and thrombin which bind to receptors on the circulating platelets activating them and causing their aggregation

- Thrombin (Factor IIa) catalyzes the hydrolysis of fibrinogen into fibrin which is incorporated into the plug stabilizing the clot and forming platelet-fibrin plug

- Fibrinolytic pathway
  - Plasminogen is converted into plasmin (fibrinolysin) which limits the growth of the clot and dissolves fibrin
- Some fibrinolytic enzymes are available for treatment of MI, pulmonary emboli and ischemic stroke

Blood drugs

- Platelet aggregation inhibitors
- Anticoagulants
- Thrombolytic agents
- Drugs used for treatment of bleeding
- Drugs used for treatment of anemia
- Drugs used for treatment of sickle cell anemia

Platelet aggregation inhibitors

- Aspirin
- Clopidogrel
- Ticlopidine
- Prasugrel
- Abciximab
- Eptifibatide
- Tirofiban
- Dipyridamole
- Cilostazol

Platelet aggregation inhibitors

- Decrease the formation or the actions of chemical signals that promote platelet aggregation
- They act by different mechanisms of action and can be used in combination for synergistic (additive) effects
- Useful for:
  - Treatment of occlusive cardiovascular diseases
  - Maintenance of vascular grafts and arterial patency
  - Adjunct to thrombin inhibitors or thrombolytic therapy in MI

Platelet aggregation inhibitors

- Aspirin
  - Mechanism of action
    - Inhibits formation of thromboxane A_2 by inhibiting cyclooxygenase 1 (COX1)
    - This inhibits platelet aggregation for the life of the platelet (7–10 days)
  - Repeated administration has a cumulative on platelet function

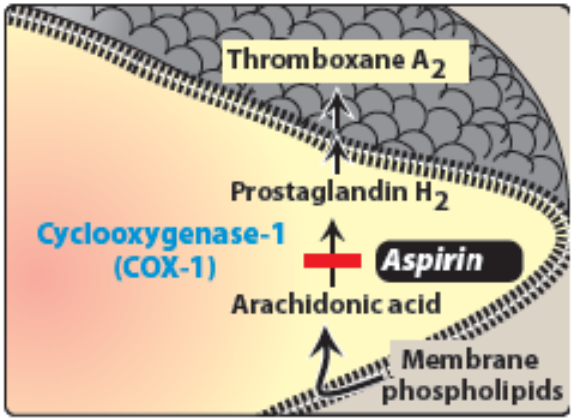


Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

Aspirin

- Used for:
  - Prophylactic treatment of transient cerebral ischemia
  - Reduction of the incidence of recurrent MI
  - Decrease mortality in pre- and post- MI patients
- Adverse effects
  - Prolongation of bleeding time
  - Increased incidence of hemorrhagic stroke
  - GI bleeding
- Aspiring should be taken 30 minutes before or 8 hours after other NSAIDs like ibuprofen which antagonize platelet inhibition by competing with aspirin for binding to COX1

Clopidogrel, ticlopidine, prasugrel

- Irreversibly inhibits binding of ADP to its receptors on platelets, thus inhibiting platelet aggregation

- Therapeutic uses
  - Ticlopidine is used for prevention of transient ischemic attacks and strokes in patients with prior cerebral thrombotic event
  - Copidogrel is approved for prevention of atherosclerotic events following recent MI and stroke and for decreasing thrombotic cardiovascular events in patients with acute coronary syndrome
  - Prasugrel is approved for decreasing thrombotic cardiovascular events in patients with acute coronary syndrome

Clopidogrel, ticlopidine, prasugrel

- Adverse effects
  - Prolonged bleeding
  - Ticlopidine causes neutropenia, and aplastic anemia
  - These drugs inhibit CYP450 enzymes, causing drug interactions

- Colpidogrel is a pro-drug, requires activation by CYP 2C9 to produce its therapeutic effect
  - (Poor metabolizers have less clinical response, and other antiplatelets should be used)

Abciximab

- Monoclonal antibody
- Binds to glycoprotein IIb/IIIa receptors and block the binding of fibrinogen inhibiting aggregation
- Given IV with aspirin or heparin
- Adverse effects:
  - Potential for bleeding

Eptifibatide and tirofiban

- Block GP IIb/ IIIa receptor (similar to abciximab)
- Decrease the incidence of thrombotic complications associated with acute coronary syndromes
- Available IV
- Adverse effects
  - Bleeding

Dipyridamole

- Coronary vasodilator
- Used prophylactically for angina pectoris
- Mechanism of action: increases intracellular levels of cAMP resulting in decreased thromboxane A synthesis

Cilostazole

- Oral antiplatelet drug with vasodilator activity
- Mechanism of action
  - Inhibit phosphodiesterase type III, preventing cAMP degradation and increasing cAMP levels which prevents platelet aggregation and promotes vasodilation
- Adverse effects:
  - Headache
  - GI effects (diarrhea, abdominal pain)

Anticoagulants

- Heparin
- Enoxaparin (low molecular weight form of heparin) (LMWH)
- Warfarin

- Mechanism of action of anticoagulant drugs
  - Inhibit the action of coagulation factors (such as the thrombin inhibitor heparin)
  - Interfere with the synthesis of coagulation factors (the vitamin K antagonist warfarin)

Blood coagulation

- Activation of clotting Factor VII by tissue factor or thromboplastin results in coagulation
  - Tissue factor is a lipoprotein expressed by activated endothelial cells, activated leukocytes, subendothelial fibroblasts and subendothelial smooth muscle cells at the site of vascular injury
- The activation of clotting Factor XII also triggers coagulation

Blood coagulation

- The activation of clotting Factors VII or XII leads to a cascade of enzyme reactions that transform various plasma factors (proenzymes) to their active enzymatic forms producing Factor Xa which converts prothrombin (Factor II) to thrombin (Factor IIa)
- Thrombin plays an important role in coagulation because it is responsible for generation of fibrin which forms the blood clot
- Coagulation is inhibited if thrombin is not formed or its function is inhibited by antithrombin III

Blood coagulation

- Endogenous inhibitors of coagulation factors
  - Protein C
  - Protein S
  - Antithrombin III
  - Tissue factor pathway inhibitor

- The mechanism of action of several anticoagulant drugs involve the activation of endogenous inhibitors

  (especially antithrombin III)

Anticoagulants

- Thrombin inhibitors
  - Heparin and low-molecular weight heparines (LMWH)
  - Dabigatran etexilate
  - Lepirudin
  - Argatroban
  - Fondaparinux
- Vitamin K antagonists
  - Warfarin

Heparin and LMWH

- Heparin is an injectable rapidly acting anticoagulant
- Used to interfere with the formation of thrombi
- LMWH
  - Enoxaparin
  - Dalteparin
  - Produced by chemical or enzymatic depolymerization of heparin
  - Also act as anticoagulants
- Heparin is administered IV, LMWHs are administered SC
- Heparin is used for prevention of thrombotic diseases such as pulmonary embolism and acute MI

Heparin and LMWH

- Mechanism of action of heparin
  - Binds to anthrombin III, and accelerate its rate of action about 1000 fold, inactivating coagulation factors
  - Antithrombin III inhibits several clotting factors including thrombin (Factor IIa) and factor Xa
  - Limit the expansion of thrombi by inhibiting fibrin formation
- Mechanism of action of LMWH
  - Bind with antithrombin III and inactivate factor Xa but do not bind as strongly to thrombin
  - Limit the expansion of thrombi by inhibiting fibrin formation

Heparin

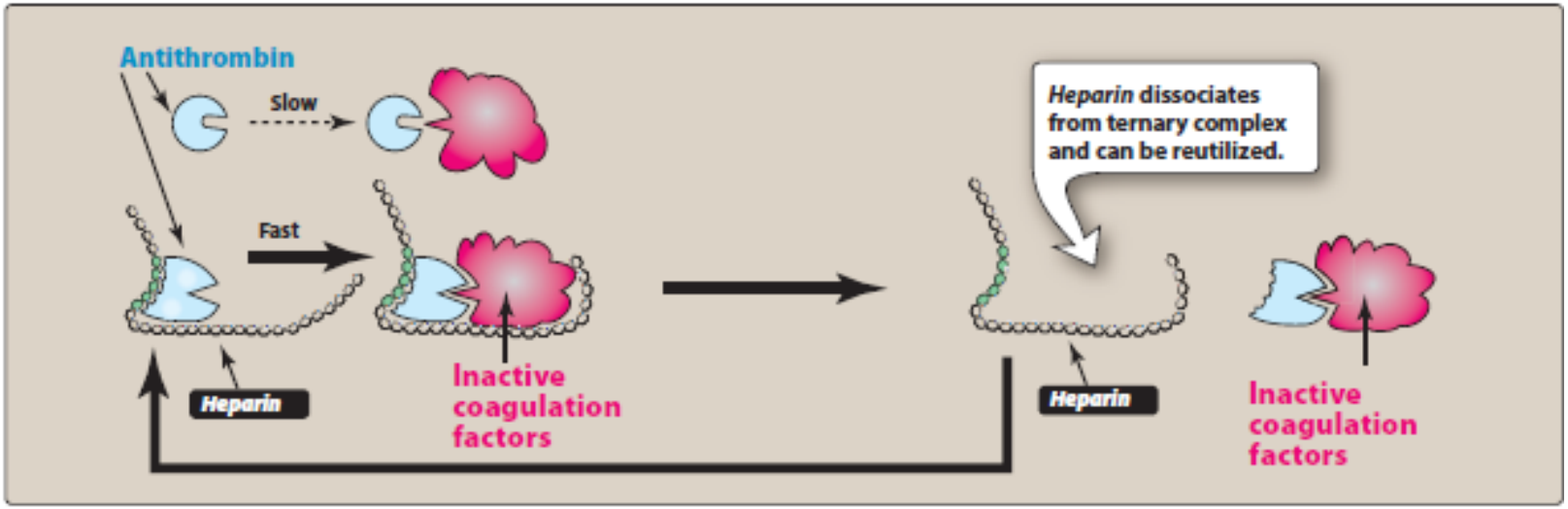


Figure 22.12
Heparin accelerates inactivation of coagulation factors by antithrombin.

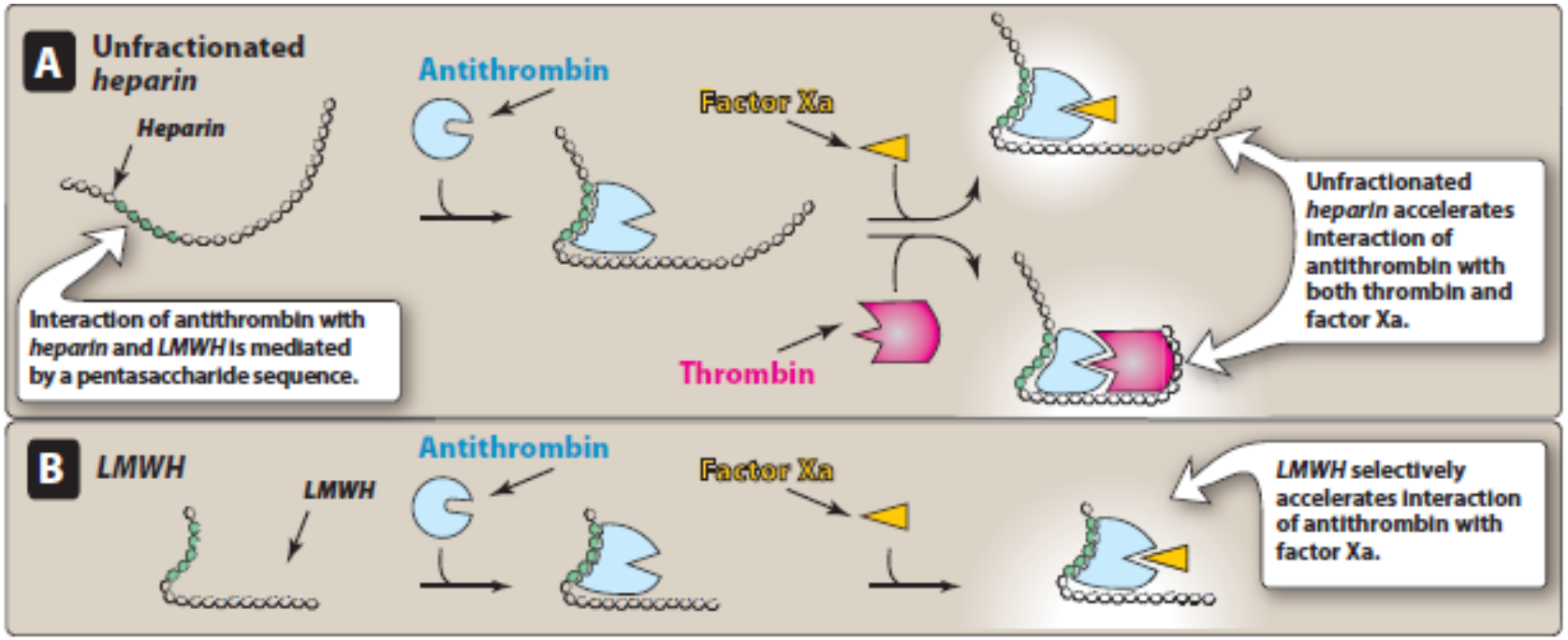


Figure 22.13

Heparin- and *low molecular weight heparin* (*LMWH*)–mediated inactivation of thrombin or factor Xa.

Heparin and LMWH

- Therapeutic uses
  - Heparin and LMWH limit the expansion of thrombi by preventing fibrin formation
  - Prevent venous thrombosis
  - Heparin is the major antithrombotic drug for treatment of acute deep vein thrombosis and pulmonary embolism reducing recurrent thromboembolic episodes incidence
  - Heparin is used prophylactically in patients undergoing elective surgery like hip replacement and used in acute MI
  - Coronary artery rethrombosis after thrombolytic therapy is reduced with heparin treatment
  - Heparin is used in extracorporeal devices like dialysis machines to prevent thrombosis
  - Heparin and LMWH can be used in pregnant women with thromboembolism

Heparin and LMWH

- LMWH are replacing heparin use
  - LMWH can be administered SC, maximum anti-Factor Xa activity occurs within 4 hours after SC
  - LMWH have predictable therapeutic and pharmacokinetic profiles
  - LMWH do not require the same intense monitoring as with heparin saving lab costs and nursing time costs

- Heparin can be administered IV or deep SC because the drug does not cross membranes, anticoagulant effect occurs within minutes of IV administration and 1-2 hours after SC

- Heparin is often administered IV in a bolus to achieve immediate anticoagulation
- This is followed by lower doses or continuous infusion of heparin for 7-10 days
- The dose is titrated so that the activated partial thromboplastin time (aPTT) is 1.5-2.5 fold that of the normal control
- LMWH do not require such testing

Heparin and LMWH

- Adverse effects:
  - Bleeding complications
    - (Antidote protamine sulfate)
  - Hypersensetivity reactions (because they're obtained from porcine sources)
  - Thrombosis: chronic administration of heparin can reduce antithrombin III activity and decrease the inactivation of coagulation factors increasing the risk of thrombosis
  - Thrombocytopenia
- Heparin is contraindicated in patients with bleeding disorders or those who had recent surgery of the brain, eye or spinal cord

Dabigatran etexilate

- Prodrug of dabigatran which is a direct thrombin inhibitor
- Administered orally
- Approved for prevention of stroke and systemic embolism in patients with atrial fibrillation
- Does not require routine monitoring (INR)
- Used as an alternative to enoxaprin for thromboprophylaxis in orthopedic surgery
- Adverse effects
  - Bleeding
  - GI adverse effects

- INR= international normalized ratio, the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used

Other parenteral anticoagulants

- Lepirudin
- Agatroban
- Fondaparinux

Lepirudin

- Direct thrombin antagonist, binds to thrombin and blocks its thrombogenic activity
- Administered IV
- Effective in treatment of heparin induced thrombocytopenia (HIT) and can prevent thromboembolic complications
- Adverse effects
  - Bleeding
- Requires monitoring of aPTT

Argatroban

- Directly inhibits thrombin
- Used prophylactically for the treatment of thrombosis in patients with HIT
- Requires monitoring by aPTT
- Metabolized in the liver and can be used in patients with renal dysfunction
- Adverse effect
  - Bleeding

Fondaparinux

- Selectively inhibits Factor Xa by binding to antithrombin III
- Used for prophylaxis of DVT that can lead to pulmonary embolism in patients undergoing hip fracture or replacement surgery or knee replacement surgery
- Can be used in patients with HIT
- Adverse effects:
  - Bleeding

Anticoagulants

Warfarin

- Mechanism of action:
  - Warfarin is vitamin K antagonist
  - Vitamin K is a cofactor for the synthesis of several protein coagulation factors including II, VII, IX, and X by the liver
  - Warfarin treatment results in the production of clotting factors with diminished activity (10%–40% of normal)
- Unlike heparin, the anticoagulant effects of warfarin are not observed until 8–12 hours after drug administration, peak effects may be delayed for 72–96 hours
- Warfarin is 99% bound to albumin

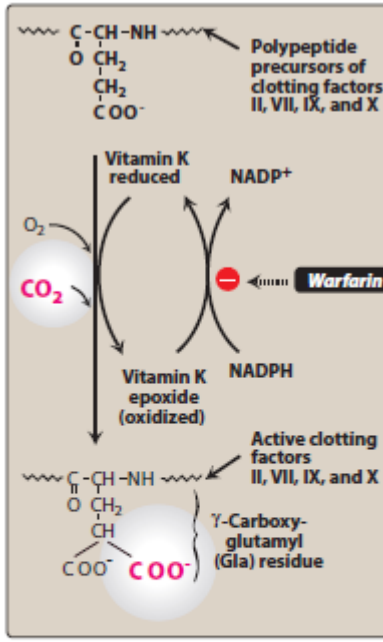


Figure 22.16
Mechanism of action of *warfarin*. NADP+ = oxidized form of nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

Warfarin

- Uses:
  - Maintenance therapy for prevention of the progression of acute deep vein thrombosis or pulmonary embolism after initial heparin treatment
  - Prevention of venous thromboembolism during orthopedic or gynecologic surgery
  - Used prophylactically in patients with acute MI, prosthetic heart valves, and chronic atrial fibrillation

Warfarin

- INR: international normalized ratio
- A laboratory test to measure blood coagulation based on prothrombin time
- INR was adopted to monitor warfarin concentration
- The goal of warfarin therapy is an INR of 2 to 3 for most indications and 2.5 to 3.5 in patients with mechanical heart valves
- Warfarin has a narrow therapeutic index, thus it is important that the INR is maintained within the optimal range
- INR values below or above the range increase the risk of thrombosis and bleeding

Warfarin

- Adverse effects
  - Bleeding disorders
- The anticoagulant effects of warfarin can be overcome by the administration of vitamin K

(reversal following administration of vitamin K takes approximately 24 hours)

- Warfarin is subject to a lot of drug interactions, especially drugs that affect its metabolism or albumin binding
- Contraindicated in pregnancy, FDA category X, can cause abortion and birth defects

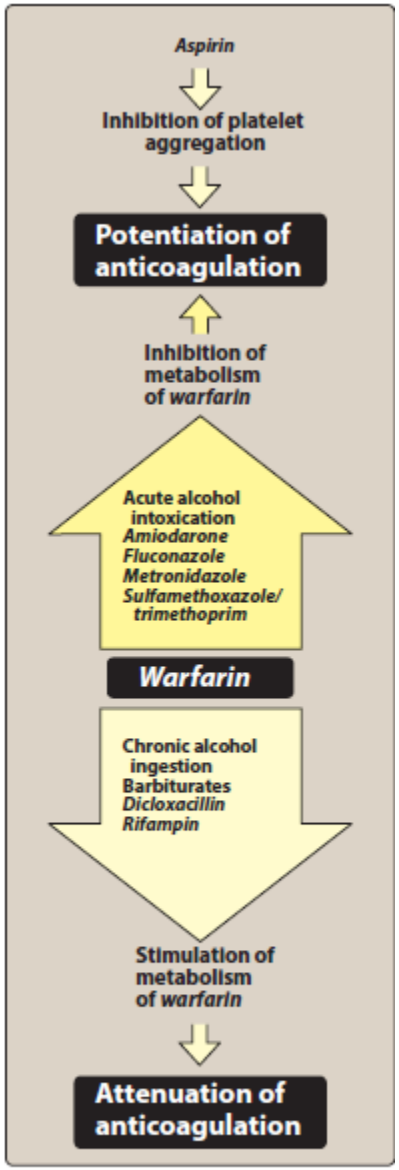
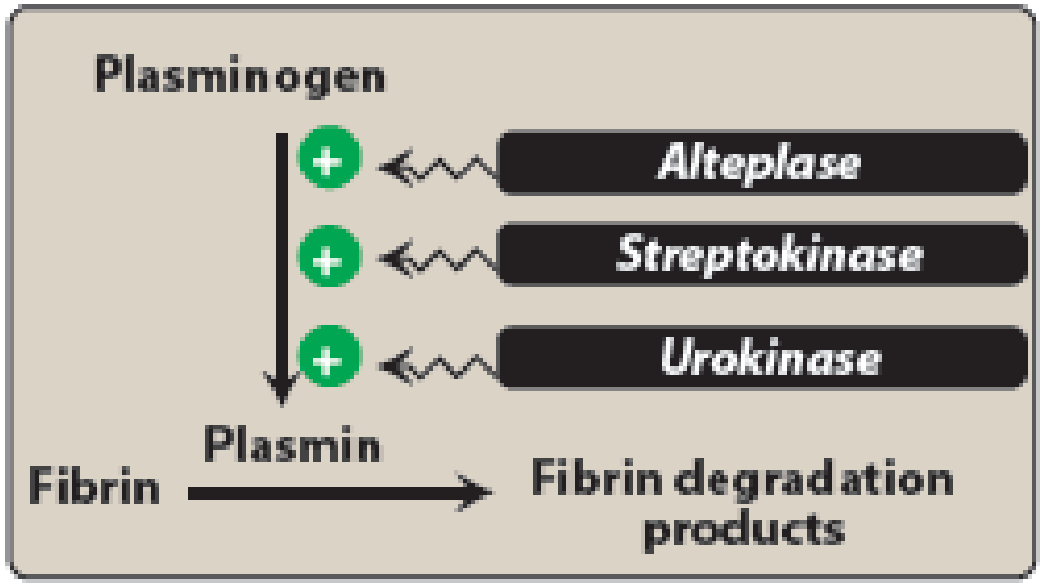


Figure 22.17
Drugs affecting the anticoagulant effect of *warfarin*.

Thrombolytic agents

- Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and dissolves clots



Thrombolytic agents

- Streptokinase
- Urokinase
- Alteplase (tPA)
- Reteplase
- Used IV for certain acute thromboembolic diseases
- May lyse both normal and pathologic thrombi

Thrombolytic agents

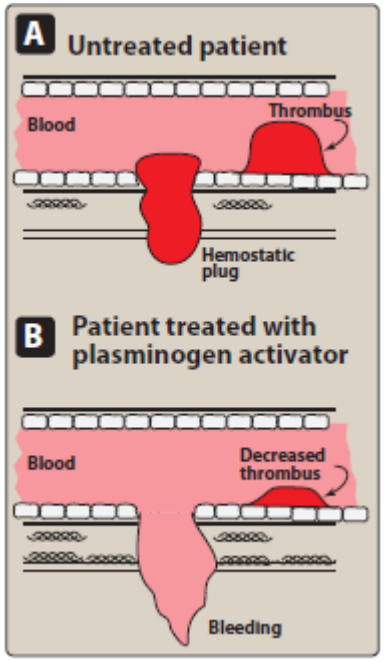
- Mechanism of action: Act either directly or indirectly to convert plasminogen to plasmin, which cleaves fibrin, thus lysing thrombi
- Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation
- Increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis
  - Antiplatelet drugs (aspirin) or antithrombotics such (heparin) are administered

Thrombolytic agents

- Therapeutic uses:
  - Used to dissolve clots that result in strokes
  - Helpful in restoring catheter and shunt function, by lysing clots causing occlusions
  - Their use for DVT and PE declined because of their tendency to cause bleeding
  - Use in treating acute MI or peripheral arterial thrombosis also decreased
- Adverse effects
  - Bleeding disorders
- Contraindicated in pregnancy, patients with healing wounds, history of cerebrovascular accidents intracranial bleeding

Streptokinase

- The first approved agents, rarely used now
- Acts on free and fibrin-bound plasminogen causing a systemic fibrinolytic state (bleeding problems)
- Forms a complex with plasminogen converting it to the active enzyme plasmin that hydrolyzes fibrin plugs
- The complex also catalyzes the degradation of fibrinogen as and clotting Factors V and VII
- Approved for use in acute PE, DVT, acute MI, arterial thrombosis, and occluded access shunts
- Adverse effects:
  - Bleeding
  - Hypersensetivity
- In the rare instance of life threatening hemorrhage, aminocaproic acid may be administered



Alteplase (tPA), reteplase

- Acts more locally on the thrombotic fibrin causing fibrinolysis
- Has low affinity for free plasminogen in the plasma
- Rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug
- Fibrin-selective (At low doses)
- Approved for the treatment of MI, massive pulmonary embolism, and acute ischemic stroke
- Alteplase is superior to streptokinase in dissolving older clots
- Alteplase administered within 3 hours of the onset of ischemic stroke improves clinical outcome
- Reteplase has a longer duration of action
- Adverse effects:
  - Bleeding complications including GI and cerebral hemorrhages
  - Alteplase can cause angioedema

Urokinase

- Produced naturally in human kidneys
- Directly cleaves plasminogen to generate active plasmin
- Approved for lysis of pulmonary emboli
- Off-label uses include treatment of acute MI, arterial thromboembolism, coronary artery thrombosis, and DVT
- Adverse effects
  - Bleeding
  - Allergic or anaphylactic reactions (Rare)

Bleeding disorders

- Bleeding disorders
  - Hemophilia, treated by transfusion of factor VIII
  - Vitamin K deficiency, treated by Vitamin K supplements
- Concentrated preparations of coagulation factors are available from human donors
- Blood transfusion is also an option for treating severe hemorrhage

Drugs used for treatment of bleeding

- Hemophilia is a consequence of a deficiency in plasma coagulation factors, most frequently Factors VIII and IX
  - Concentrated preparations of these factors are available from human donors

- Blood transfusion is also an option for treating severe hemorrhage

Drugs used for treatment of bleeding

- Aminocaproic acid and tranexamic acid
  - Orally active
  - Inhibit plasminogen activation
  - Side effect: Intravascular thrombosis

Drugs used for treatment of bleeding

- Protamine sulfate
  - Antagonizes the anticoagulant effects of heparin
  - Positively charged protamine interacts with negatively charged heparin, forming a stable complex without anticoagulant activity
  - Adverse effects:
    - Hypersensitivity, dyspnea, flushing, bradycardia, and hypotension when rapidly injected

Drugs used for treatment of bleeding

- Vitamin K
  - Administered to stop bleeding problems due to oral anticoagulants (warfarin)
  - Response to vitamin K is slow, requiring about 24 hours to synthesize new coagulation factors
  - immediate action is required, plasma should be infused
- Aprotinin
  - Stops bleeding by blocking plasmin
  - Adverse effects:
    - Renal dysfunction
    - Hypersensitivity (anaphylactic) reactions

Medication	Antidote for Bleeding Caused by	Adverse Effects	Monitoring Parameters
Aminocaproic acid *Tranexamic acid*	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis	PT/INR

Antihyperlipidemic drugs

- Coronary artery disease is a leading cause of death

- Coronary artery disease is correlated with:
  - High levels of low-density lipoprotein (LDL) cholesterol
  - High levels of triglycerols
  - Low levels of high-density lipoprotein (HDL) cholesterol
  - Smoking
  - Hypertension
  - Obesity
  - Diabetes

- Hyperlipidemias can be due to lifestyle like lack of exercise or excess saturated fatty acid diet or from genetic defects in lipoprotein metabolism

- Lifestyle changes and drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30% to 40%

- Antihyperlipidemic drugs should be taken indefinitely, because if therapy is terminated plasma lipid levels return to pretreatment levels

Serum levels

- Total cholesterol
  - Desirable values <200 mg/dL or <5.2 mmol/L
  - High >240 mg/dL or >6.2 mmol/L

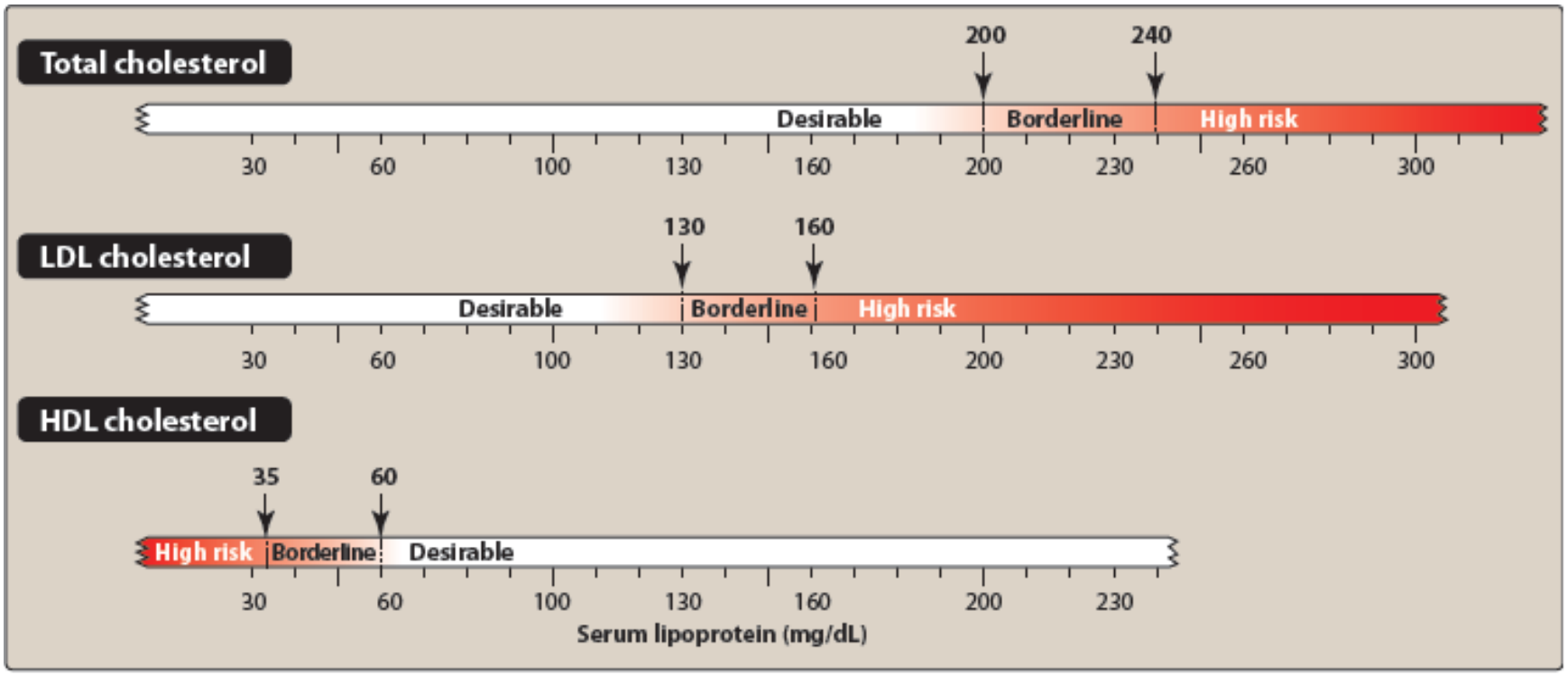
- LDL cholesterol
  - Ideal <100 mg/dL or <2.6 mmol/L

  (<70 mg/dL or<1.8 mmol/L for people at very high risk of heart disease)
  - High >160 mg/dL or >4.1 mmol/L

Serum levels

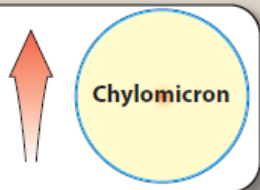
- Triglycerides
  - Desirable <150 mg/dL or <1.7 mmol/L
  - High >200 mg/dL or >2.3 mmol/L

- HDL
  - Best >60 mg/dL or >1.6 mmol/L
  - Poor <40 mg/dL or <1 mmol/L (Men)
  - Poor <50 mg/dL or <1.3 mmol/L (Women)


Total cholesterol
200
240
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
LDL cholesterol
130
160
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
HDL cholesterol
35
60
High risk
Borderline
Desirable
30
60
100
130
160
200
230
Serum lipoprotein (mg/dL)

Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.

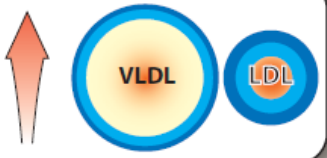


Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.

Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .

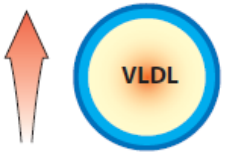


Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.

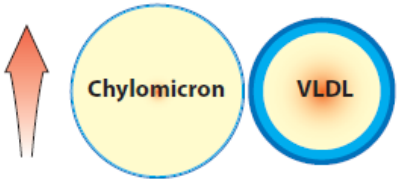
Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL and TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.



Type V (FAMILIAL MIXED HYPERTRIGLYCERIDEMIA)

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes *niacin*, and/or *fenofibrate*, or a statin.



Hyperlipidemias

- Primary treatment goal of hyperlipidemias:
  - Reduction of LDL

- Treatment options of hypercholesterolemia
  - Lifestyle changes: diet, exercise, weight reduction can decrease LDL and increase HDL
  - Patients usually do not modify their lifestyle enough to lower LDL and then pharmacological agents need to be added

Antihyperlipidemic drugs

- Used for elevated serum lipids
- Mechanism of action could be one of these:
  - Decreasing production of lipoproteins carriers of cholesterol and triglycerides
  - Increasing degradation of lipoproteins
  - Decreasing cholesterol synthesis
  - Decreasing cholesterol absorption
  - Increasing cholesterol removal from the body
- Should be accompanied by low dietary intake of saturated and trans fat and close monitoring of caloric intake

Antihyperlipidemic drugs

- HMG CoA reductase inhibitors
- Niacin
- Fibrates
- Bile binding resins
- Cholesterol absorption inhibitor
- Omega-3 fatty acids

HMG CoA reductase inhibitors

- 3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors lower elevated LDL cholesterol levels decreasing coronary events and death from CHD
- Inhibit the first enzymatic step of cholesterol synthesis
- First-line treatment for patients with elevated LDL cholesterol
- First line for patients with elevated risk of ASCVD
- Therapeutic benefits
  - Plaque stabilization
  - Improvement of coronary endothelial function
  - Inhibition of platelet thrombus formation
  - Anti-inflammatory activity

HMG CoA reductase inhibitors

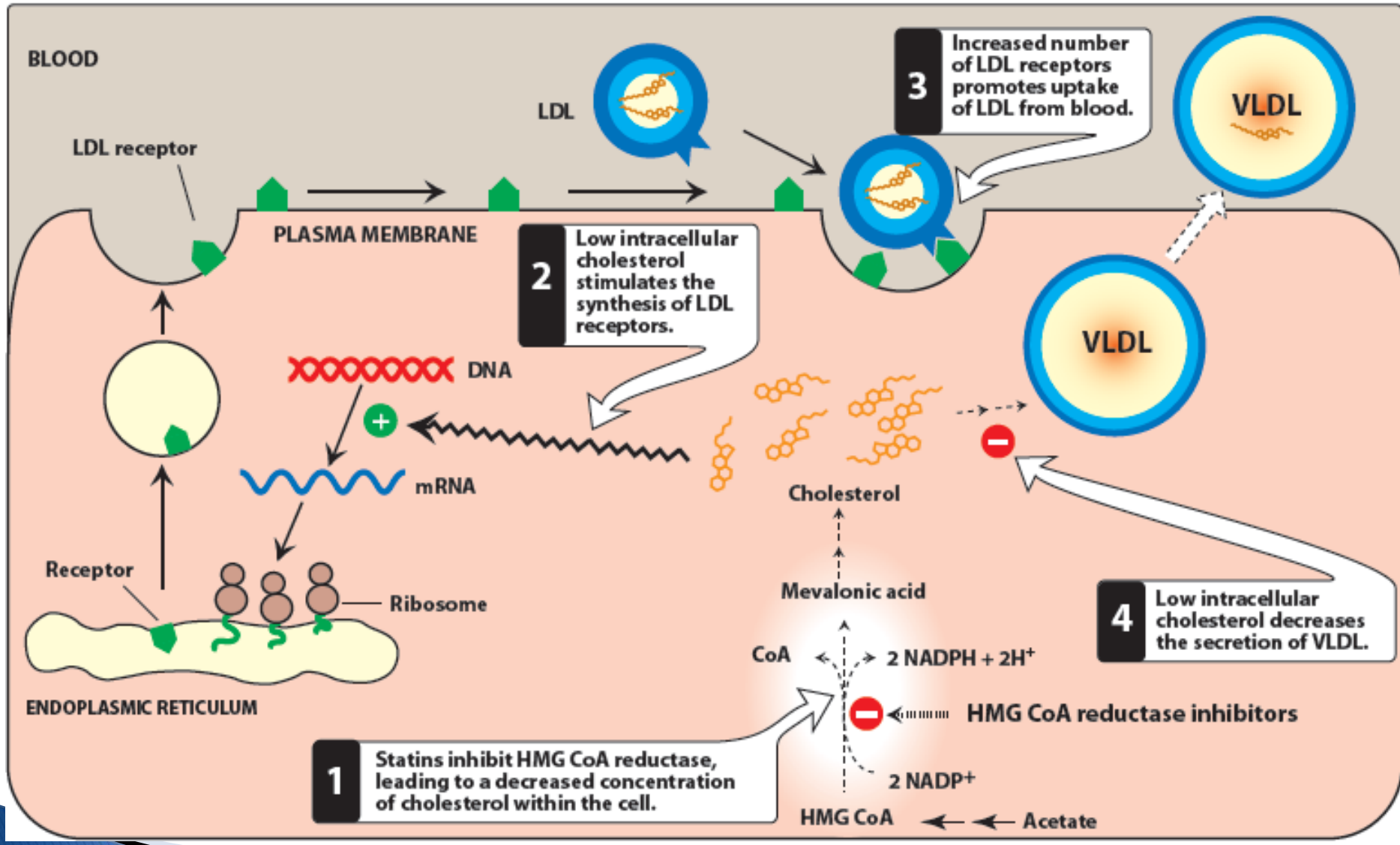
- Commonly known as statins
- Include
  - Atorvastatin
  - Fluvastatin
  - Simvastatin
  - Pravastatin
  - Rosuvastatin
  - Pitavastatin

HMG CoA reductase inhibitors

- Lower LDL
- Mechanism of action
  - Analogs of HMG, the precursor of cholesterol
  - Inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis
  - By inhibiting *de novo* cholesterol synthesis, they deplete intracellular supply of cholesterol
  - Depletion of intracellular cholesterol causes the cell to increase the number of LDL receptors that can bind and internalize circulating LDL
  - Plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism
  - Decrease triglyceride levels and may increase HDL cholesterol levels in some patients

HMG CoA reductase inhibitors

- The dominant effect is on the liver because statins undergo a marked first-pass extraction by the liver
- Pitavastatin, rosuvastatin and atorvastatin are the most potent
- Effective in lowering plasma cholesterol levels in all types of hyperlipidemias
- Patients who are homozygous for familial hypercholesterolemia lack LDL receptors and benefit much less from treatment with these drugs


BLOOD
LDL
LDL receptor
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	15	20	10	13

HMG CoA reductase inhibitors

- Adverse effects
  - Abnormalities in liver function
    - Evaluate liver function and measure serum transaminase levels periodically
  - Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) (Rare)
- Drug interactions: The HMG CoA reductase inhibitors may increase warfarin levels
  - Monitor INR frequently
- Contraindicated in Pregnancy, nursing mothers, children or teenagers

Liver failure

Myopathy

Contraindicated in pregnancy

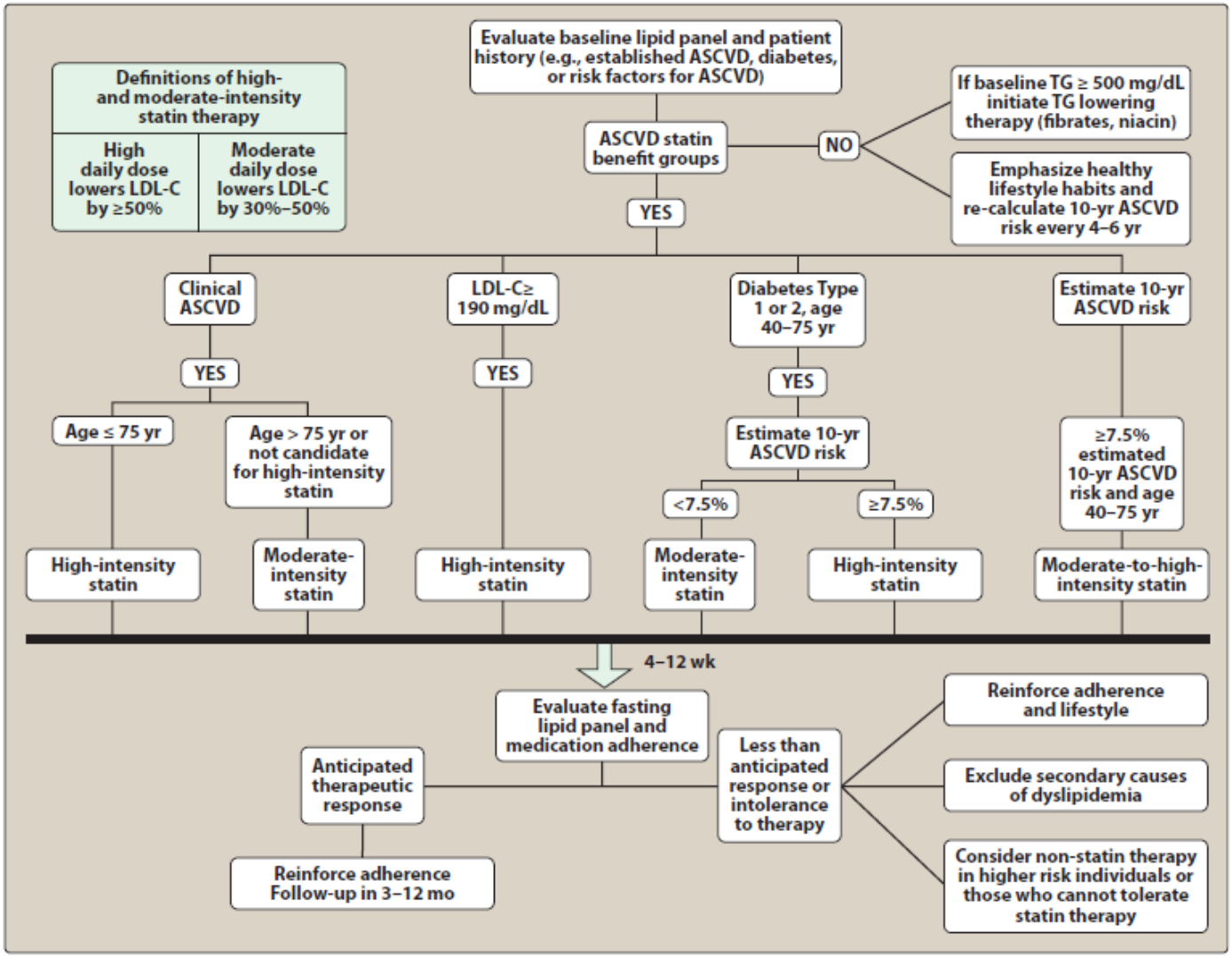


Figure 23.4

Treatment guidelines for hyperlipidemia. ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

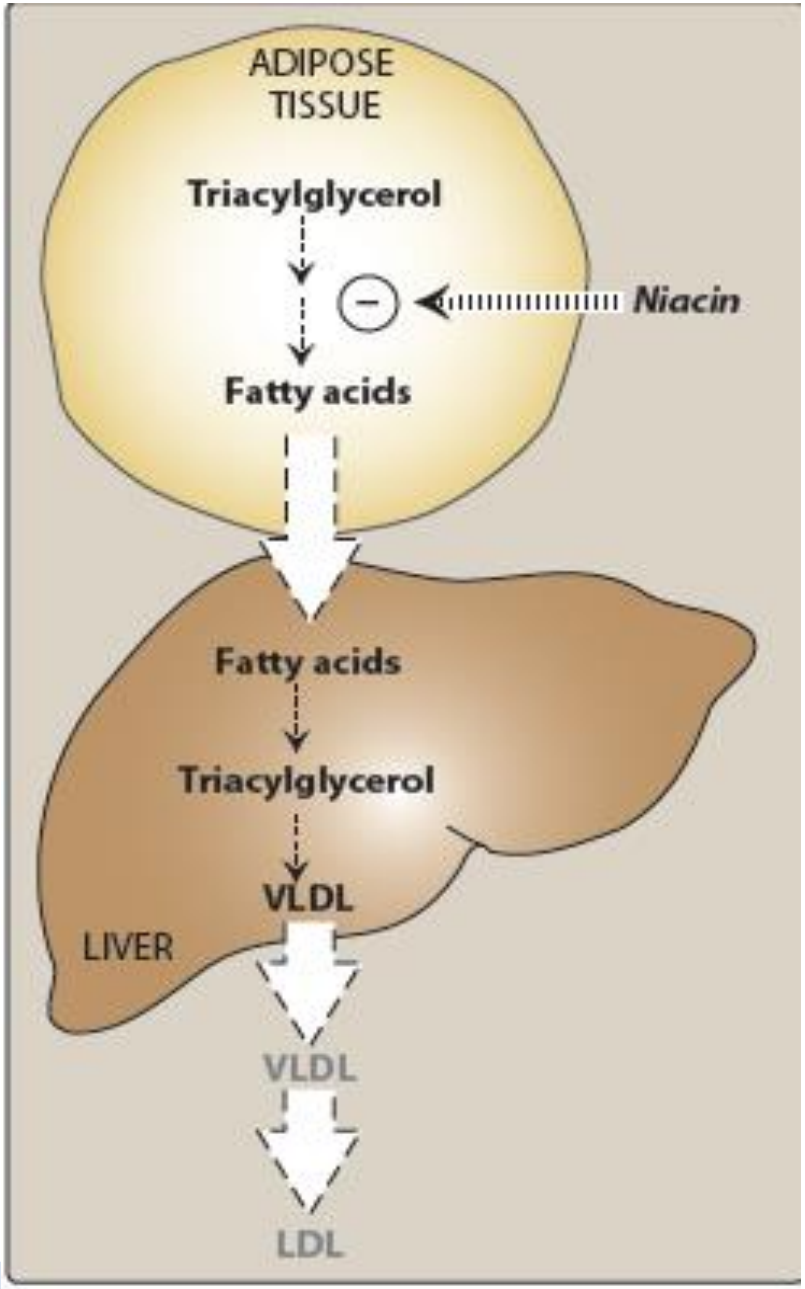
Niacin (nicotinic acid)

- The most effective agent for increasing HDL (the “good” cholesterol carrier) levels
- Can Reduce LDL (the “bad” cholesterol carrier) levels
- Can be used in combination with statins

Niacin

- Mechanism of action:
  - Inhibits lipolysis in adipose tissue, primary producer of circulating free fatty acids
  - The liver uses the circulating fatty acids as a major precursor for triacylglycerol synthesis
  - A reduction in the VLDL concentration also results in a decreased plasma LDL concentration
  - Both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered
  - Increases HDL cholesterol levels
  - Increases secretion of tissue plasminogen activator and lowers the level of plasma fibrinogen, reversing some of the endothelial cell dysfunction

Niacin


ADIPOSE TISSUE
Triacylglycerol
Niacin
Fatty acids
Fatty acids
Triacylglycerol
VLDL
LIVER
VLDL
LDL

Niacin

- Adverse effects
  - Intense cutaneous flush and pruritus
  - Nausea and abdominal pain
  - Hyperuricemia
  - Hepatotoxicity

Fibrates

- Fenofibrate
- Gemfibrozil
- Lower serum triacylglycerols and LDL cholesterol and increase HDL levels
- Mechanism of action
  - Activate the peroxisome proliferator-activated receptors (PPARs) leading to decreased triacylglycerol by increasing the expression of lipoprotein lipase
  - Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII

Fibrates

- Adverse effects
  - Mild GI disturbances
  - Lithiasis: (formation of gallstones) due to increased biliary cholesterol excretion
  - Myositis (inflammation of voluntary muscle)
- Drug interactions: fibrates compete with warfarin for binding with plasma proteins, potentiating anticoagulant activity
  - INR should be monitored
- Contraindications:
  - Pregnant or lactating women
  - Severe hepatic and renal dysfunction
  - Preexisting gallbladder disease

Bile acid binding resins

- Cholestyramine
- Colestipol
- Colesevelam
- Mechanism of action:
  - Bind to bile acids and bile salts in the small intestine forming a complex that gets excreted in feces, this causes increased conversion of cholesterol into bile acids decreasing the intracellular cholesterol concentration and activating hepatic uptake of cholesterol-containing LDL particles

Bile acid binding resins

- No absorption occurs, they are excreted in feces
- Adverse effects
  - GI disturbances (constipation, nausea, and flatulence)
  - Impaired absorption of fat soluble vitamins (A, D, E, &K)
- Drug interactions:
  - Cholestyramine and colestipol interfere with the intestinal absorption of many drugs (tetracycline, phenobarbital, digoxin, warfarin, pravastatin, fluvastatin, aspirin, and thiazide diuretics)
    - Drugs should be taken at least 1–2 hours before, or 4–6 hours after the bile acid–binding resins

Cholesterol absorption inhibitor

- Ezetimible
  - Inhibits absorption of cholesterol in the small intestine leading to a decrease in the delivery of intestinal cholesterol to the liver
  - This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood

Omega-3 fatty acids

- Docosahexaenoic and eicosapentaenoic acids
- Icosapent ethyl
- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids used for triglyceride lowering
- Inhibit VLDL and triglyceride synthesis in the liver
- Can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides
- Have not been shown to reduce cardiovascular morbidity and mortality
- The most common side effects include GI effects (abdominal pain, nausea, diarrhea)

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Figure 23.12
Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

Combination drug therapy