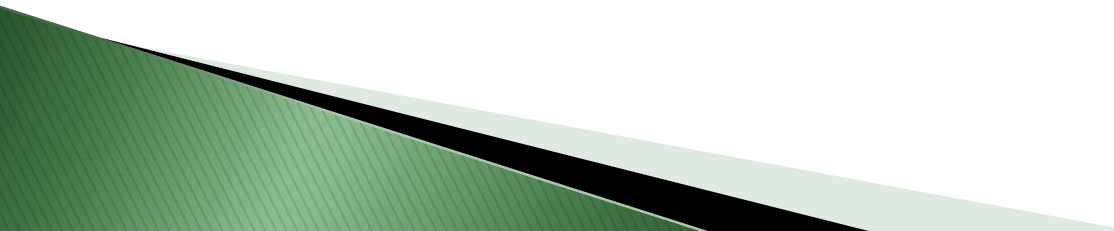

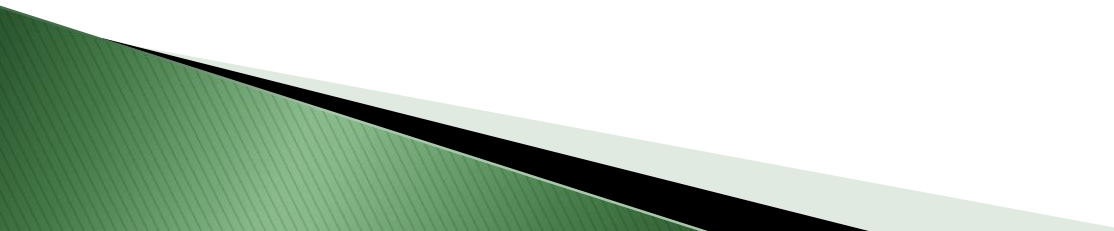
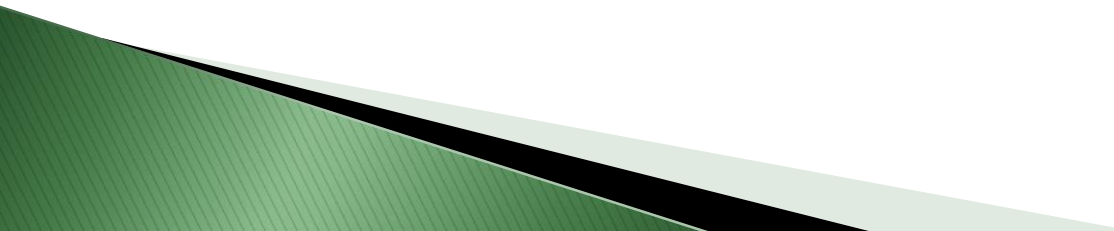


Anticoagulants and Antiplatelet agents

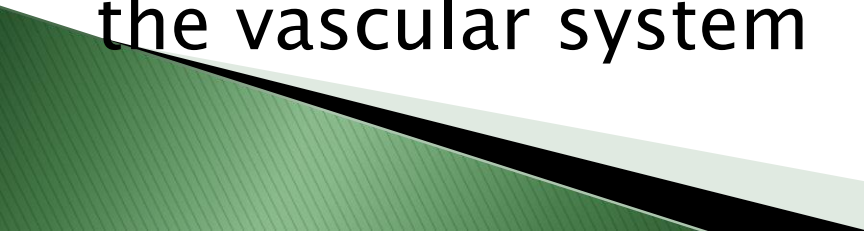
- ▶ **Blood dysfunctions**
 - Thrombosis
 - Bleeding
 - Circulation problems
 - Anemia
- 

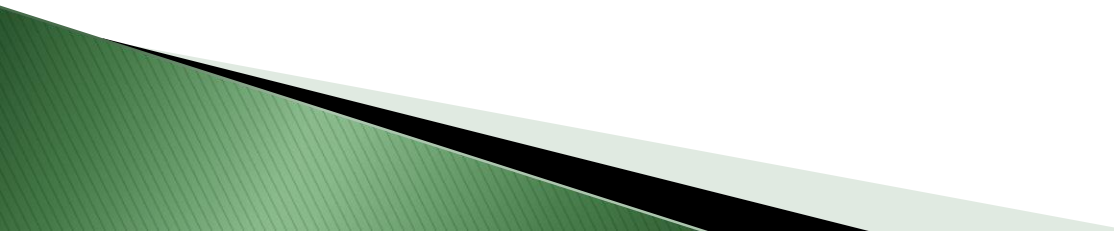
- ▶ Thrombosis: Formation of unwanted clot in a blood vessel
 - ▶ Thrombotic disorders
 - Acute myocardial infarction
 - Deep vein thrombosis
 - Pulmonary embolism
 - Acute ischemic stroke
 - ▶ Treatment of thrombotic disorders
 - Anticoagulants
 - Fibrinolytics
- 

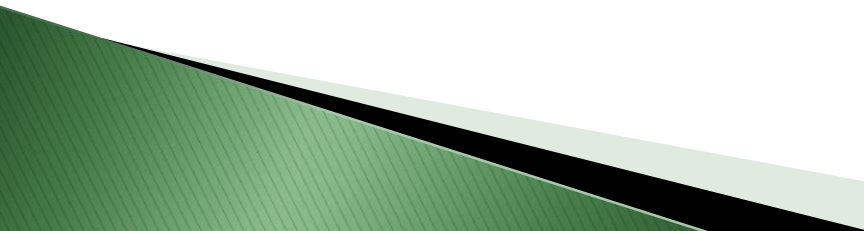
- ▶ Thrombus: a clot that adheres to a vessel wall
 - ▶ Embolus: an intravenous clot that floats in the blood
 - ▶ Thrombi and emboli are dangerous, they occlude blood vessels and deprive tissues of oxygen and nutrients
- 

- ▶ 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
- 

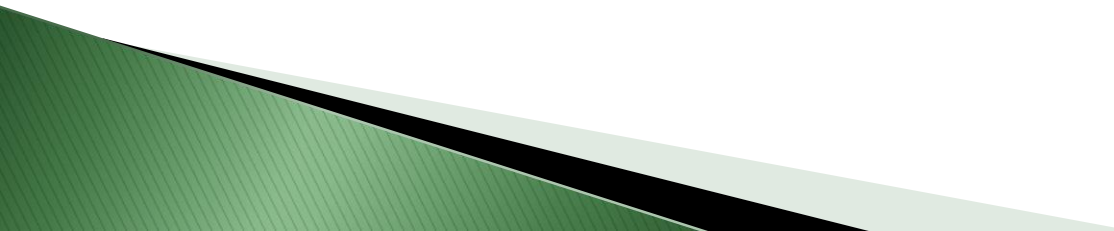
- ▶ Platelets response to vascular injury
 - Physical trauma to vascular system such as a cut triggers a series of interactions between platelets, endothelial cells and coagulation cascade that stop the blood loss from a damaged blood vessel
 - Initially there is a vasospasm of the damaged blood vessel 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
- 

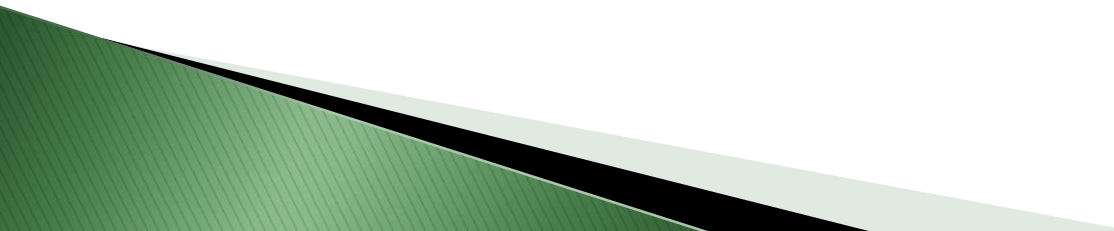
- ▶ Nitric oxide and prostacyclin are synthesized by the endothelium, they inhibit platelet aggregation
 - Damage to the endothelium decreases prostacyclin levels leading to platelet aggregation
 - ▶ Platelet membranes contain receptors for thrombin, prostacyclin, thromboxanes & exposed collagen
 - ▶ 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
 - These bind to receptors on the circulating platelets activating them and causing their aggregation
 - ▶ Thrombin (Factor IIa) catalyzes the hydrolysis of fibrinogen to fibrin which is incorporated into the plug stabilizing the clot
- 

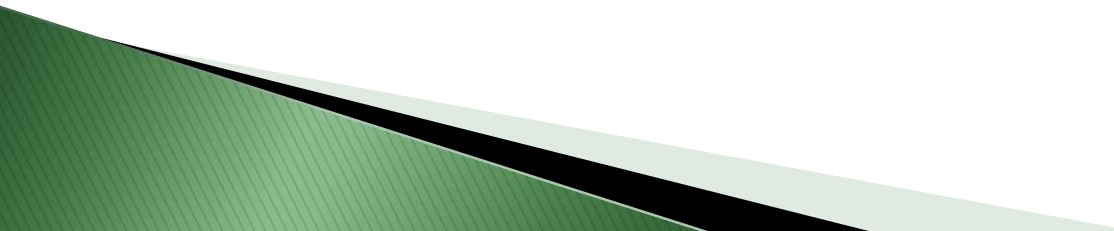
- ▶ Fibrinolytic pathway
 - Plasminogen is converted into plasmin (fibrinolysin) which limits the growth of the clot and dissolves fibrin

 - ▶ Some fibrinolytic enzymes are available for treatment of MI, pulmonary emboli and ischemic stroke
- 

Anticoagulants and antiplatelets

- ▶ Platelet aggregation inhibitors
 - ▶ Anticoagulants
 - ▶ Thrombolytic agents
- 

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 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

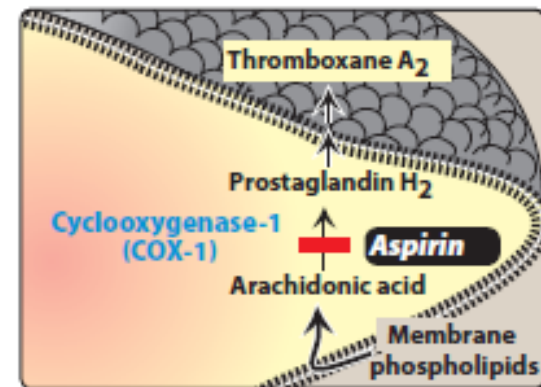


Figure 22.6

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
- ▶ Aspirin 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
 - Clopidogrel is approved for prevention of atherosclerotic events following recent MI and stroke and for decreasing thrombotic CV events in ACS
 - Prasugrel is approved for decreasing thrombotic cardiovascular events in patients with ACS

Clopidogrel, ticlopidine, prasugrel

- ▶ Adverse effects
 - Prolonged bleeding
 - Ticlopidine causes neutropenia, and aplastic anemia
 - These drugs inhibit CYP450 enzymes, causing drug interactions
- ▶ Clopidogrel is a prodrug, requires activation by CYP 2C19 to produce its therapeutic effect
 - (Poor metabolizers have less clinical response, and other antiplatelets should be used)

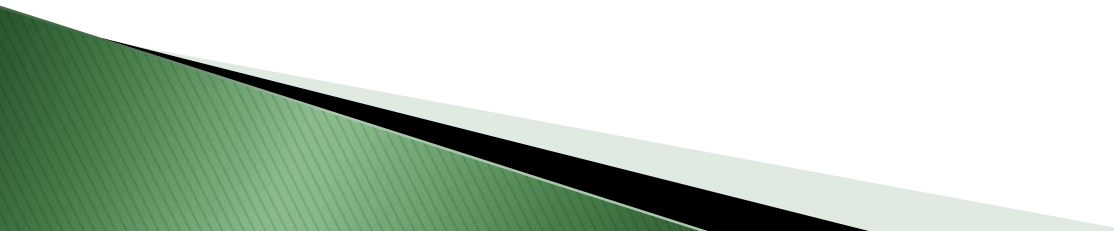
Abciximab

- ▶ 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 ACS
- ▶ Available IV
- ▶ Adverse effects
 - Bleeding

Dipyridamole

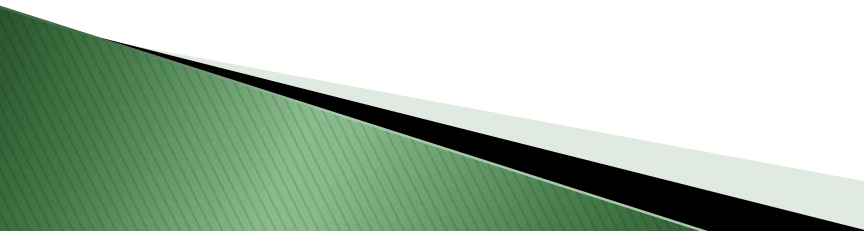
- ▶ Coronary vasodilator
 - ▶ Used prophylactically for angina pectoris
 - ▶ MOA: increases intracellular levels of cAMP resulting in decreased thromboxane A synthesis
- 

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

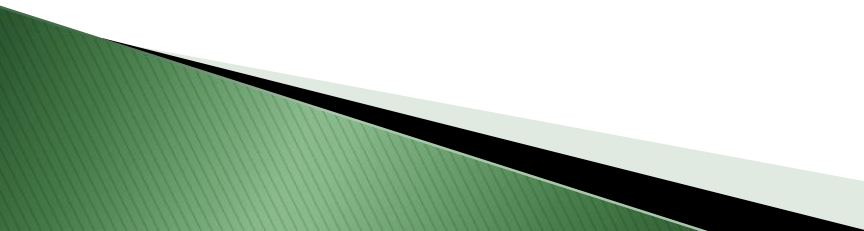
- ▶ Heparin
 - ▶ Enoxaparin (LMWH)
 - ▶ Warfarin

 - ▶ 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
 - ▶ 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 antithrombin III, and accelerates 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

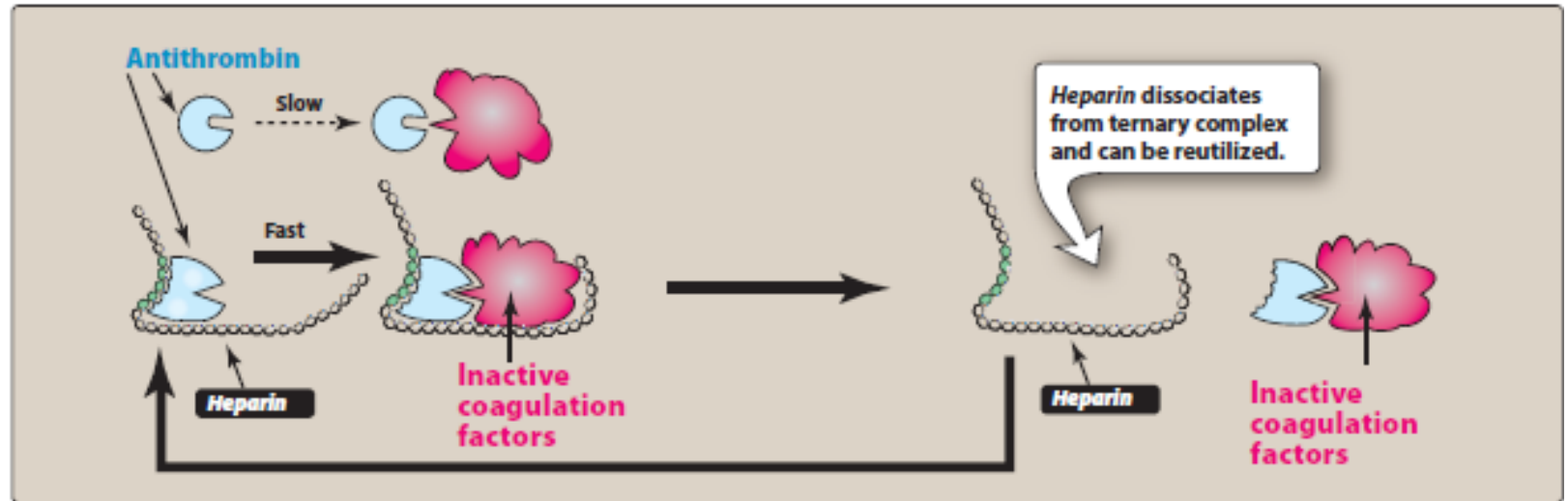


Figure 22.12

Heparin accelerates inactivation of coagulation factors by antithrombin.

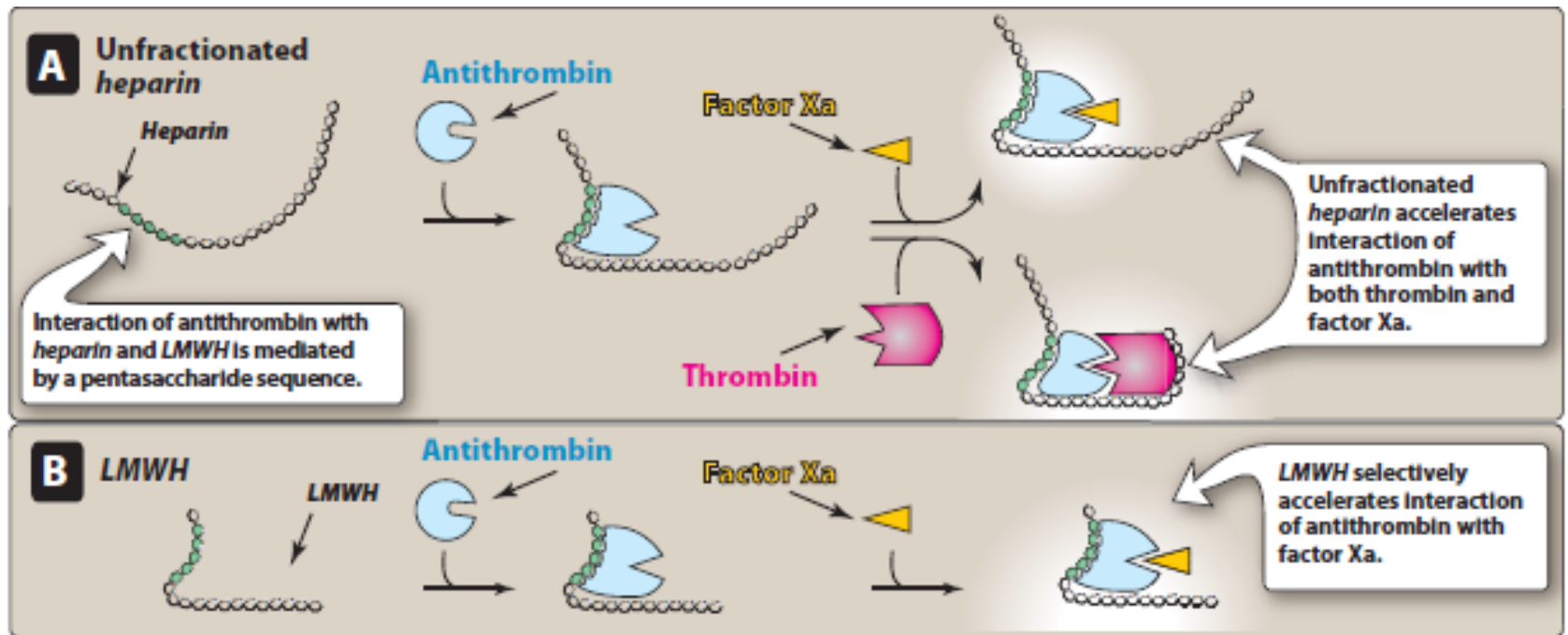


Figure 22.13

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

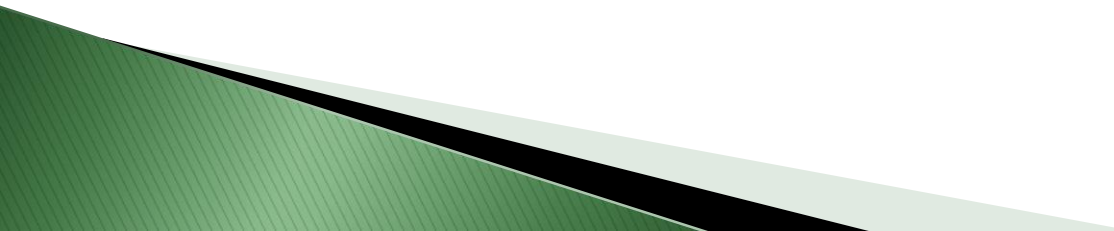
Heparin and LMWH

▶ Therapeutic uses

- Limit expansion of thrombi by preventing fibrin formation
- Prevent venous thrombosis
- Heparin is the major antithrombotic drug for treatment of acute DVT and PE reducing recurrent thromboembolic episodes incidence
- Heparin is used prophylactically in patients undergoing elective surgery like hip replacement and 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 because they do not cross the placenta due to the large size and negative charge

Heparin and LMWH

- ▶ LMWH are replacing heparin use
 - LMWH can be administered SC, maximum anti-Factor Xa activity occurs within 4 hours
 - LMWH have predictable therapeutic and PK 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 deep 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

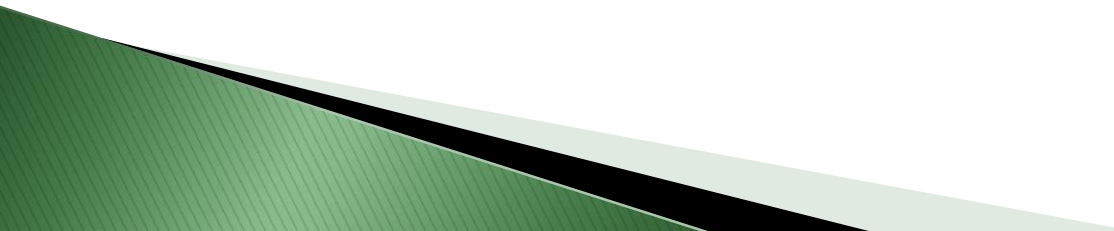
- ▶ Adverse effects:
 - Bleeding complications
 - (Antidote protamine sulfate)
 - Hypersensitivity reactions
 - Thrombosis: chronic administration of heparin can reduce antithrombin III activity and decrease the inactivation of coagulation factors increasing the risk of thrombosis
 - Thrombocytopenia
- ▶ 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
- 

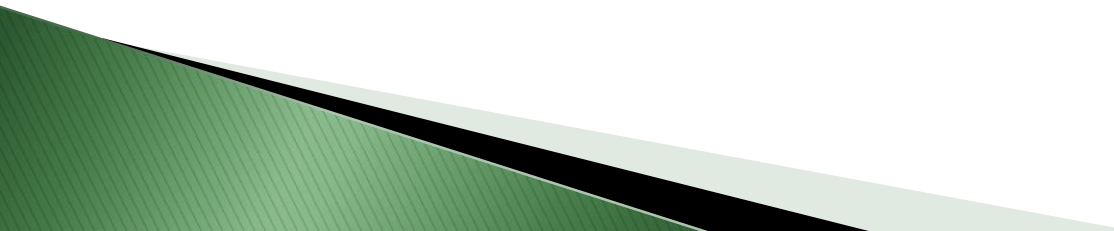
Lepirudin

- ▶ 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 PE in hip fracture or replacement surgery or knee replacement surgery patients
 - ▶ 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

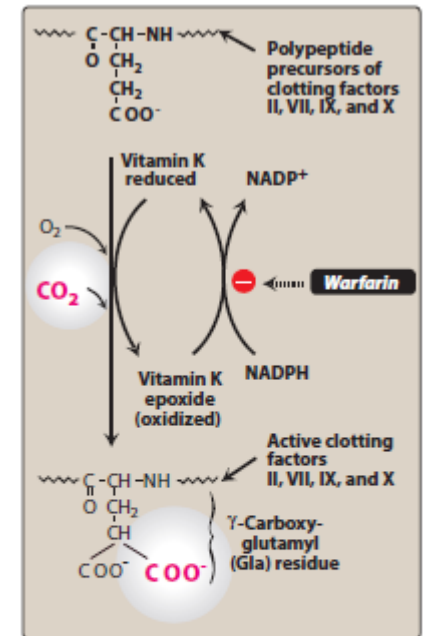


Figure 22.16


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 DVT or PE 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

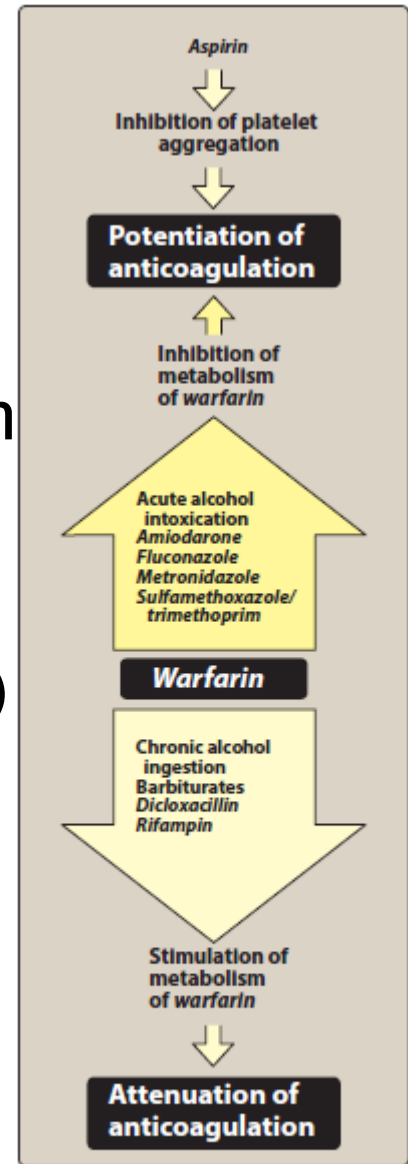
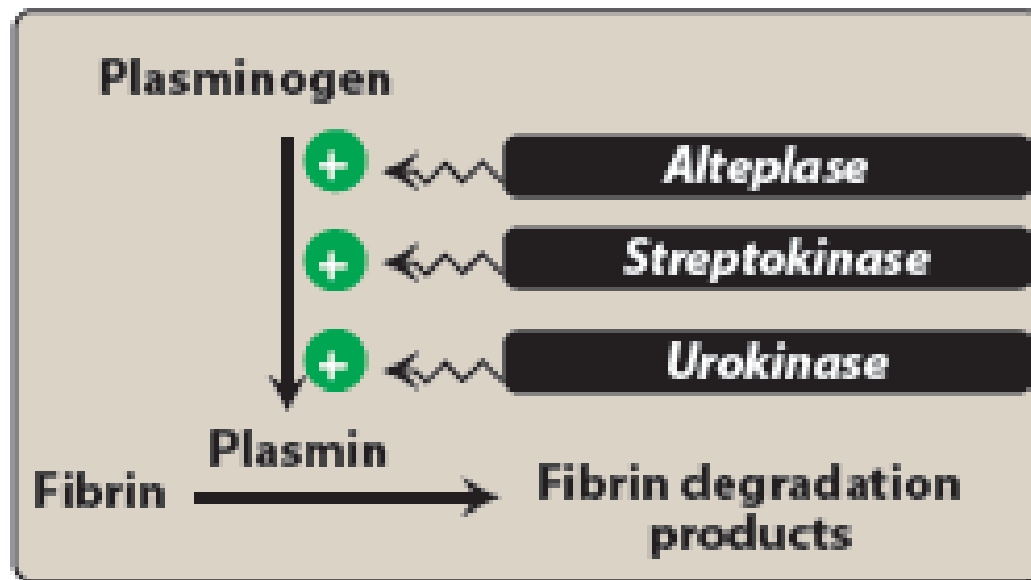


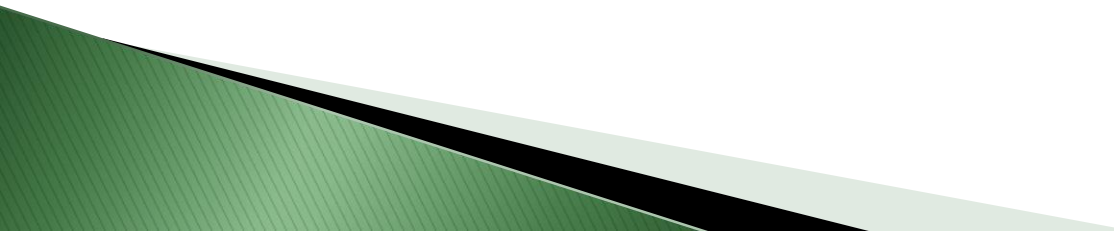
Figure 22.17
Drugs affecting the anticoagulant effect of warfarin.

Thrombolytic agents

- ▶ Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin 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

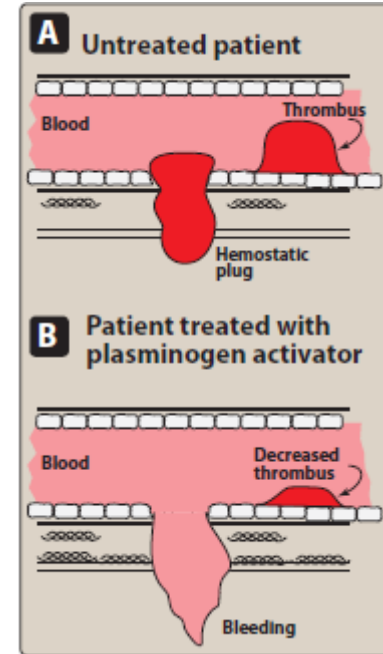
- ▶ Mechanism of action: Act either directly or indirectly to convert plasminogen to plasmin, which cleaves fibrin, thus lysing thrombi
 - ▶ Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation
 - ▶ Increased local thrombi may occur as the 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 plasmin
- ▶ 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 ischemic stroke onset 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 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

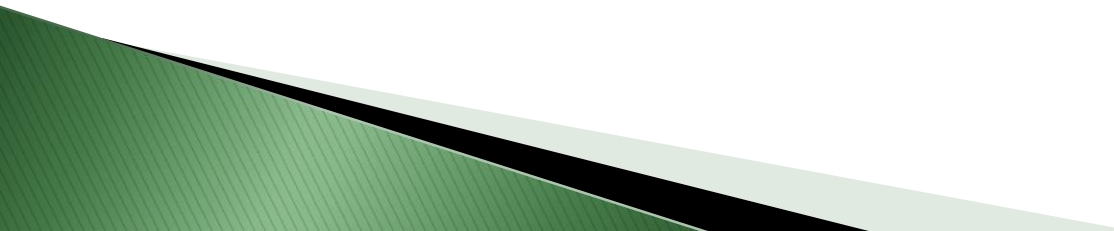
▶ Aprotinin

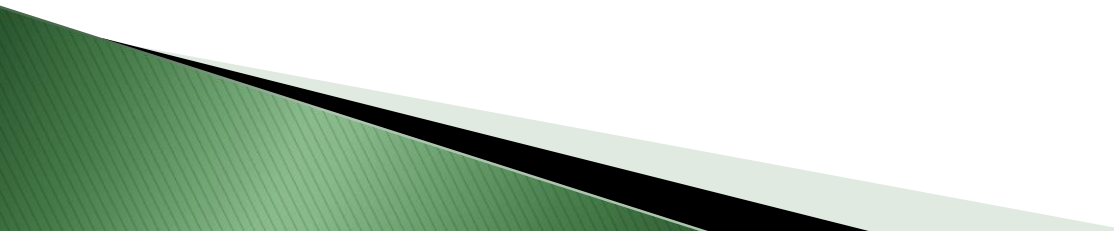
- Stops bleeding by blocking plasmin
- Adverse effects:
 - Renal dysfunction
 - Hypersensitivity (anaphylactic) reactions

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

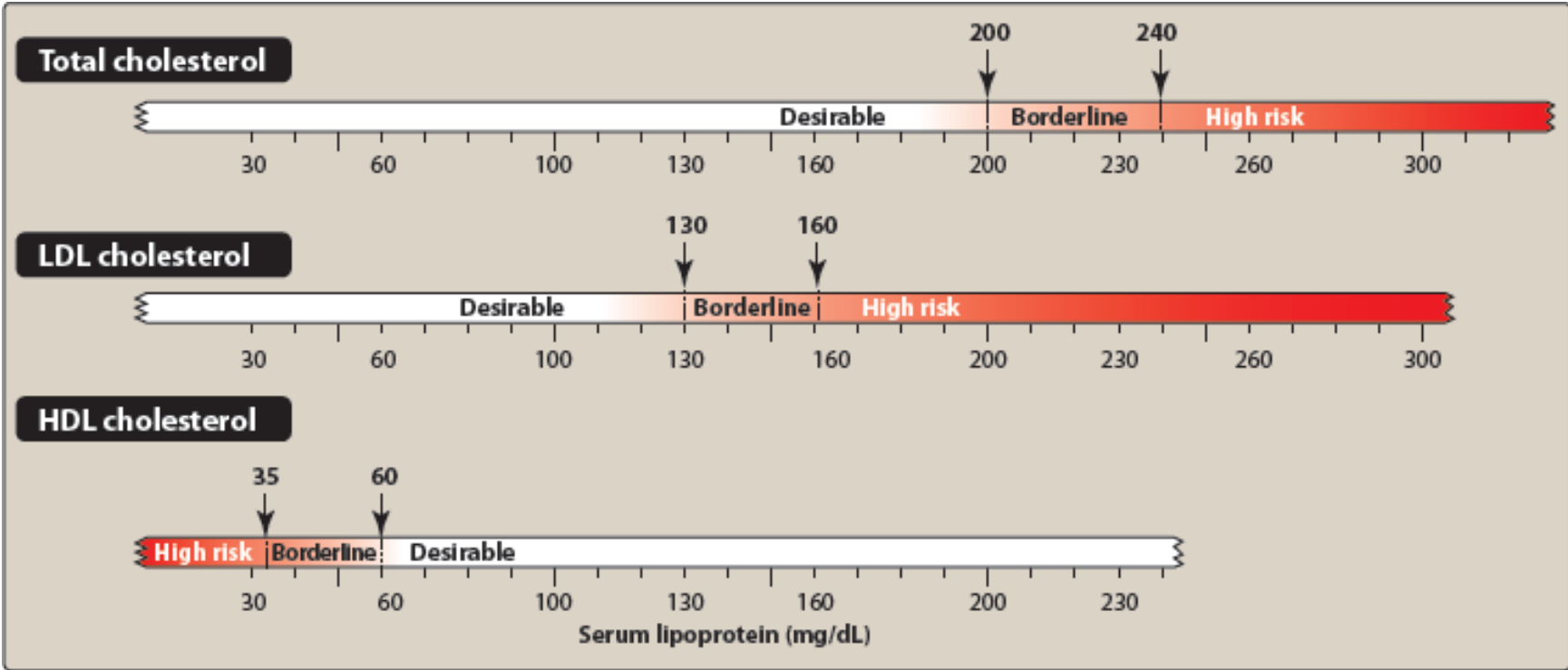
Serum levels

▶ Triglycerides

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

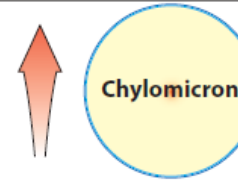
▶ HDL

- 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)



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.



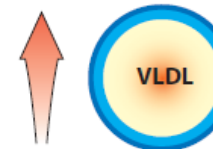
Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- 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.



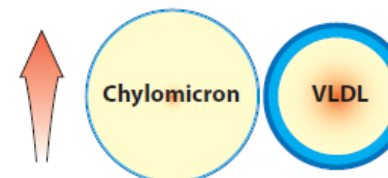
Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- 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

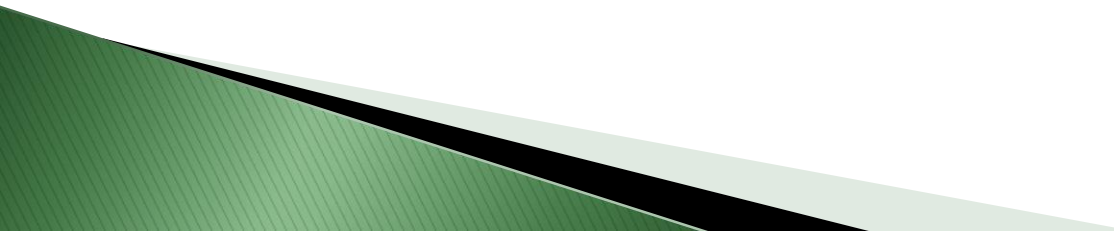
HMG CoA reductase inhibitors

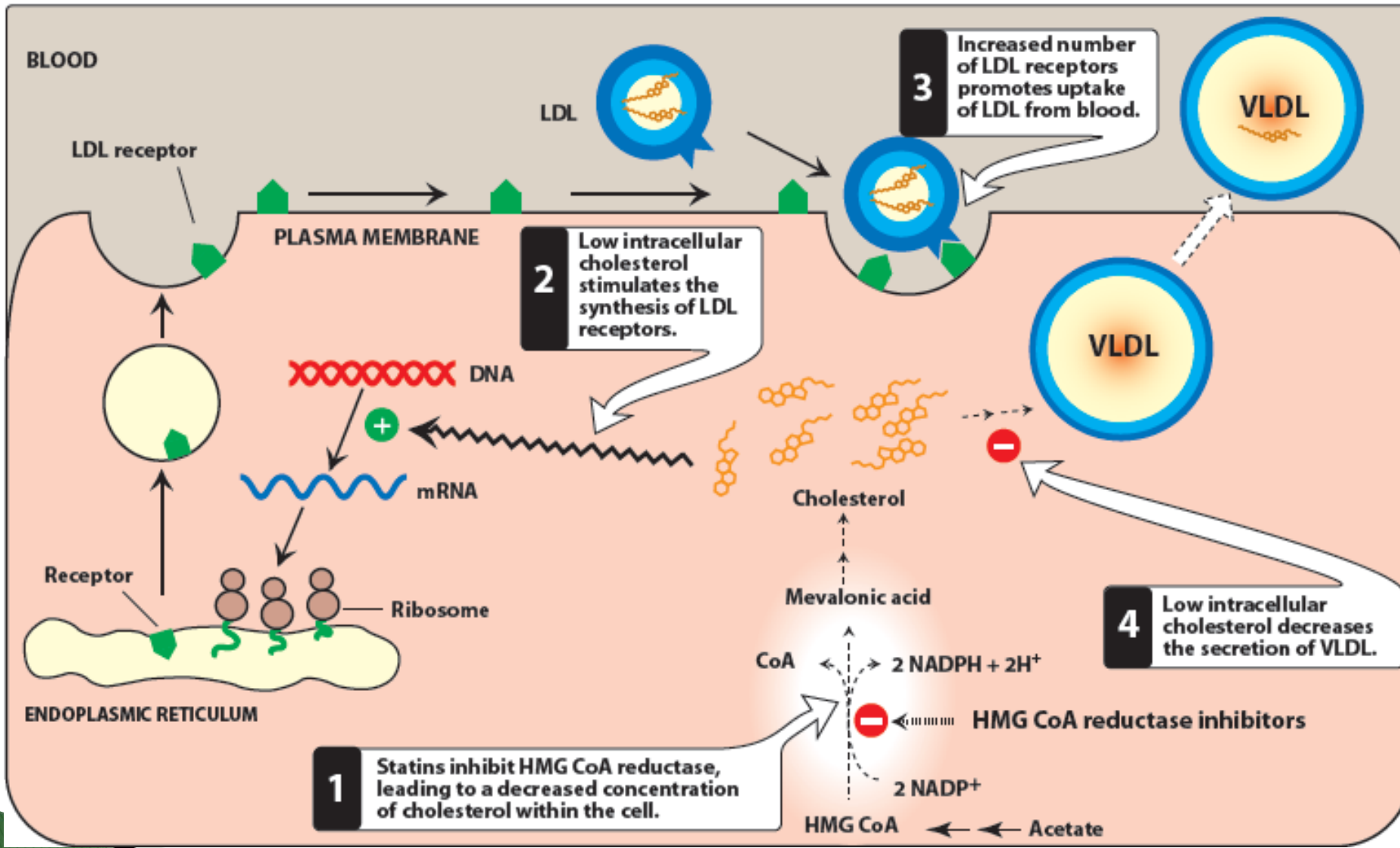
- ▶ Commonly known as statins
- ▶ Include
 - Atorvastatin
 - Fluvastatin
 - Simvastatin
 - Pravastatin
 - Rosuvastatin
 - Pitavastatin

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

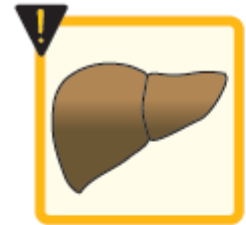
- ▶ The dominant effect is on the liver because statins undergo a marked first-pass extraction by the liver
 - ▶ Pitavastatin, rosuvastatin and atorvastatin are the most potent
 - ▶ Effective in lowering plasma cholesterol levels in all types of hyperlipidemias
 - ▶ Patients who are homozygous for familial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



Characteristic	<i>Atorvastatin</i>	<i>Fluvastatin</i>	<i>Lovastatin</i>	<i>Pitavastatin</i>	<i>Pravastatin</i>	<i>Rosuvastatin</i>	<i>Simvastatin</i>
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

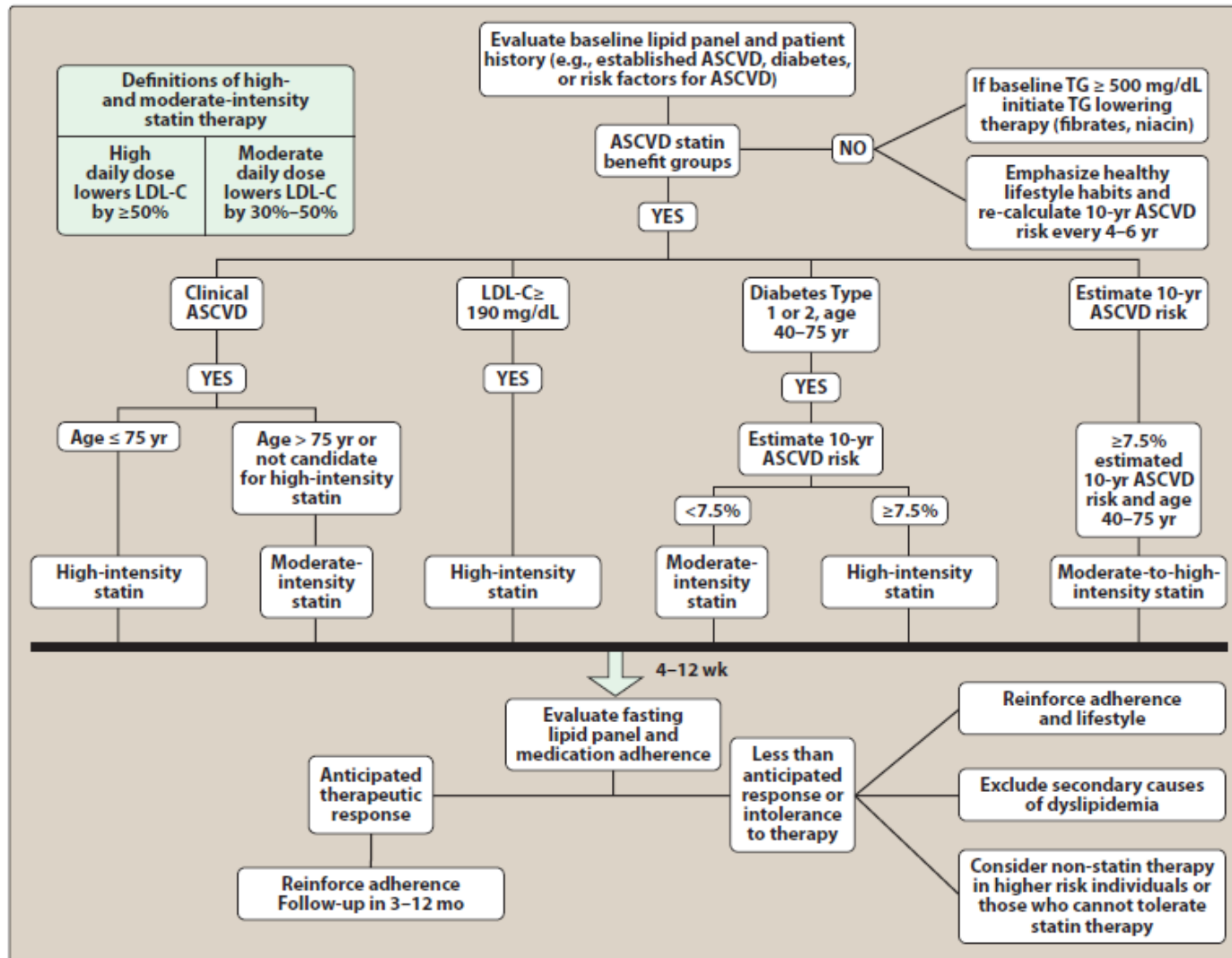
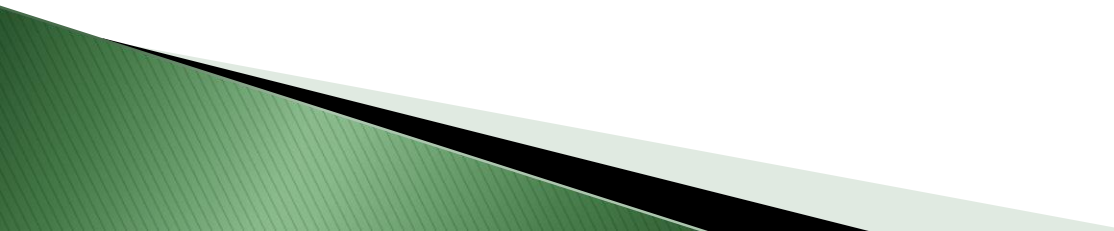


Figure 23.4

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

Niacin (nicotinic acid)

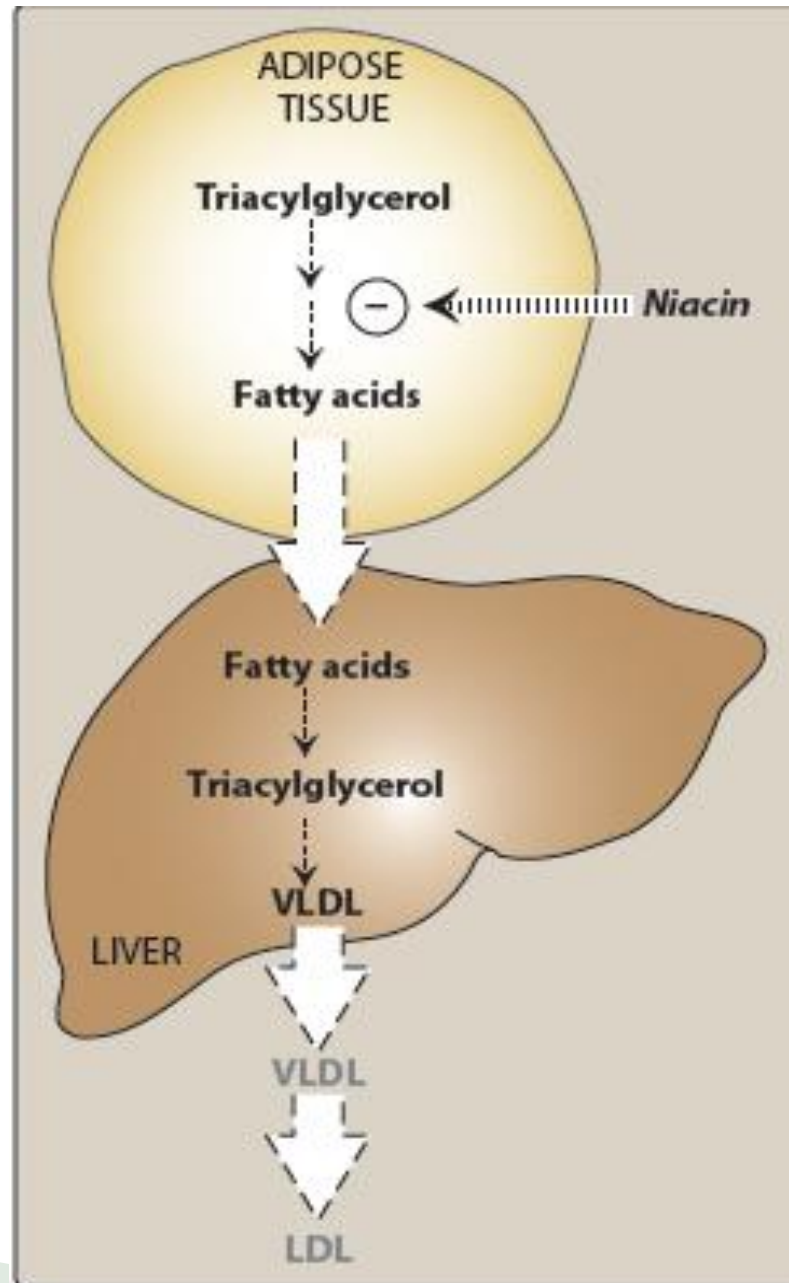
- ▶ The most effective agent for increasing HDL (the “good” cholesterol carrier) levels
 - ▶ Can Reduce LDL (the “bad” cholesterol carrier) levels
 - ▶ Can be used in combination with statins
- 

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

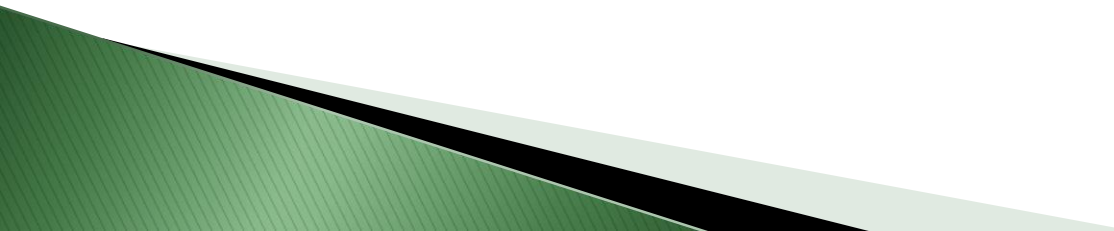
Niacin



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

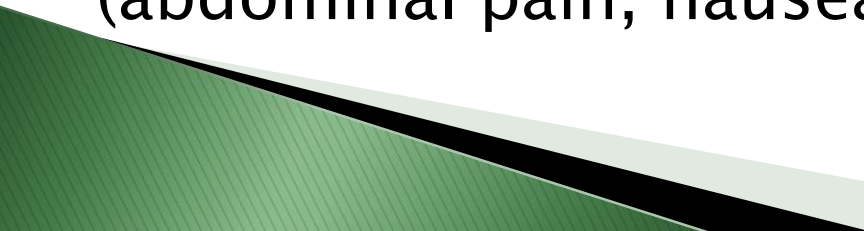
- ▶ No absorption occurs, they are excreted in feces
- ▶ Adverse effects
 - GI disturbances (constipation, nausea, and flatulence)
 - Impaired absorption of fat soluble vitamins (A, D, E, &K)
- ▶ Drug interactions:
 - Cholestyramine and colestipol interfere with the intestinal absorption of many drugs (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

▶ Ezetimibe

- 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

