- Drugs affecting the blood (part 2)
- Antihyperlipidemic drugs

Lecture 11

College of Pharmacy

By:

Assist. Prof. Dr. Rafat Abdulhassan Mohammed Jawad

B. Argatroban

Argatroban is a **synthetic parenteral anticoagulant** that is derived from L-arginine. It is a **direct thrombin inhibitor**. Argatroban is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT, and it is also approved for use during PCI in patients who have or are at risk for developing HIT.

C. Bivalirudin and desirudin

Bivalirudin and desirudin are **parenteral anticoagulants** that are analogs of hirudin, a **thrombin inhibitor** derived from saliva of the medicinal leech. These drugs are selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin.

D. Fondaparinux

Fondaparinux is **a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa**. By selectively binding to antithrombin III, fondaparinux potentiates (300- to 1000-fold) the innate neutralization of factor Xa by antithrombin III. Fondaparinux is approved for use in the treatment of DVT and PE and for the prophylaxis of venous thromboembolism in the setting of orthopedic and abdominal surgery.

➢ Vitamin K Antagonists

Coumarin anticoagulants owe their action to the ability to **antagonize the cofactor functions of vitamin K.**

A. Warfarin

1. Mechanism of action

- Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver.
- These factors undergo vitamin K–dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ-carboxyglutamic acid residues (Figure 1).
- Vitamin K levels in humans are maintained by the action of the enzyme Vitamin K reductase which 'recycles' Vitamin K. Warfarin inhibits Vitamin K reductase thus prevents the activation of the clotting factors

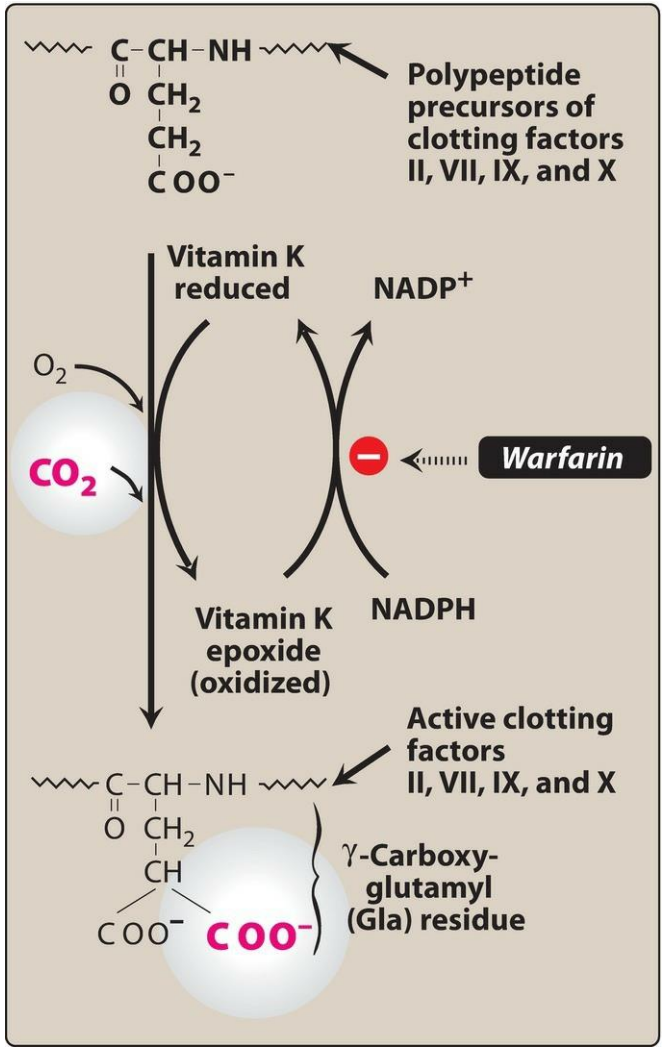


Figure 1: Mechanism of action of warfarin. NADP+ = oxidized form of nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

- Warfarin treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient γ-carboxyglutamyl side chains.
- Unlike heparin, the anticoagulant effects of warfarin are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours.
- The anticoagulant effects of warfarin can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours.

2. Therapeutic use

- Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome.
- It is also used for prevention of venous thromboembolism following orthopedic surgery.

3. Pharmacokinetics

- Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation).
- Warfarin is highly bound to plasma albumin.

- Warfarin readily crosses the placental barrier.
- The mean half-life of warfarin is approximately 40 hours, but this value is highly variable among individuals.
- Warfarin is metabolized by the CYP450 system (mainly CYP2C9) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect; see figure 2.

4. Adverse effects

- The principal adverse effect of warfarin is bleeding.
- Skin lesions and necrosis are rare complications of warfarin therapy.
- Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with warfarin therapy.
- Warfarin is teratogenic and is contraindicated in pregnancy.

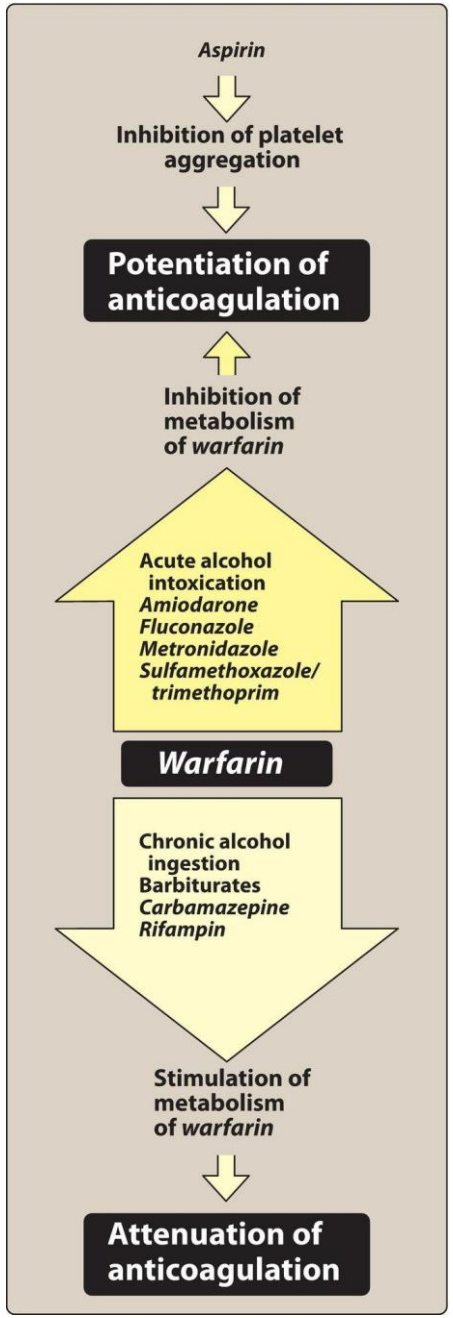


Figure 2: Drugs affecting the anticoagulant effect of warfarin

Direct Oral Anticoagulants

A. Dabigatran

1. Mechanism of action

Dabigatran etexilate is an **oral direct thrombin inhibitor**. Both clot-bound thrombin and free thrombin are inhibited by dabigatran.

2. Therapeutic use

- Dabigatran is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- It may also be used in the treatment of DVT and PE in patients who have already received parenteral anticoagulants and as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE.
- The drug is contraindicated in patients with mechanical prosthetic heart valves and is not recommended in patients with bioprosthetic heart valves.

3. Pharmacokinetics

It is administered orally; and hydrolyzed to the active drug, dabigatran, by various plasma esterases. It is a substrate for P-glycoprotein (P-gp) and is eliminated renally.

4. Adverse effects

- The major adverse effect, like other anticoagulants, is bleeding.

- Dabigatran should be used with caution in renal impairment or in patients over the age of 75, as the risk of bleeding is higher in these groups. Idarucizumab may be used to reverse bleeding in severe cases.
- GI adverse effects are common with dabigatran and may include dyspepsia, abdominal pain, esophagitis, and GI bleeding.
- Abrupt discontinuation should be avoided, as patients may be at increased risk for thrombotic events.

B. Direct oral factor Xa inhibitor

Apixaban, betrixaban, edoxaban, and rivaroxaban are **oral inhibitors of factor Xa**. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin.

➢ Thrombolytic Drugs

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

Common characteristics of thrombolytic agents

1. Mechanism of action

The thrombolytic agents act either **directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi** (Figure 3).

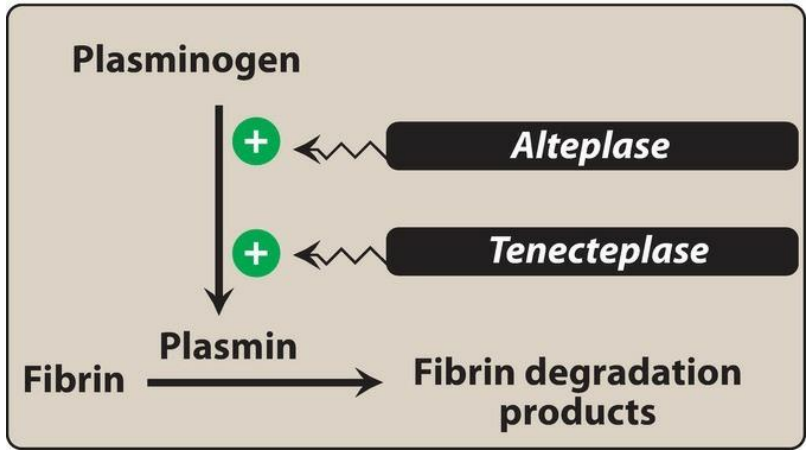


Figure 3: Activation of plasminogen by thrombolytic drugs

- Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis.

2. Therapeutic use

- Originally used for the treatment of DVT and serious PE, thrombolytic drugs are currently used less frequently because of tendency to cause serious bleeding.
- Thrombolytic agents are usually administered intravenously.
- Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions.
- They are also used to dissolve clots that result in strokes.

3. Adverse effects

- Thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major adverse effect.
- These drugs are contraindicated in pregnancy and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.

Alteplase and tenecteplase

- Alteplase (formerly known as tissue plasminogen activator or tPA).
- Tenecteplase with a longer half-life and greater binding affinity for fibrin than alteplase.
- Aoflteplase is said to be “fibrin selective” at low doses; and it is approved for the treatment of MI, massive PE, and acute ischemic stroke.
- Tenecteplase is approved only for use in acute MI.
- Alteplase has a very short half-life (5 to 30 minutes), and therefore, a portion the total dose is injected intravenously as a bolus, and the remaining drug is administered over 1 to 3 hours, depending on the indication.
- Tenecteplase has a longer half-life and, therefore, may be administered as an intravenous bolus.
- Alteplase may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

➢ Drugs Used to Treat Bleeding

- Bleeding problems may have their origin in **naturally occurring pathologic conditions, such as hemophilia**, or **as a result of fibrinolytic states that may arise after surgery**.
- The **use of anticoagulants may also give rise to hemorrhage.**
- **Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding** (Figure 4).

- Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections.
- Blood transfusion is also an option for treating severe hemorrhage.

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
Idarucizumab	*Dabigatran*	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis	PT/INR

Figure 4: Summary of drugs used to treat bleeding. aPTT = activated partial thromboplastin time, CBC = complete blood count, CVA = cerebrovascular accident, INR = international normalized ratio, PT = prothrombin time.

➢ Agents Used to Treat Anemias

MEDICATION	ADVERSE EFFECTS	DRUG INTERACTIONS	MONITORING PARAMETERS
TREATMENT OF ANEMIA			
Cyanocobalamin/B_{12}	Injection site pain Arthralgia Dizziness Headache Nasopharyngitis Anaphylaxis	Proton pump inhibitors—may decrease oral absorption of vitamin B_{12}	Vitamin B_{12} Folate Iron
Erythropoietin/epoetin alfa	Edema Pruritus Nausea/vomiting Hypertension CVA Thrombosis	*Darbepoetin alfa*—duplication of therapy can lead to increased adverse events	H/H Serum ferritin Blood pressure
Darbepoetin alfa	Edema Dyspnea Hypertension CVA Thrombosis	*Epoetin alfa*—duplication of therapy can lead to increased adverse events	H/H Serum ferritin Blood pressure
Folic acid	Bad taste in mouth Nausea Confusion Irritability	*Cholestyramine*—may interfere with absorption	CBC Serum folate
Iron	Pruritus N/V/D Headache Anaphylaxis	*Deferoxamine*—chelates iron *Dimercaprol*—chelates iron	H/H Serum iron TIBC Transferrin Reticulocyte count
TREATMENT OF SICKLE CELL ANEMIA			
Hydroxyurea	Myelosuppression Skin ulcer Secondary leukemia Elevated liver enzymes	HIV medications—*hydroxyurea* can decrease CD4 counts Salicylates—increase bleeding risk *Probenecid*—↑ uric acid	CBC

Figure 5: Medications for the management of anemia. CBC = complete blood count; CVA = cerebrovascular accident; H/H = hemoglobin and hematocrit; N/V/D = nausea/vomiting/diarrhea; TIBC = total iron binding capacity.

IRON FORMULATION	BRAND NAME(S)	ELEMENTAL IRON (%)	NOTES
Ferrous gluconate	Fergon, Ferro-Tab	12	• Less elemental iron, but similar tolerability to *ferrous sulfate*
Ferric ammonium citrate	Iron citrate	18	• Less bioavailable than ferrous salts • Must be reduced to ferrous form in the intestine
Ferrous sulfate	Fer-in-Sol, Feratab	20	• Most common oral iron supplement • Low cost with good effectiveness and tolerability
Ferrous sulfate, anhydrous	Slow-Fe	30	• Extended-release formulation of *ferrous sulfate* (once-daily dosing) • Higher cost than *ferrous sulfate*
Ferrous fumarate	Ferretts, Ferrimin, Hemocyte	33	• Similar effectiveness and tolerability to *ferrous sulfate* • Almost no taste compared to other iron salts
Carbonyl iron	Icar, Feosol	100	• Microparticles of purified iron • Dissolves in the stomach to form HCl salt to be absorbed • Less toxic than iron salts due to slower absorption rate (continued iron release for 1 to 2 days)
Polysaccharide-iron complex	Bifera, NovaFerrum, Nu-Iron 150	100	• Tasteless and odorless • Once-daily elemental iron dose similar to twice-daily *ferrous sulfate*

Figure 6: Characteristics of various iron formulations.

➢ Antihyperlipidemic drugs

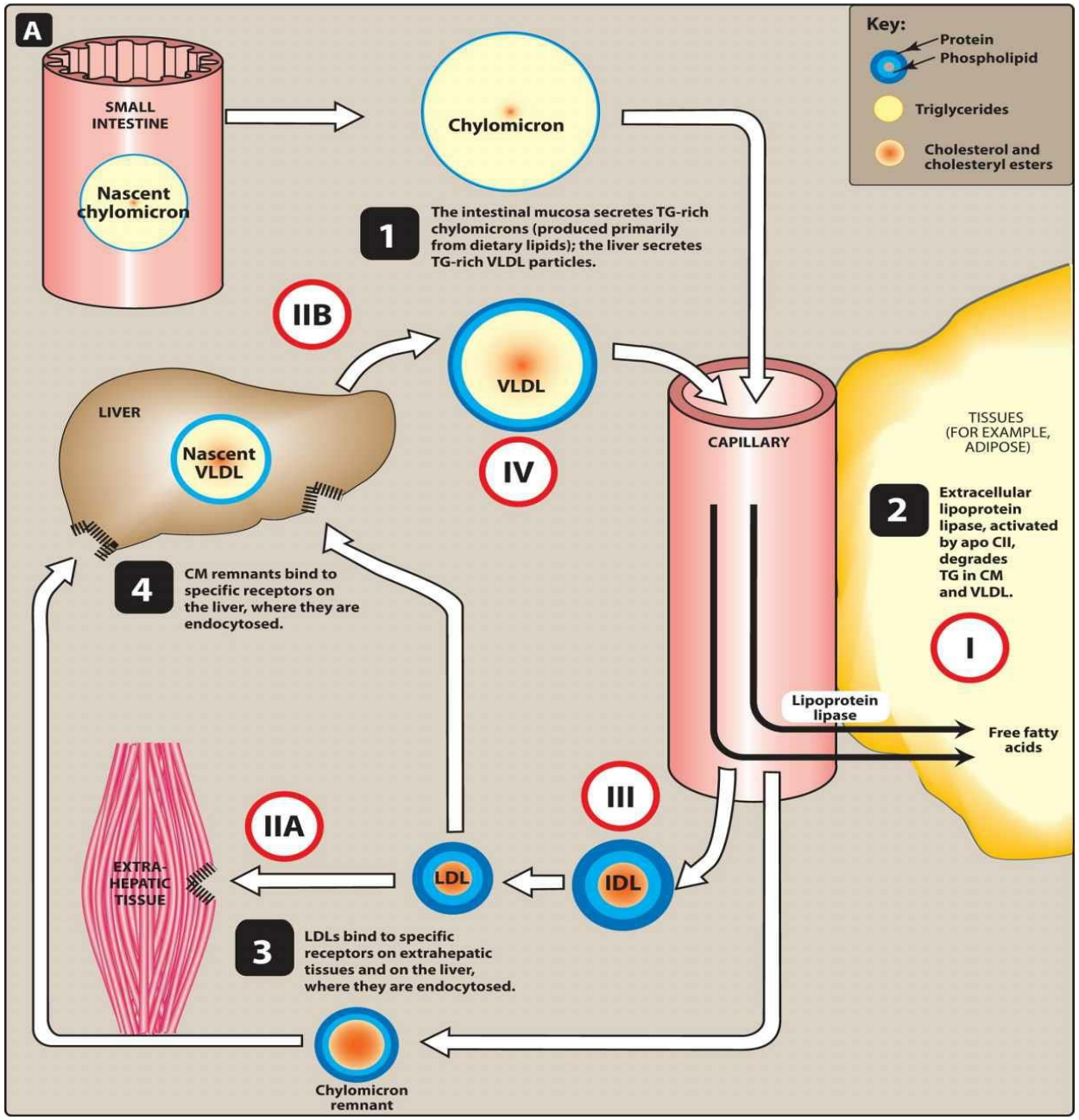
- Coronary heart disease (CHD) is the leading cause of death worldwide.
- **CHD is correlated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, and low levels of high-density lipoprotein cholesterol (HDL-C).**

- Elevated cholesterol levels (hyperlipidemia) may be due to:
  - Lifestyle factors (for example, lack of exercise or diet containing excess saturated fats).
  - Inherited defect in lipoprotein metabolism
  - Or, more commonly, from a combination of genetic and lifestyle factors.

- Antihyperlipidemic drugs (Figure 7) are often taken indefinitely to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) in select patients and to control plasma lipid levels.

HMG CoA REDUCTASE INHIBITORS (STATINS)
Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin ALTOPREV
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR
NIACIN
Niacin NIASPAN, SLO-NIACIN
FIBRATES
Gemfibrozil LOPID
Fenofibrate TRICOR, TRIGLIDE
BILE ACID SEQUESTRANTS
Colesevelam WELCHOL
Colestipol COLESTID
Cholestyramine PREVALITE, QUESTRAN
CHOLESTEROL ABSORPTION INHIBITOR
Ezetimibe ZETIA
OMEGA-3 FATTY ACIDS
Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, VARIOUS OTC PREPARATIONS
Icosapent ethyl VASCEPA
PCSK9 INHIBITORS
Alirocumab PRALUENT
Evolocumab REPATHA

Figure 7: Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3methylglutaryl coenzyme A; OTC = over-the-counter; PCSK9 = proprotein convertase



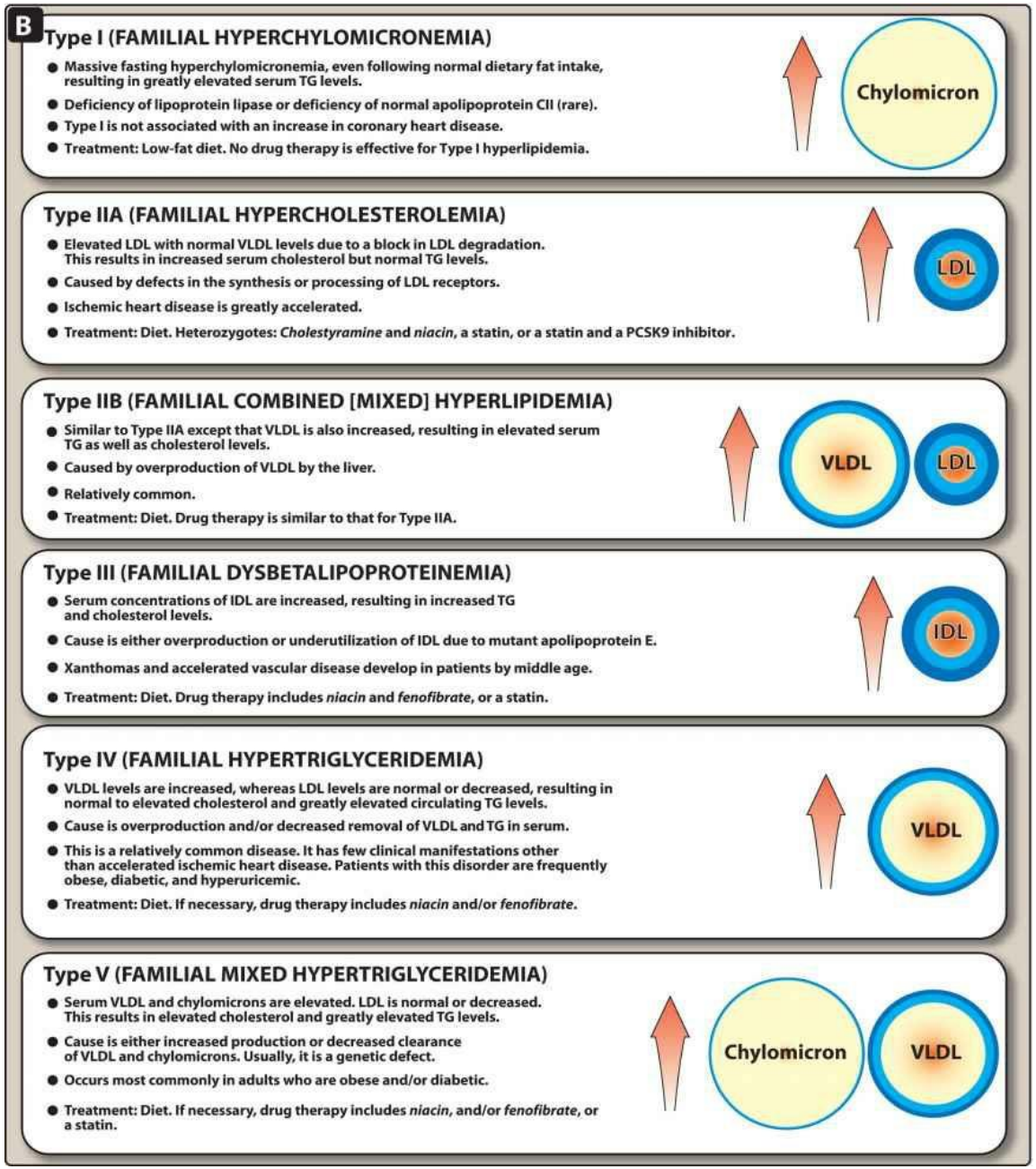


Figure 8: Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. apo CII = apolipoprotein CII found in chylomicrons and VLDL; CM = chylomicron; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin kexin type 9; TG = triglyceride; VLDL = very–low-density lipoprotein.

Drugs for Hyperlipidemia

A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins)

1. Mechanism of action

- **Lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin** are **competitive inhibitors of HMG CoA reductase**, **the rate-limiting step in cholesterol synthesis.**
- Rosuvastatin and atorvastatin are the most potent LDL-C lowering statins, followed by pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin.
- The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL-C in some patients.

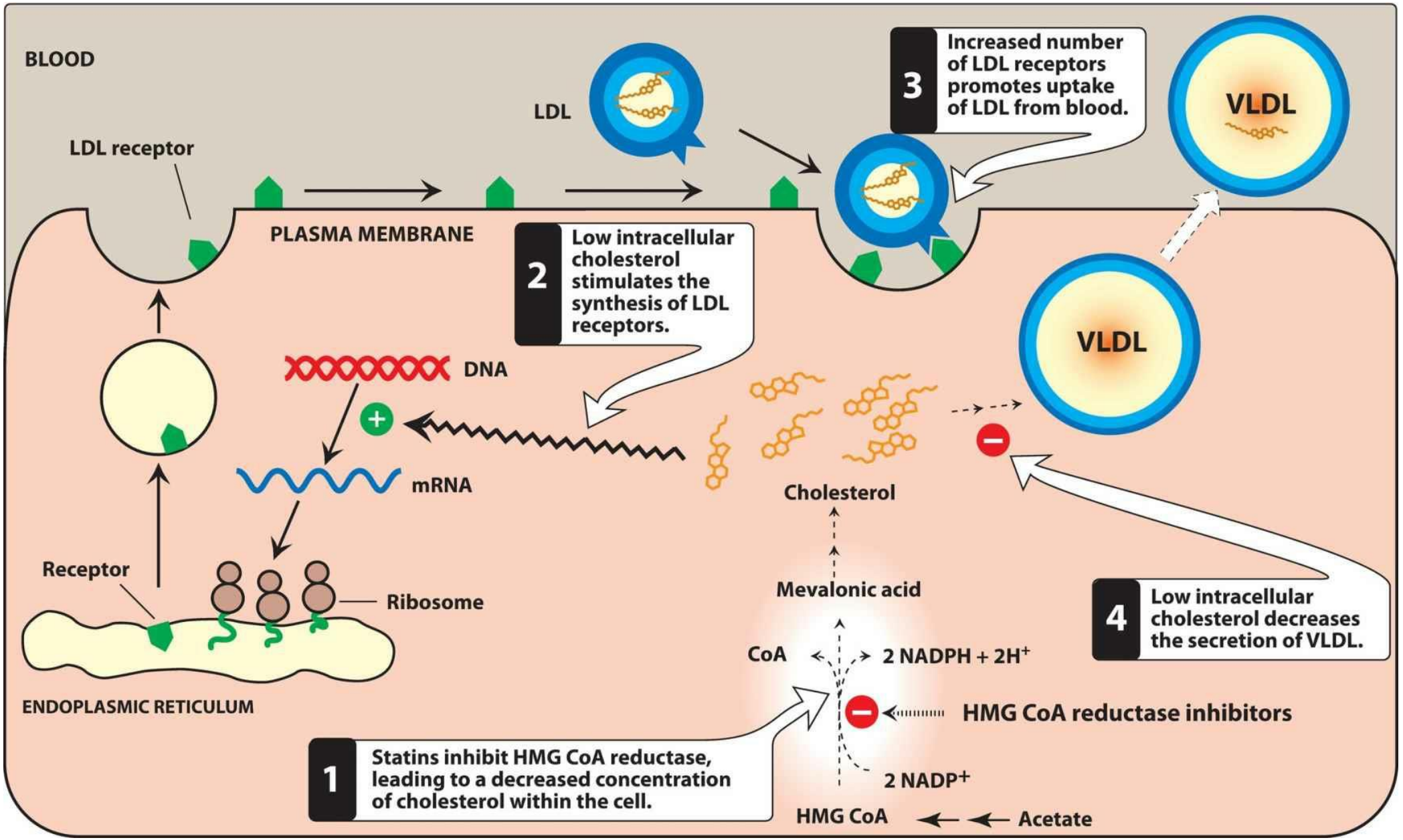


Figure 9: Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase by the statin drugs. LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.

2. Therapeutic uses

- These drugs are used to lower the risk of ASCVD events for patients in the four statin benefit groups.
- Statins are effective in lowering plasma cholesterol levels in all types of hyperlipidemias.
- However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.

3. Pharmacokinetics

- Lovastatin and simvastatin are lactones that are hydrolyzed to the active drug.
- The remaining statins are all administered in their active form.
- Absorption of the statins is variable (30% to 85%) following oral administration.
- All statins are metabolized by cytochrome P450 (CYP450) isoenzymes in the liver, except pravastatin.
- Excretion takes place principally through bile and feces, but some urinary elimination also occurs.

4. Adverse effects

- Elevated liver enzymes may occur with statin therapy.
- The adverse effects of these drugs include myositis, rhabdomyolysis, anxiety, irritability, hepatotoxicity, and elevations in aminotransferases.
- Plasma creatine kinase levels should be determined in patients with muscle complaints. Drug interaction occurs with other drugs.
- These drugs are contraindicated during pregnancy, lactation, and active liver disease.

B. Niacin (nicotinic acid)

- Niacin reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C.
- It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day.
- Niacin can be used in combination with statins.

1. Mechanism of action

- At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids (Figure 10).
- Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

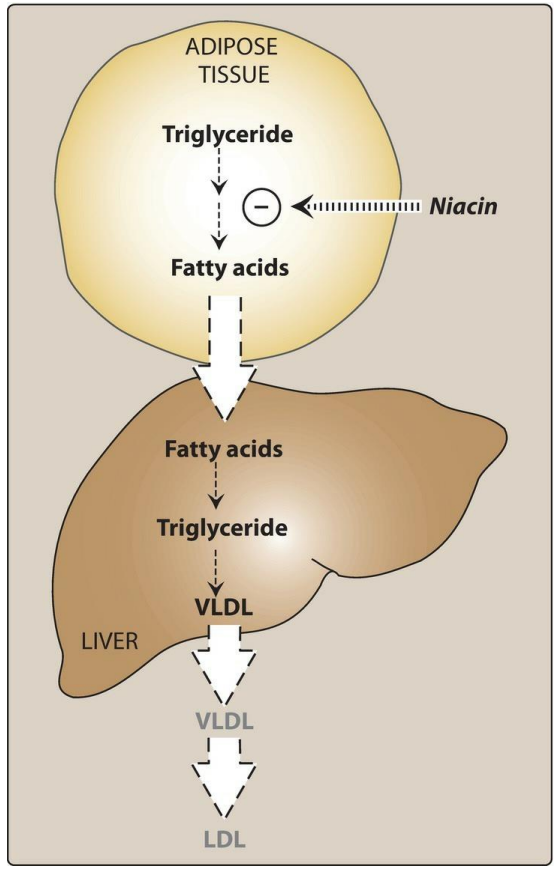


Figure 10: Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic very–low-density lipoprotein (VLDL) synthesis and production of low-density lipoprotein (LDL) in the plasma.

2. Therapeutic uses

- It is useful in the treatment of familial hyperlipidemias.
- It is also used to treat other severe hypercholesterolemias, often in combination with other agents.

3. Pharmacokinetics

- Niacin is administered orally.
- It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD).
- Niacin, its nicotinamide derivative, and other metabolites are excreted in the urine.

4. Adverse effects

- The most common adverse effects of niacin are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus.
- Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin-mediated.
- Some patients also experience nausea and abdominal pain.
- Niacin inhibits tubular secretion of uric acid and, thus, predisposes patients to hyperuricemia and gout.
- Impaired glucose tolerance and hepatotoxicity have also been reported.
- The drug should be avoided in active hepatic disease or in patients with an active peptic ulcer.

C. Fibrates

Fenofibrate and gemfibrozil are derivatives of **fibric acid that lower serum triglycerides and increase HDL-C.**

1. Mechanism of action

- Fibrates stimulate the activity of peroxisome proliferating activating receptors (PPARs), are members of nuclear receptor (See, figure 11).
- Fibrates reduce hepatic synthesis of cholesterol, which further reduces plasma triglycerides.
- Fibrates also increase HDL-C by increasing the expression of apo AI and apo AII.
- Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.

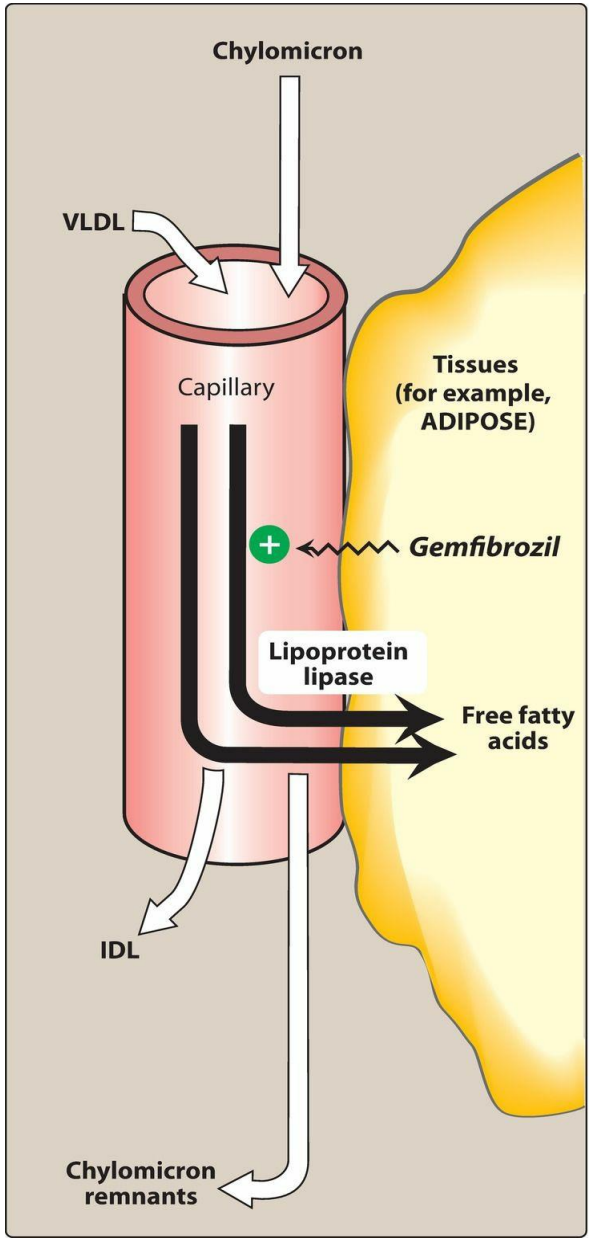


Figure 11: Activation of lipoprotein lipase by gemfibrozil. VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein.

2. Therapeutic uses

The fibrates are used in the treatment of hypertriglyceridemias. They are particularly useful in treating type III hyperlipidemia (dysbetalipoproteinemia), in which intermediate-density lipoprotein particles accumulate.

3. Pharmacokinetics

Gemfibrozil and fenofibrate are completely absorbed after oral administration and distribute widely, bound to albumin. Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates.

4. Adverse effects

- The most common adverse effects are mild gastrointestinal (GI) disturbances.
- There is a predisposition to form gallstones.
- Myositis can occur, and muscle weakness or tenderness should be evaluated.
- Myopathy and rhabdomyolysis have been reported in patients taking gemfibrozil and statins together.
- The use of gemfibrozil is contraindicated with simvastatin, and should be avoided with the use of any statin.
- Both fibrates may increase the effects of warfarin.
- Fibrates should not be used in patients with severe hepatic or renal dysfunction, in patients with preexisting gallbladder disease or biliary cirrhosis.

D. Bile acid sequestrants

Bile acid sequestrants (resins) **have significant LDL-C lowering effects**, although **the benefits are less than those observed with statins.**

1. Mechanism of action

- Cholestyramine, colestipol, and colesevelam are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 12).
- The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration.
- This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile.
- Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol containing LDL-C particles, leading to a decrease in plasma LDL-C.

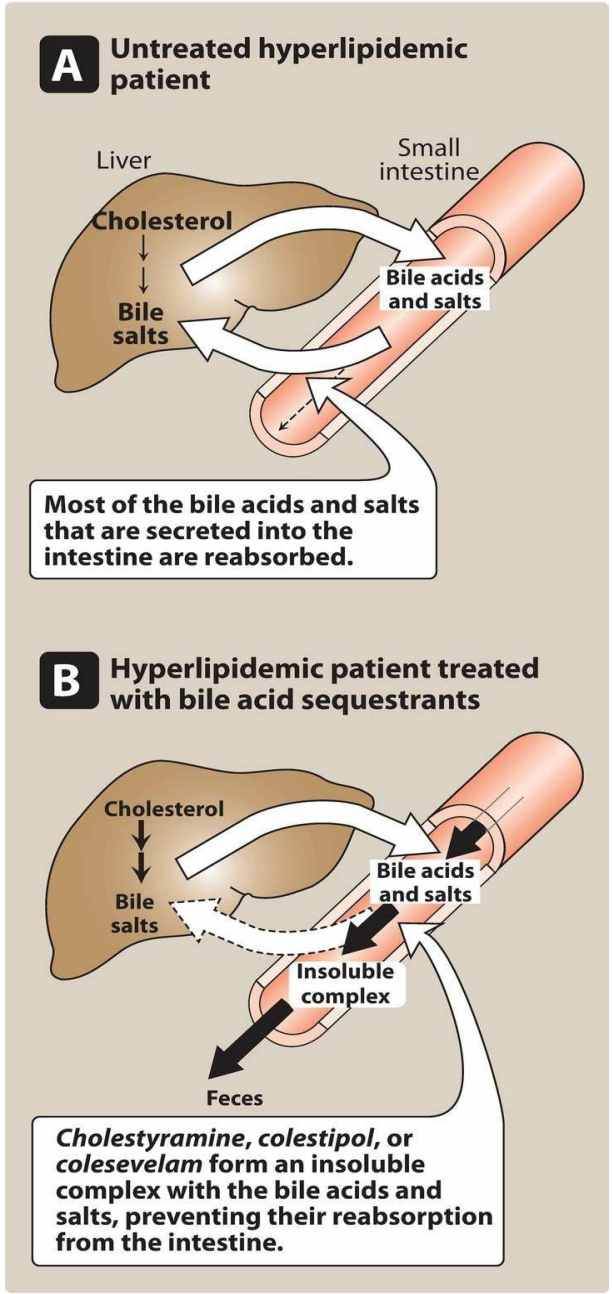


Figure 12: Mechanism of bile acid sequestrants.

2. Therapeutic uses

- The bile acid sequestrants are useful for treating type IIA and type IIB hyperlipidemias.
- Cholestyramine can also relieve pruritus.
- Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects.

3. Pharmacokinetics

Bile acid sequestrants are insoluble in water and have large molecular weights. After oral administration, they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.

4. Adverse effects

- The most common adverse effects are GI disturbances, such as constipation, nausea, and flatulence. Colesevelam has fewer GI side effects than other bile acid sequestrants.
- These agents may impair the absorption of the fat-soluble vitamins and they interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone).
- Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid sequestrants.
- These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (greater than 400 mg/dL).

E. Cholesterol absorption inhibitor

- **Ezetimibe selectively inhibits absorption of dietary and biliary 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.
- Ezetimibe is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk, or in statin-intolerant patients.
- Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion.
- Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.
- Adverse effects are uncommon with the use of ezetimibe.

F. Proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9)

Figure 13.shows the mechanism of action of PCSK9

- **Alirocumab and evolocumab** are PCSK9 inhibitors, which are fully humanized monoclonal antibodies.
- These agents are used in addition to maximally tolerated statin therapy in patients with heterozygous or homozygous familial hypercholesterolemia
- In patients with clinical ASCVD who require additional LDL-C lowering.
- When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%).

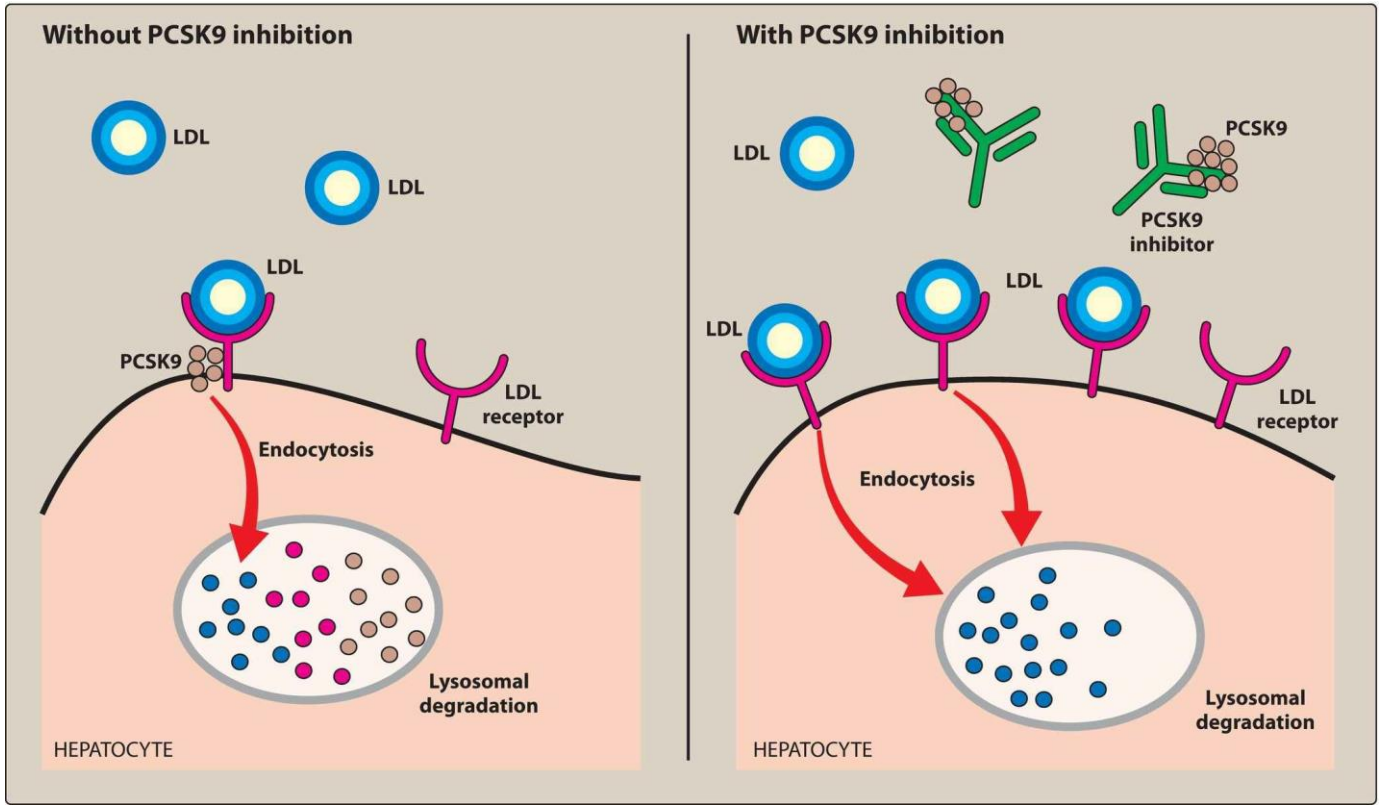


Figure 13: Mechanism of action of PCSK9 inhibitors

- They may also be considered for patients with high ASCVD risk and statin intolerance.
- PCSK9 inhibitors are only available as subcutaneous injections and are administered every two to four weeks.
- Monoclonal antibodies are not eliminated by the kidneys and have been used in dialysis patients or those with severe renal impairment.
- The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.

G. Omega-3 fatty acids

- **Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering.** Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver.
- Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation.
- Icosapent ethyl is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C.
- Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with elevated triglycerides (≥500 mg/dL).
- They have not been shown to reduce cardiovascular morbidity and mortality.
- The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelet agents.

H. Combination drug therapy

- It is sometimes necessary to **use two antihyperlipidemic drugs to achieve treatment goals**.
- Patients with established ASCVD, an elevated 10-year risk of ASCVD, or those that do not achieve intended LDL-C reductions on maximally tolerated statin therapy may be considered for combination therapy.
- Ezetimibe and PCSK9 inhibitors can be considered for add-on therapy, since there is evidence that these combinations further reduce ASCVD events in patients already taking statin therapy.
- Combination drug therapy is not without risks. Liver and muscle toxicity occur more frequently with lipid-lowering drug combinations.


Thank You!