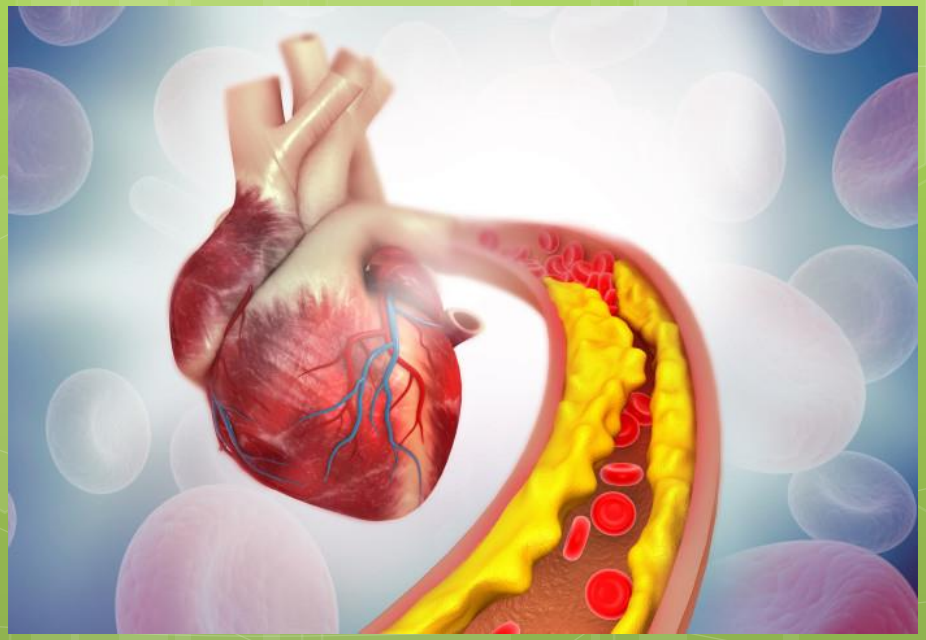

Antihyperlipidemic Drugs

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- Atherosclerosis (ATCS) is a disorder in which lipid deposits on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow, a major contributor in the development of heart disease.
- Lipids are necessary molecules for human life.
- Cholesterol and phospholipids are essential components of cell membranes, and cholesterol is the precursor to steroid compounds that fulfill vital physiologic functions.
- Triglycerides, composed of three fatty acids and glycerol, are oxidized to generate energy for muscle contraction and metabolic reactions.

- Plasma lipids are insoluble in water and must be bound to a lipid-containing protein (lipoprotein) for transportation throughout the body.

- These consist of a central core of hydrophobic lipid (including triglycerides and cholesteryl esters) encased in a hydrophilic coat of polar phospholipid, free cholesterol and **apoprotein**

- Apoproteins bind to specific receptors that mediate uptake of lipoprotein particles into liver, blood or other tissues
- Metabolic disorders that involve elevations in any lipoprotein species are termed hyperlipoproteinemias or hyperlipidemias.

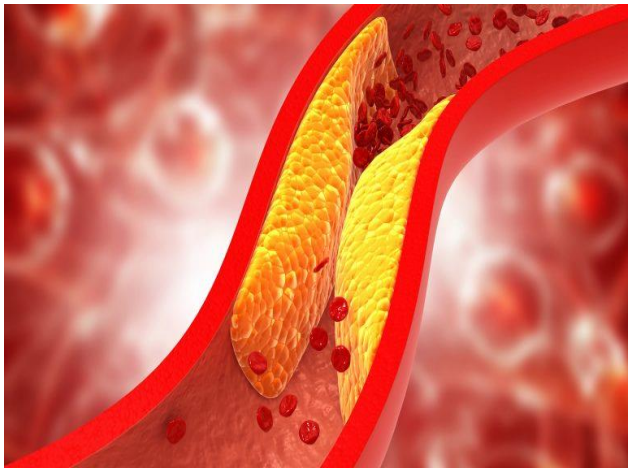
- **Elevated cholesterol levels (hyperlipidemia) may be due to:**
- lifestyle factors (for example, lack of exercise or diet containing excess saturated fats).
- An inherited defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors

Types and Characteristics of Hyperlipoproteinemia

TYPES	INCIDENCE	TOTAL CHOLESTEROL CONCENTRATION (MG/DL)	TRIGLYCERIDE CONCENTRATION (MG/DL)
Homozygous Familial Hyperlipidemia			
Hypercholesterolemia	Rare	>300	<250
Hypertriglyceridemia	Rare	<250	>300
Mixed hyperlipidemia	Rare	>250	>300
Polygenic-Environmental Hyperlipidemia			
Hypercholesterolemia	Common	200–270	<250
Mixed hyperlipidemia	Less common	>200	>300
Secondary Hyperlipidemia			
Caused by alcoholism, diabetes mellitus, uremia, or use of β-adrenoceptor antagonists,* isotretinoin, oral contraceptives, or thiazide diuretics†	Common	Normal or increased†	Increased
Caused by hypothyroidism, nephrotic syndrome, or obstructive liver disease	Less common	Increased	Normal or slightly increased

The clinically important lipoproteins are:

1. Low-density lipoproteins (LDL)
2. Very-low-density lipoprotein (VLDL)
3. Chylomicrons
4. HDL



- **Low-density lipoproteins (LDL):**

✓ Transport cholesterol to the peripheral cells.

✓ When the cells have all the cholesterol they need, the excess cholesterol is discarded into the blood. This can result in an excess of cholesterol, which can penetrate the walls of the arteries, resulting in atherosclerotic plaque formation.

✓ Elevation of the LDL increases the risk for heart disease.

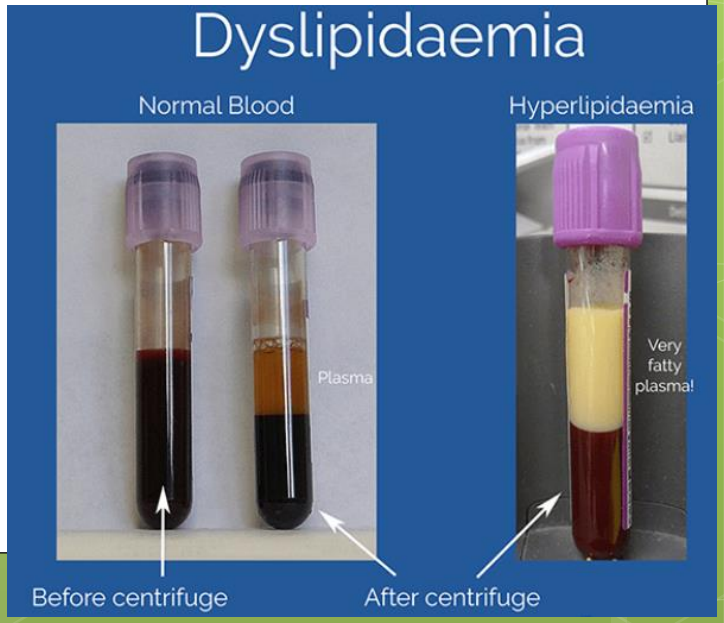
- **Very-Low-Density Lipoprotein (VLDL):** is a carrier for triglycerides to peripheral tissues.
- ✓ VLDL is not directly measured in the blood but is estimated by dividing the triglyceride value by 5 (for example, a triglyceride value of 150 mg/dL correlates to a VLDL of 30).

- **High-density lipoproteins (HDL):**
- ✓ Take cholesterol from the peripheral cells and bring it to the liver (reverse cholesterol transport), where it is metabolised and excreted. by the gallbladder
- ✓ The higher the HDL, the lower the risk for development of ATCS.
- ✓ It is desirable to see an increase in the HDL ("good" lipoprotein) because of the protective nature of its properties against the development of atherosclerosis and a decrease in the LDL

- **Chylomicrons**: are large triglyceride-rich lipoproteins produced in enterocytes from dietary lipids— namely, fatty acids, and cholesterol. Chylomicrons are composed of a main central lipid core that consists primarily of triglycerides, however like other lipoproteins, they carry esterified cholesterol and phospholipids.

- Hyperlipidaemia can be diagnosed by **lipoprotein profile**, which is a laboratory tests used to measure the blood lipid and can provide valuable information on the important cholesterol levels, such as:

1. Total cholesterol
2. LDL (the harmful lipoprotein)
3. HDL (the protective lipoprotein)
4. Triglycerides



Antihyperlipidemic drugs

- lifestyle modifications (such as diet, exercise, and weight loss) , along with drug therapy, can lead to a 30% to 40% reduction in CHD mortality.

- **Drugs for Hyperlipidemia:**

1. HMG-CoA reductase inhibitors
2. Bile acid sequestrants
3. Fibric acid derivatives
4. Niacin
5. Cholesterol absorption inhibitor
6. Proprotein convertase subtilisin kexin type 9 (PCSK9)inhibitors
7. Omega-3 fatty acids

1. HMG CoA reductase inhibitors (Statins):

- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors
- Lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin
- They are first-line treatment for patients with elevated risk of ASCVD to reduce the occurrence of ASCVD events
- Lower LDL-C by 20% to 60%, , resulting in a substantial reduction in coronary events and death from CHD.
- HDL-C levels are increased by up to 10%

- Therapeutic benefits include atherosclerotic plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and vascular anti-inflammatory activity.

Mechanism of action:

- Are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis.
- By inhibiting cholesterol synthesis, they deplete the intracellular supply of cholesterol.
- Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDL-C.
- Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL-C catabolism.
- The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL-C in some patients.
- Rosuvastatin and atorvastatin are the most potent LDL-C lowering statins, followed by pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin.

- [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.]

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	2–3	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

Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Therapeutic uses:

1. Statins are effective in lowering plasma cholesterol levels in all types of hyperlipidemias.
2. Patients with any form of clinical ASCVD
3. Patients with primary LDL-C levels of ≥190 mg/dL
4. Patients with diabetes mellitus, 40 to 75 years of age, with LDL-C levels of 70 to 189 mg/dL
5. Patients without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk ≥7.5%.
6. Patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs

Pharmacokinetics:

1. Lovastatin and simvastatin are inactive prodrugs that are hydrolyzed to the active metabolites.
2. The remaining statins are all administered in their active form.
3. All statins are metabolized by cytochrome P450 (CYP450), except pravastatin.
4. Statins with shorter half-lives are taken in the evening or at bedtime to ensure inhibition of nocturnal cholesterol biosynthesis.
5. Atorvastatin and rosuvastatin can be taken at any time of day.
6. Lovastatin should be taken with the evening meal to facilitate its absorption, whereas the other drugs can be taken without regard to food.
7. Lovastatin and simvastatin cross the blood- brain barrier and can cause sleep disturbances in some patients.
8. Excretion takes place principally through bile and feces, but some urinary elimination also occurs

Adverse effect :

1. Most common: including abdominal cramps, constipation, diarrhea, and heartburn.

2. Elevated liver enzymes : liver function should be evaluated prior to starting therapy or if a patient has symptoms consistent with liver dysfunction as hepatic insufficiency can cause drug accumulation.

3. Myopathy and rhabdomyolysis (disintegration of skeletal muscle), which occur in 0.2% of patients, plasma creatine kinase levels should be determined in patients with muscle complaints, risk factors include:

- ✓ Renal insufficiency
- ✓ Vitamin D deficiency
- ✓ Hypothyroidism
- ✓ Advanced age, female sex

- ✓ Use of drugs that increase the risk of muscle adverse effects, such as azole antifungals, protease inhibitors, cyclosporine, erythromycin, gemfibrozil, or niacin.
- ✓ Simvastatin is metabolized by CYP450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis.

4. The HMG COA reductase inhibitors may **also increase the effect of warfarin.** So, it is important to evaluate the international normalised ratio (INR) when initiating a statin or changing the dosage.

5. These drugs are **contraindicated during pregnancy, lactation, and active liver disease**

2. Fibrates (Fenofibrate, Clofibrate and gemfibrozil):

Are fibric acid derivatives that lower serum triglycerides and increase HDL-C.

Mechanism of action:

- ✓ The peroxisome proliferator-activated receptors {PPARs} are members of the nuclear receptor family that regulate lipid metabolism.
- ✓ PPARs are activated upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs(fibrates) :

1. Fibrates bind to PPARs ⟶ increased expression of lipoprotein lipase ⟶ increased FFAs lipolysis ⟶ decreased TGs synthesis.
2. Fibrates decrease apolipoprotein (apo)CII concentration ⟶ decrease TGs
3. Fibrates also increase HDL-C by increasing the expression of apo AI and apo All.

Therapeutic uses:

1. Hypertriglyceridemias.
2. Type **III hyperlipidemia** (dysbetalipoproteinemia), in which intermediate density lipoprotein(IDL) particles accumulate.
3. Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels

Pharmacokinetics:

- ✓ Gemfibrozil and fenofibrate are completely absorbed after oral administration and distribute widely, bound to albumin.
- ✓ Fenofibrate is a prodrug, which is converted to the active moiety fenofibric acid.
- ✓ Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates.

Adverse effects:

1. The most common adverse effects are **mild gastrointestinal (GI) disturbances.**
2. Because these drugs increase biliary cholesterol excretion, there is a predisposition to form **cholelithiasis (gallstones) or cholecystitis**
3. **Myositis (**inflammation of a voluntary muscle) can occur, and muscle weakness or tenderness should be evaluated (more common in patients with renal insufficiency).
4. **Myopathy and rhabdomyo**lysis have been reported in patients taking gemfibrozil and statins together, So, the use of gemfibrozil is contraindicated with statins
5. Both fibrates may **increase the effects of warfarin**. Therefore, INR should be monitored more frequently
6. Fibrates contrandicated in patients with severe hepatic or renal dysfunction, preexisting gallbladder disease or biliary cirrhosis.

3. Bile acid sequestrants (resins):

Cholestyramine, colestipol, and colesevelam: significant LDL-C lowering effects, although the benefits are less than those observed with statins.

Mechanism of action:

- ✓ are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine.
- ✓ 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
- ✓ intracellular cholesterol concentrations decrease ⟶ up-regulation of cell surface LDL receptors ⟶ increased hepatic uptake of cholesterol-containing LDL-C particles ⟶ decrease in plasma LDL-C.

Therapeutic uses:

1. In treating type IIA and type IIB hyperlipidemia (often in combination with diet or niacin)
2. [Note: In those rare individuals who are homozygous for type IIA and functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.]
3. Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis.
4. Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects
5. The resins have also been used to treat chronic diarrhea due to bile acid malabsorption

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, they are totally excreted in feces.
- Cholestyramine and colestipol are available as a powder for mixing with water or juice just before administration, and cholestyramine is also marketed as a chewable bar.
- To obtain the maximal effect on serum cholesterol levels, these drugs must be taken before each meal and at bedtime.
- Colesevelam is a newer resin available as solid tablets that are usually taken twice daily with meals.

Adverse effects:

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

4. Niacin (nicotinic acid) :

- ✓ Reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C.
- ✓ It also lowers triglycerides by 20% - 35% at typical doses of 1.5 to 3 g/ day.
- ✓ Niacin can be used in combination with statins, and fixed-dose combinations of long-acting niacin with lovastatin and simvastatin are available.

Mechanism of action:

- ✓ Niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids.
- ✓ The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis.
- ✓ Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

Therapeutic uses:

1. It is useful in the treatment of **familial hyperlipidemias**, because niacin lowers plasma levels of both cholesterol and triglycerides,
2. It is also used to treat other severe hypercholesterolemias, often in combination with other agents.

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.
- ✓ [Note: Administration of nicotinamide alone does not decrease plasma lipid levels.]

Adverse effects:

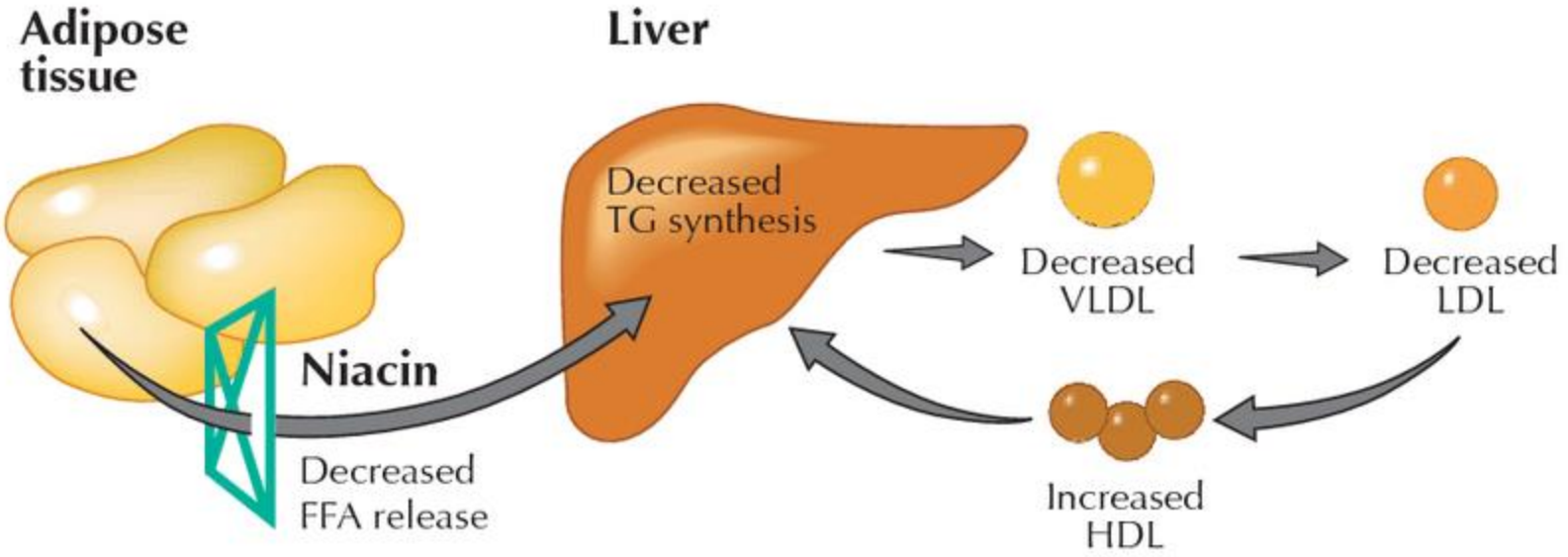
1. The most common adverse effects of niacin are **an intense cutaneous flush** accompanied by an uncomfortable feeling of warmth and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin-mediated.

2. **Nausea and abdominal pain**. Slow titration of the dosage or use of the sustained-release formulation of niacin reduces bothersome initial adverse effects.

3. **Hyperuricemia and gout:** niacin inhibits tubular secretion of uric acid

4. **Impaired glucose tolerance and hepatotoxicity**

5. The drug should be avoided in active hepatic disease or in patients with an active peptic ulcer

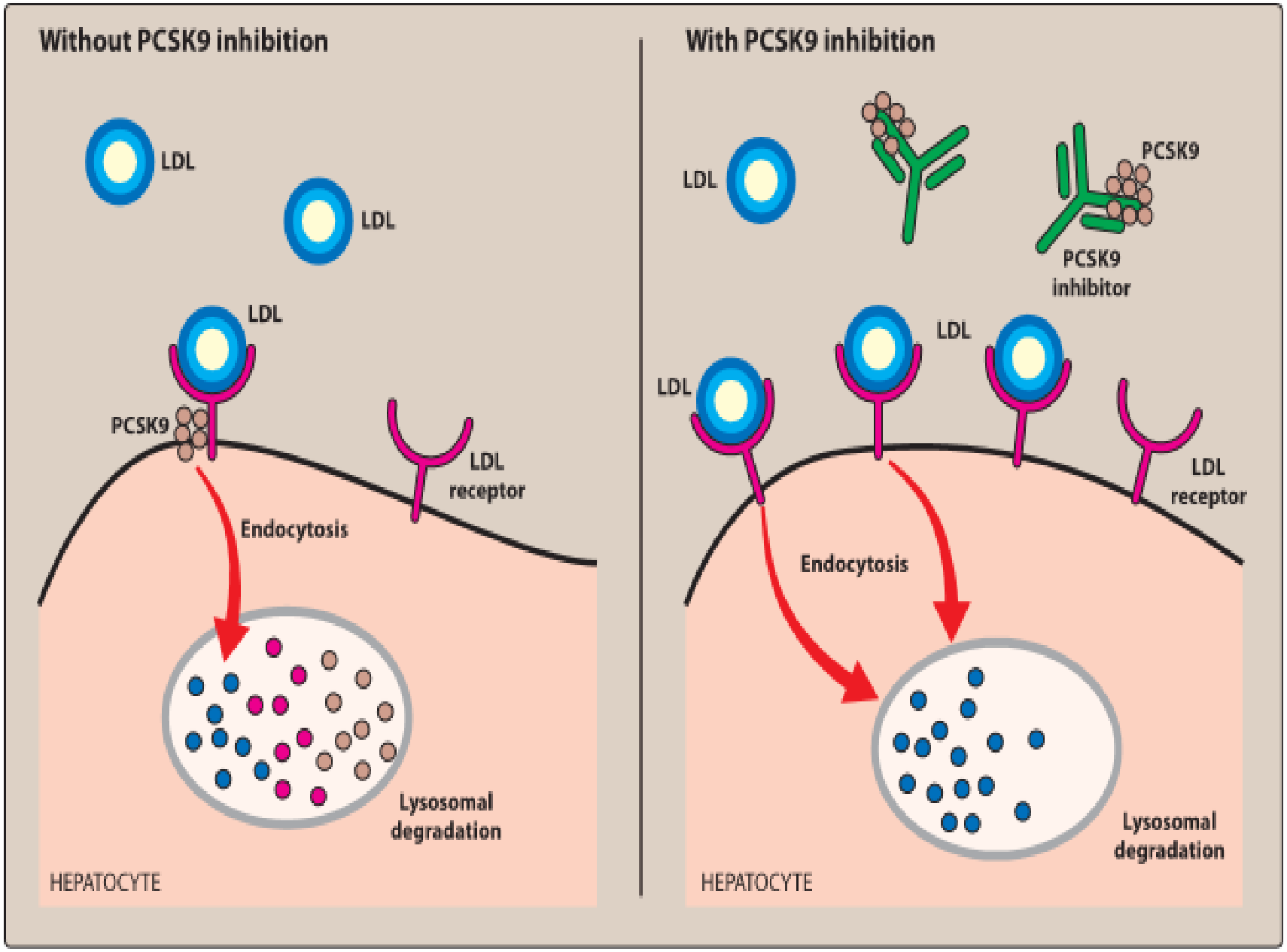

Adipose tissue
Liver
Decreased TG synthesis
Decreased VLDL
Decreased LDL
Niacin
Decreased FFA release
Increased HDL

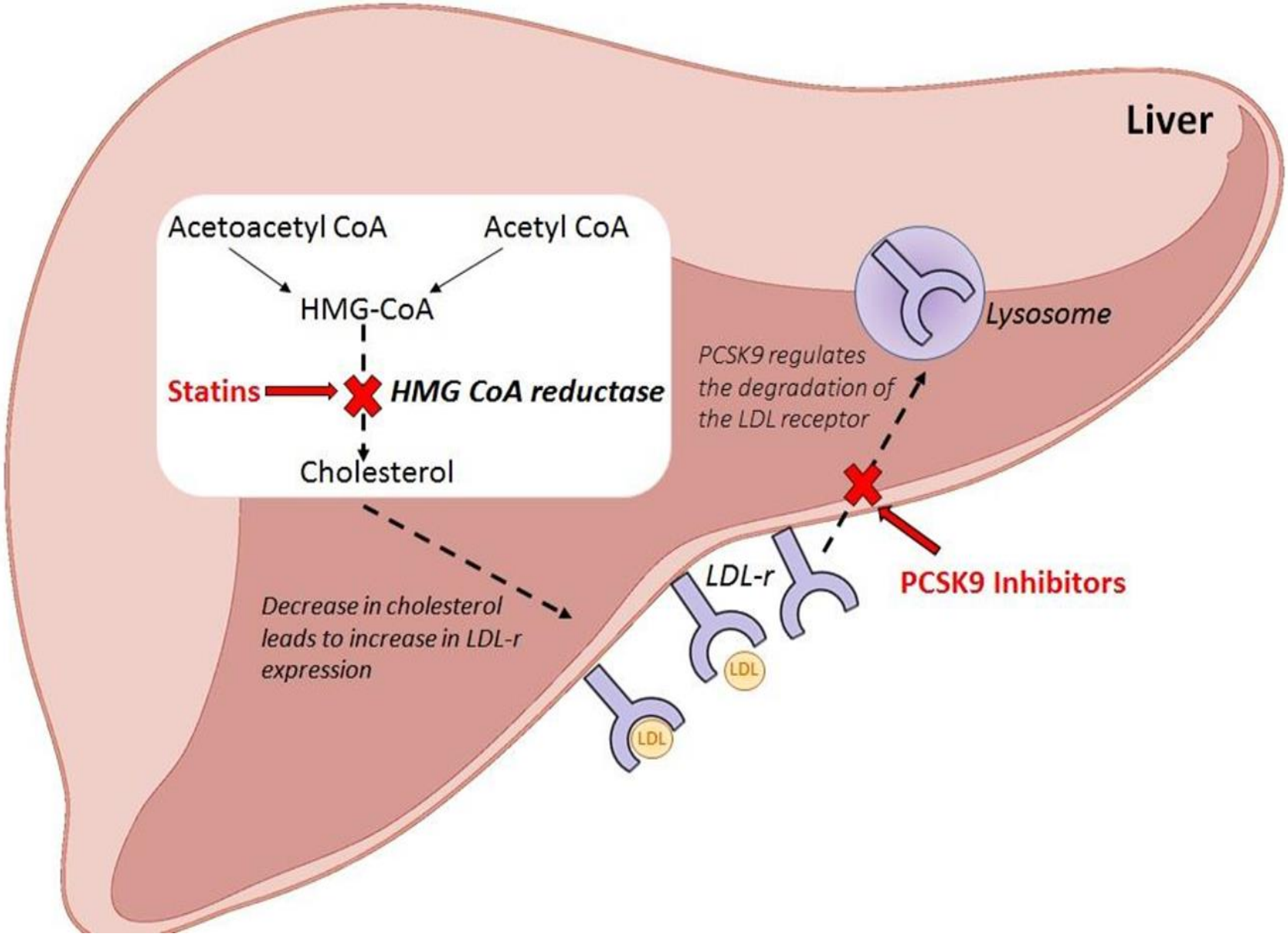
5. **Cholesterol absorption inhibitor :**

- ✓ 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 lowers LDL-C by approximately 18% to 23%.
- ✓ Due its modest LDL-C lowering, it is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk, or in statin-intolerant patients.
- ✓ 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.

6. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors :

- ✓ PCSK9 an enzyme produced in the liver, binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of LDL receptors
- ✓ By inhibiting the PCSK9 enzyme, more LDL receptors are available to clear LDL-C from the serum.
- ✓ Alirocumab and evolocumab are PCSK9 inhibitors, which are fully humanized monoclonal antibodies.
- ✓ These agents are used in combination with statin therapy in patients with heterozygous or homozygous familial hypercholesterolemia, or in patients with clinical ASCVD who require additional LDL-C lowering.


Without PCSK9 inhibition
LDL
LDL
LDL
PCSK9
LDL receptor
Endocytosis
Lysosomal degradation
HEPATOCYTE
With PCSK9 inhibition
LDL
PCSK9
PCSK9 inhibitor
LDL
LDL
LDL receptor
Endocytosis
Lysosomal degradation
HEPATOCYTE


Liver
Acetoacetyl CoA
Acetyl CoA
HMG-CoA
Statins
HMG CoA reductase
Cholesterol
Lysosome
PCSK9 regulates the degradation of the LDL receptor
LDL-r
PCSK9 Inhibitors
Decrease in cholesterol leads to increase in LDL-r expression
LDL
LDL

- When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%).
- 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.
- PCSK9 inhibitors are generally well tolerated. The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.

7. 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.
- ✓ The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon.
- ✓ Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C.
- ✓ Prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone.

- ✓ **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).
- ✓ Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality.

The most common side effects:

1. Gl effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste.
2. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelet agents.

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	↓	↑	↓
PCSK9 inhibitors	↓↓↓↓↓	↑↑	↓

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