Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 7

DRUGS FOR HYPERLIPIDEMIA

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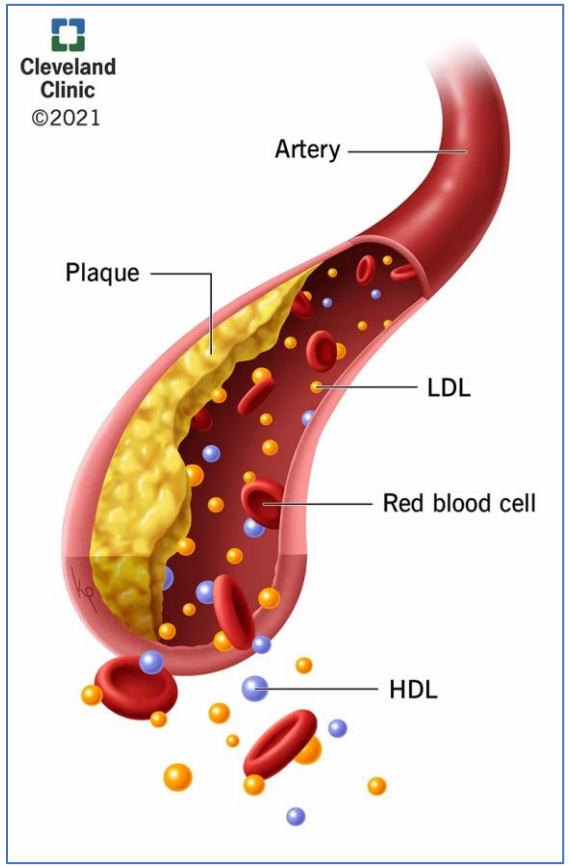
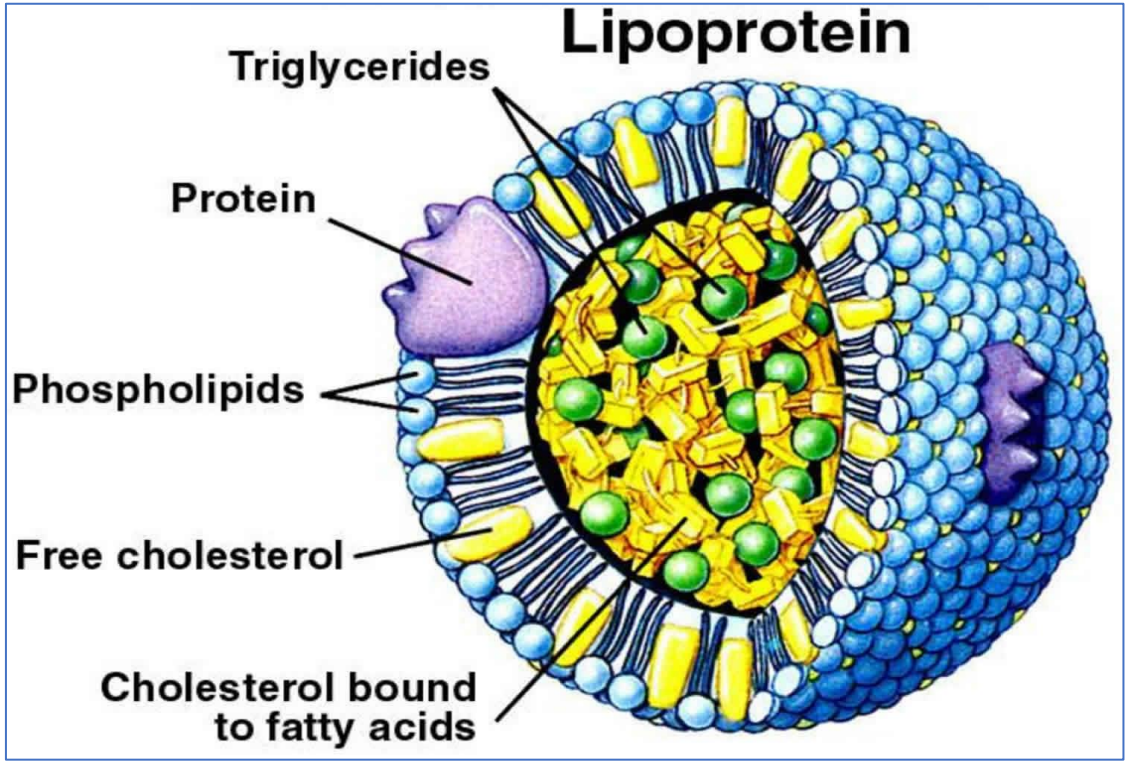
OVERVIEW

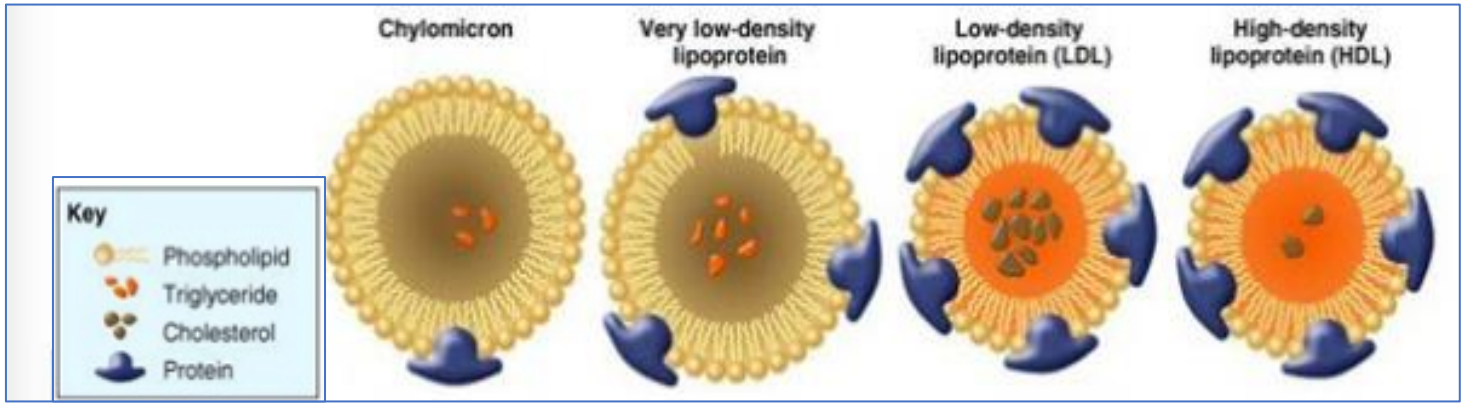
- **CHD** is correlated with **elevated levels** of LDL-C & TG, and **low levels** of HDL-C.
- Elevated cholesterol levels (**hyperlipidemia**) may be due to **lifestyle factors** or **inherited defect** in lipoprotein metabolism or a combination of **both**.
- Appropriate lifestyle changes, along with drug therapy, can lead to a **30% to 40%** reduction in CHD **mortality**.
- Antihyperlipidemic **drugs** are often taken **indefinitely** to **reduce the risk** of atherosclerotic cardiovascular disease (**ASCVD**).



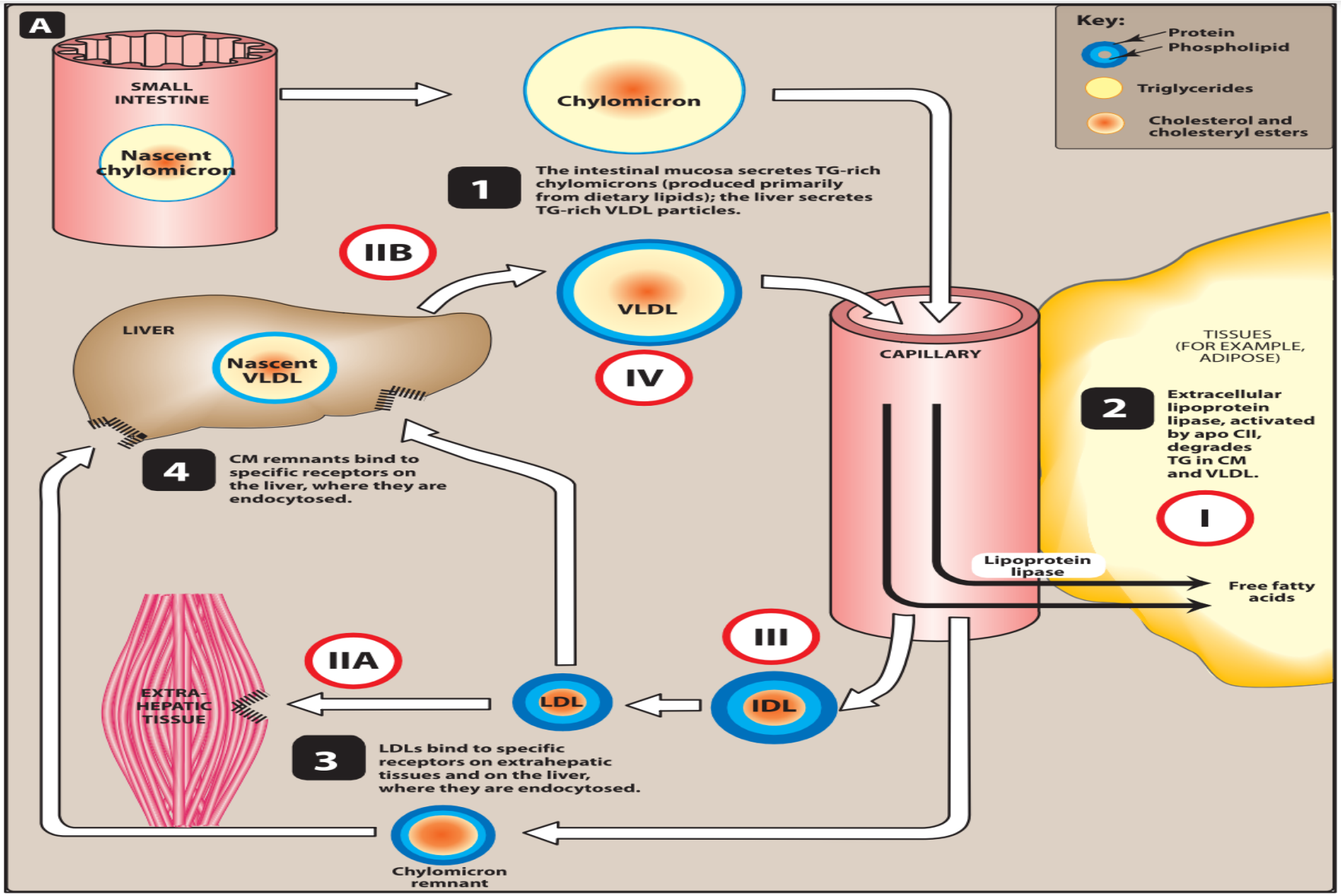
- **Note:** ASCVD includes CHD, stroke, and peripheral arterial disease.

Physiology of HDL, LDL, & VLDL





Physiology of HDL, LDL, & VLDL



LEVELS of HDL, LDL, VLDL, & TG FOR ADULTS

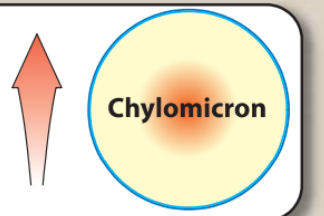
AMOUNT (mg/dL)	TOTAL	LDL	HDL	TRIGLYCERIDES
Ideal	<200	<100	>60	<150
Borderline	200–239	130–159	Women: 40–59 Men: 50–59	150–199
Too high or low	>240	High: 160–189 Very high: >190	Women: <40 Men: <50	High: 200–499 Very high: >500

FAMILIAL HYPERLIPDEMIA TYPES

B

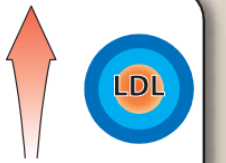
Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- 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.



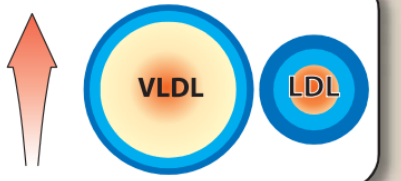
Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- 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*, a statin, or a statin and a PCSK9 inhibitor.



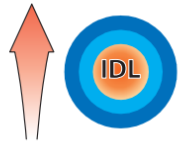
Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- 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.



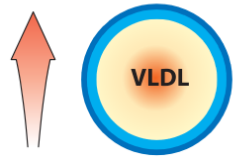
Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- 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.



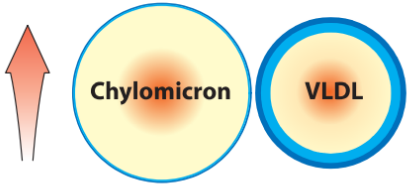
Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- 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.



ANTIHYPERLIPIDEMIC DRUG

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

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, VARIOUS OTC PREPARATIONS
Icosapent ethyl VASCEPA

PCSK9 INHIBITORS

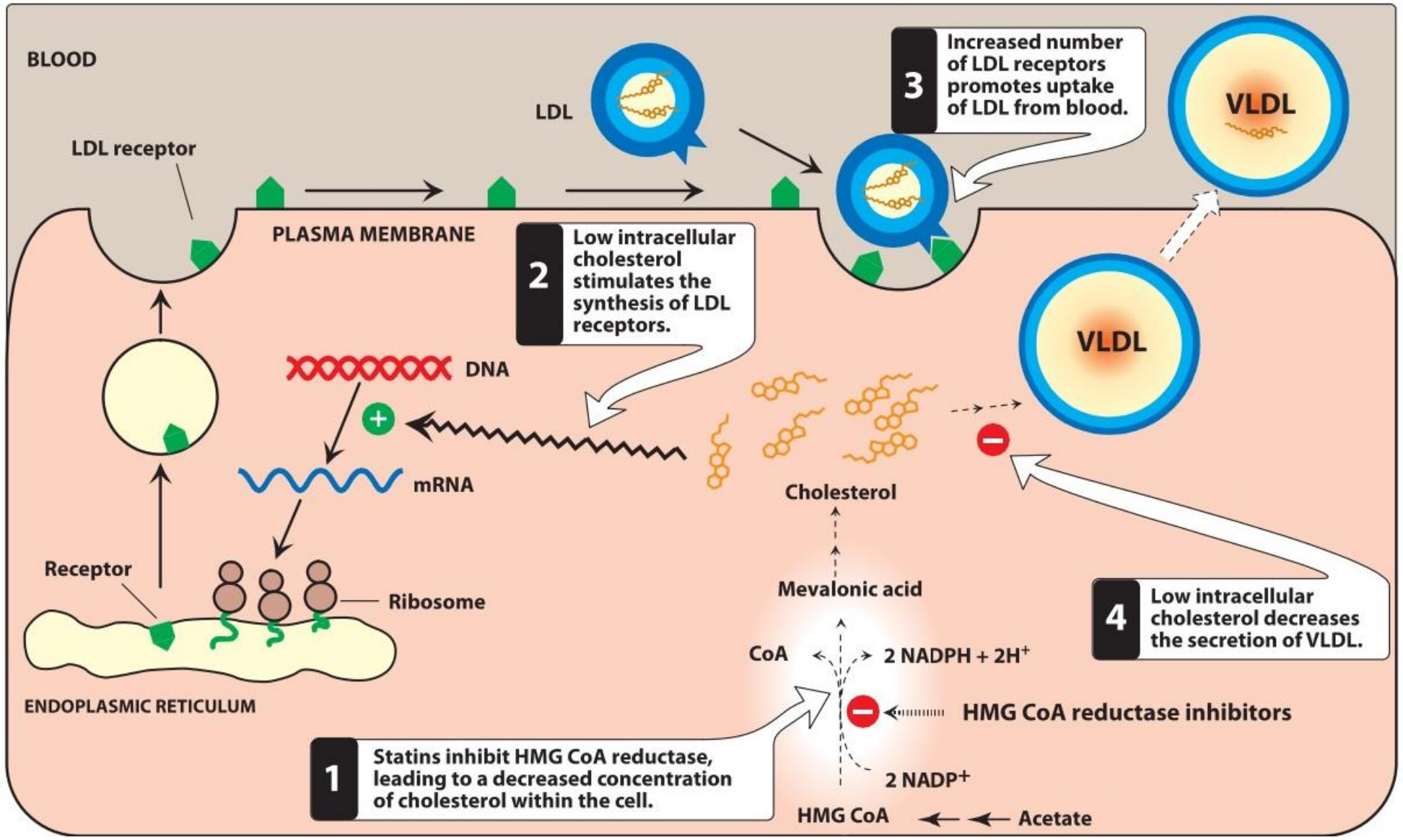
Alirocumab PRALUENT
Evolocumab REPATHA

1. HMG CoA reductase inhibitors (Statins)

Mechanism of action:

- They are **competitive inhibitors of HMG CoA reductase**, the rate-limiting step in **cholesterol synthesis**.
- By inhibiting de novo 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.
- They **also decrease TG** levels and may **increase HDL-C** in some patients.

1. HMG CoA reductase inhibitors



1. HMG CoA reductase inhibitors

- **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 hyperlipidemia**.
- However, patients who are **homozygous** for **familial hypercholesterolemia** lack LDL receptors and, therefore, **benefit much less** from treatment with these drugs.

1. HMG CoA reductase inhibitors

Pharmacokinetics:

- **Lovastatin** and **simvastatin** 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 isoenzymes** in the liver, **except pravastatin**.
- **Excretion** takes place principally through **bile and feces**, but **some urinary** elimination also occurs.

1. HMG CoA reductase inhibitors

Adverse effects:

- **Elevated liver enzymes** may occur with statin therapy.
- **Myopathy** and **rhabdomyolysis** (disintegration of skeletal muscle; rare)
- **Plasma creatine kinase** levels should be determined in patients with muscle complaints.
- These drugs are **contraindicated** during **pregnancy, lactation, and active liver disease**.

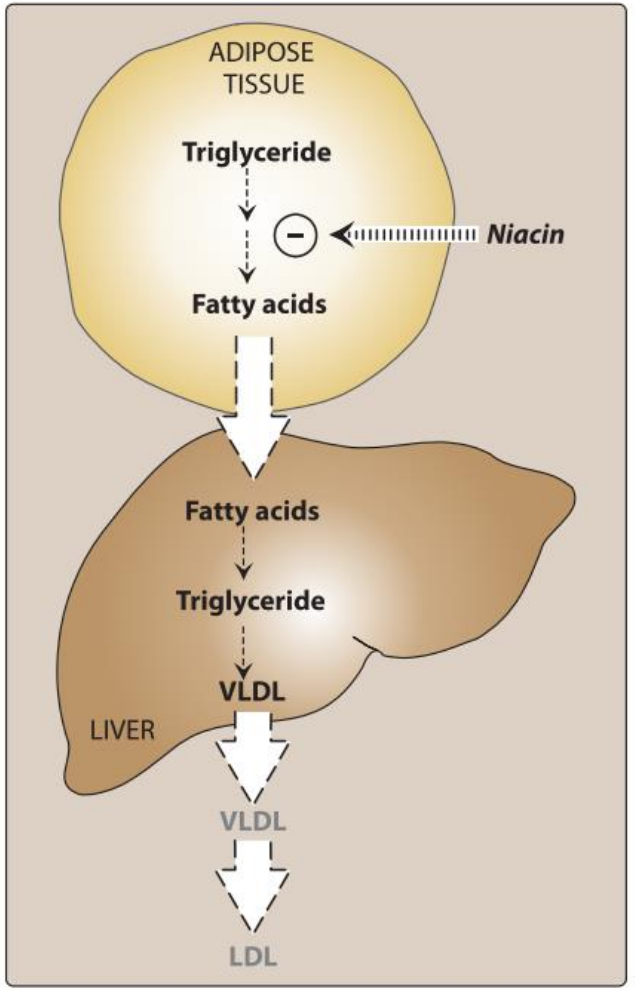
2. Niacin (nicotinic acid)

- It **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**, and fixed-dose combinations (**FDC**) of long-acting niacin with **lovastatin** and **simvastatin** are available.

2. Niacin (nicotinic acid)

Mechanism of action:

- At **gram doses**, 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 TG synthesis**.
- **Reduced** liver **TG** levels decrease **hepatic VLDL production**, which in turn **reduces LDL-C plasma** concentrations.



2. Niacin (nicotinic acid)

Therapeutic uses:

- **Because** niacin lowers plasma levels of **both cholesterol and TG**, it is useful in the treatment of **familial hyperlipidemias**.
- It is also used to treat other **severe hypercholesterolemias**, often in **combination** with other agents.

Pharmacokinetics:

- Niacin is administered **orally** then **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**.
- Administration of nicotinamide **alone** does **not decrease** plasma lipid levels.

2. Niacin (nicotinic acid)

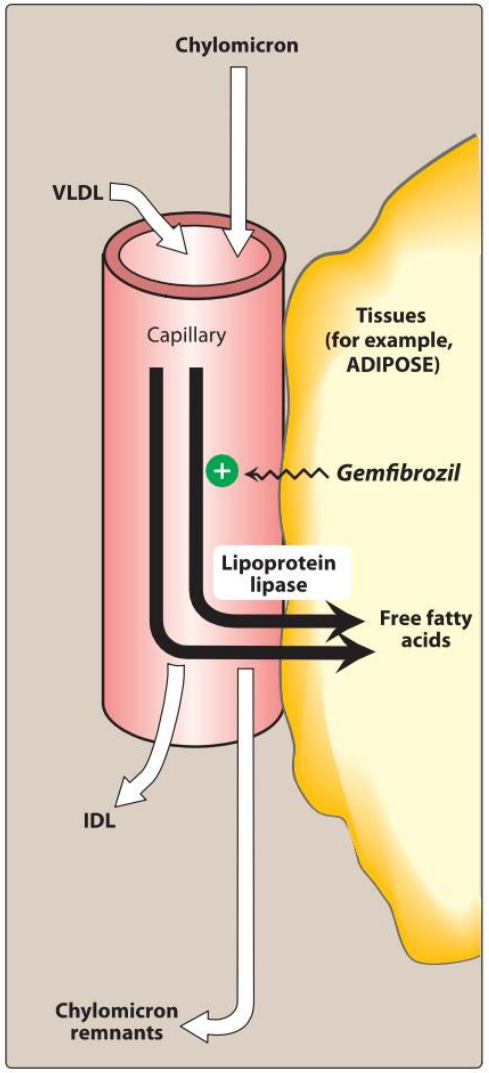
Adverse effects:

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

3. Fibrates

Mechanism of action:

- The peroxisome proliferator-activated receptors (**PPARs**) are members of the **nuclear receptor family** that regulate **lipid metabolism**.
- **PPARs** function as **ligand-activated transcription factors**. Upon **binding** to their natural **ligands** (fatty acids or eicosanoids) or **antihyperlipidemic** drugs, PPARs are **activated**.
- They **then bind** to peroxisome proliferator response elements, which ultimately leads to **decreased TG** through **increased** expression of **lipoprotein lipase** and **decreased apolipoprotein (apo) CII**.
- **Fenofibrate** is more effective than **gemfibrozil** in lowering TG levels.
- **Fibrates** also **increase HDL-C** by **increasing** the expression of **apo AI and apo AII**.



3. Fibrates

Therapeutic uses:

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

Pharmacokinetics:

- Gemfibrozil and fenofibrate are **completely absorbed** after **oral** administration and **distributed 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.

3. Fibrates

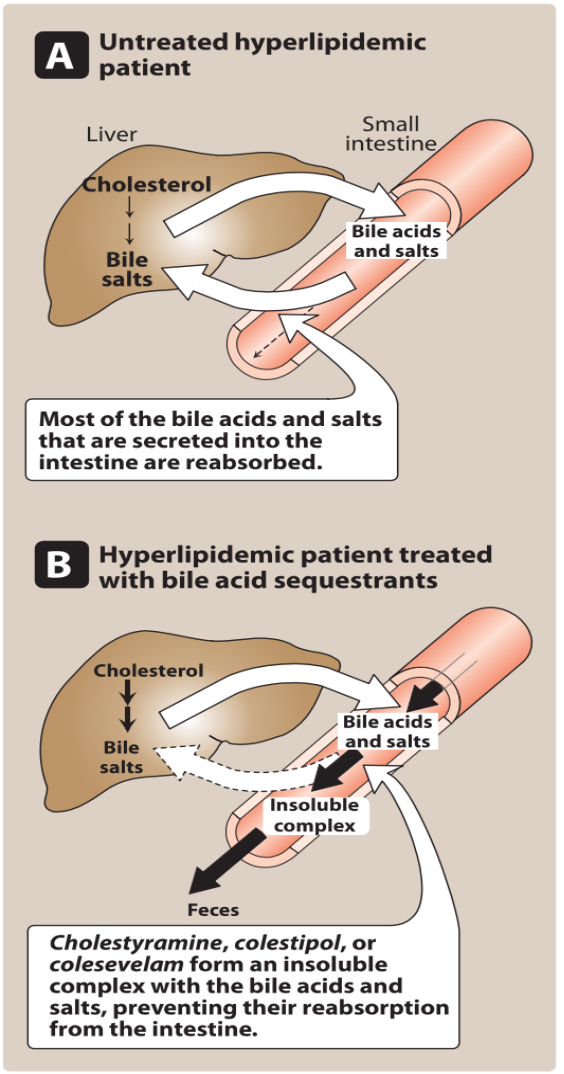
Adverse effects:

- The most common adverse effects are **mild gastrointestinal (GI) disturbances.**
- There is a predisposition to form **gallstones**.
- **Myositis** (inflammation of a voluntary muscle) 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, in general, the use of gemfibrozil with any statin should be avoided. **??**

4. Bile acid sequestrants

Mechanism of action:

- They 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 conc.**.
- This causes **hepatocytes** to **increase the conversion** of **cholesterol to bile acids**, which are essential components of the **bile**.
- Consequently, **intracellular** cholesterol conc. **decrease**, which activates an **increased** hepatic **uptake** of **LDL-C particles**, leading to a **decrease** in **plasma LDL-C** by an **up-regulation** of cell surface **LDL receptors**.
- Include **Cholestyramine, colestipol,** and **colesevelam**



4. Bile acid sequestrants

Therapeutic uses:

- They are **useful** (often in **combination** with **diet or niacin**) for treating **type IIA and type IIB hyperlipidemias**.
- **Cholestyramine** can also relieve **pruritus** caused by an **accumulation of bile acids** in patients with **biliary stasis**.
- **Colesevelam** is also indicated for **DM type II** due to its **glucose-lowering effects**.

Pharmacokinetics:

- After **oral** administration, they are **neither absorbed nor metabolically altered** by the **intestine**.
- Instead, they are **totally excreted in feces**.

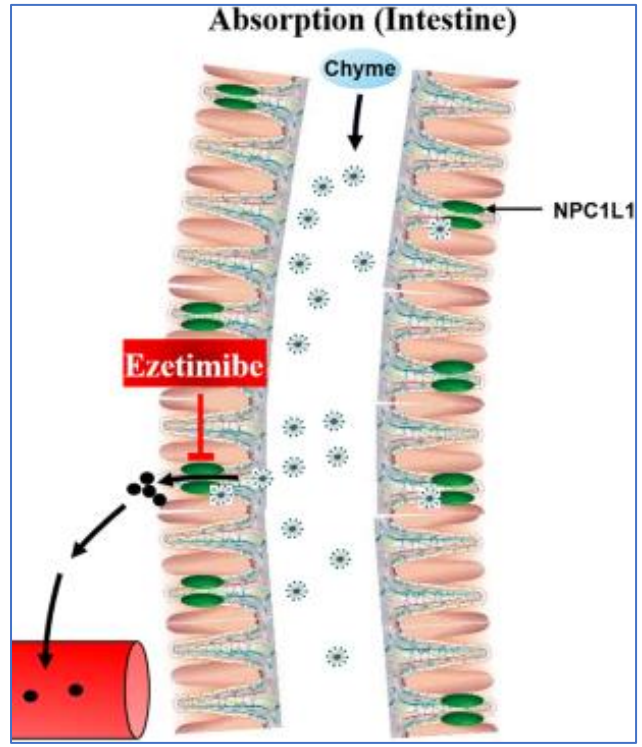
4. Bile acid sequestrants

Adverse effects:

- **GI disturbances**, such as constipation, nausea, and flatulence (Colesevelam less one).
- These agents may **impair the absorption** of the **fat-soluble vitamins** (A, D, E, and K).
- 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 TG** levels and are **contraindicated** in patients with significant **hypertriglyceridemia** (>400 mg/dL).

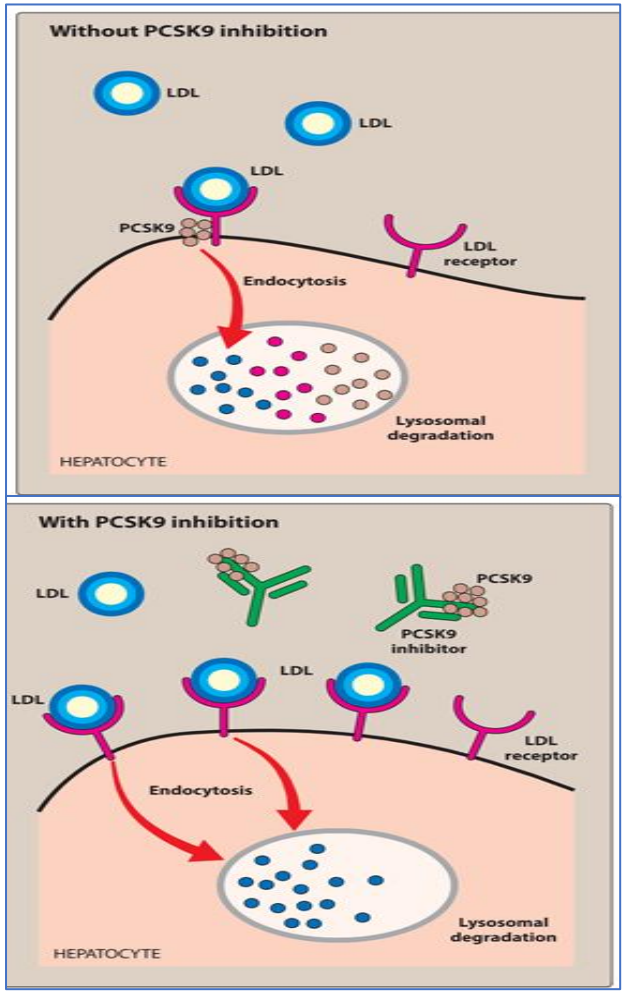
5. Cholesterol absorption inhibitor

- **Ezetimibe inhibits the 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 the **clearance of cholesterol from the blood**.
- Ezetimibe **lowers LDL-C** by approximately **18% to 23%.**
- Due to its **modest LDL-C lowering**, ezetimibe is often used as an **adjunct to maximally tolerated statin**.
- Patients with moderate to severe **hepatic insufficiency** should **not** be treated with ezetimibe. ?



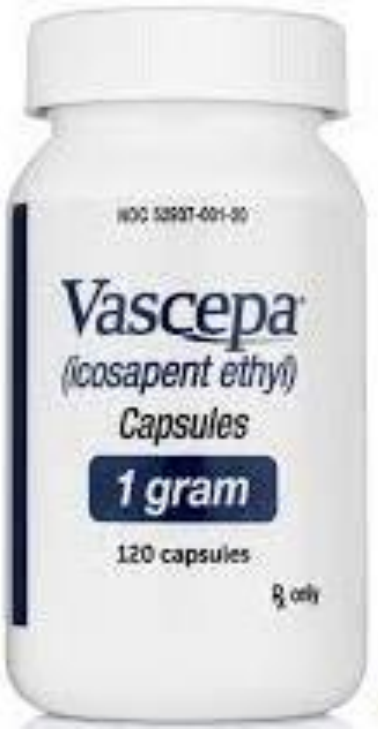
6. Proprotein convertase subtilisin kexin type 9 inhibitors

- **PCSK9** is an enzyme predominately produced in the liver, **binds then degrades the LDL receptor** on the surface of hepatocytes.
- By **inhibiting the PCSK9** enzyme, **elevate LDL receptors** are available to **clear LDL-C from the serum**.
- **Alirocumab** and **evolocumab** are PCSK9 inhibitors, only available as **SC** injections, and are administered every **2-4 weeks**.
- These agents are used in **addition to maximally tolerated statin** therapy in patients with **heterozygous** or **homozygous familial hypercholesterolemia**, *or* in patients with clinical **ASCVD who require additional LDL-C lowering**. (LDL-C lowering (50% to 70%)
- The **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 **TG 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 **TG** by 25% to 30%, with small **increases** in **LDL-C** and HDL-C.
- **Icosapent ethyl** contains **only EPA** and, unlike other fish oil supplements, does **not significantly raise LDL-C**.
- **Bleeding risk** can be increased in those who are **concomitantly** taking **anticoagulants or antiplatelet agents**.



Characteristics of anti hyperlipidemic drug families

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	↓↓↓↓↓	↑↑	↓

Thank You