بسم الله الرحمن الرحيم

Pharmacology of CVS
Lecture 2: Drugs for treatment of hyperlipidemia

By
Dr. Mohammad Salem

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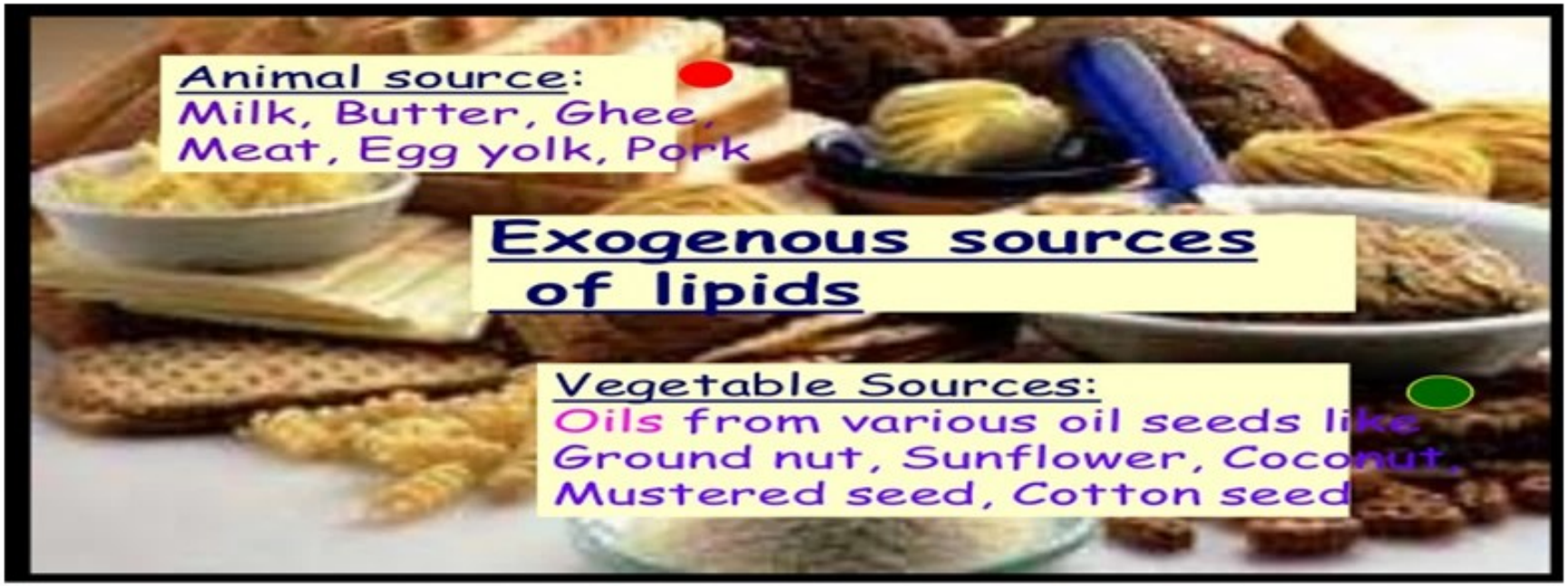
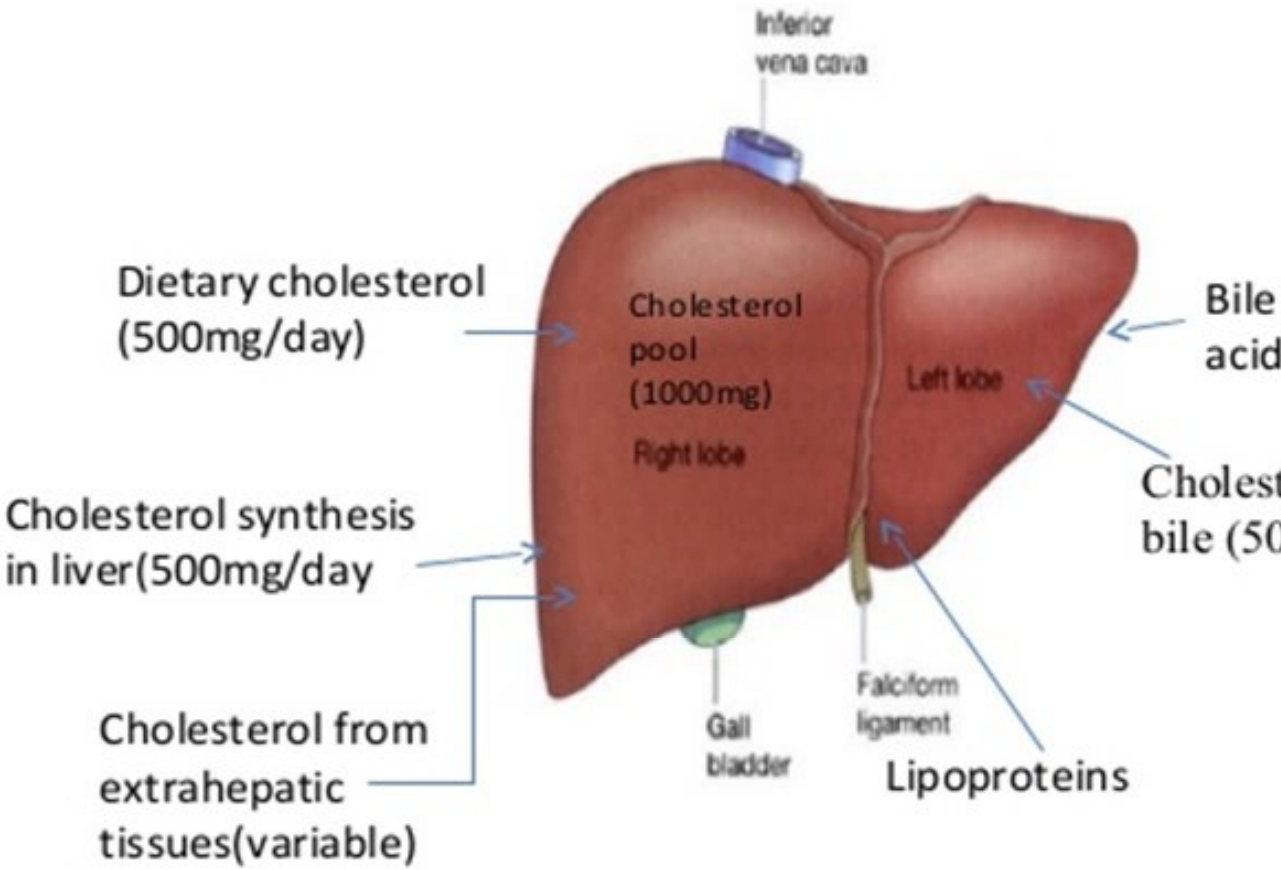
Sources and functions of lipids

Lipids (fats) are either absorbed from food (**exogenous**) or synthesized by the liver (**endogenous**), although all lipids are physiologically important, **Triglycerides** (TGs) and **cholesterol** contribute most to disease.

The primary function of **TGs** is to store energy in adipocytes and muscle cells; **cholesterol** is a ubiquitous constituent of cell membranes, steroids, bile acids, and signaling molecules.



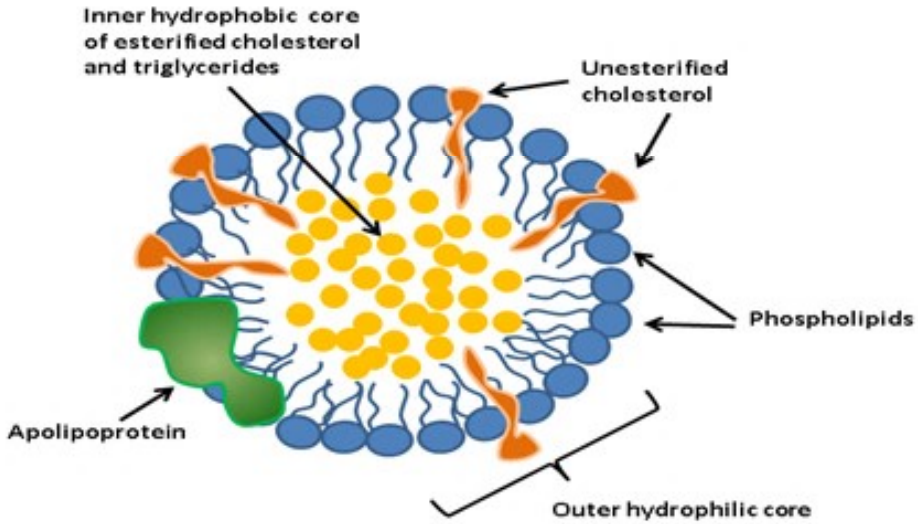
Major sources of liver cholesterol and its utilizations.

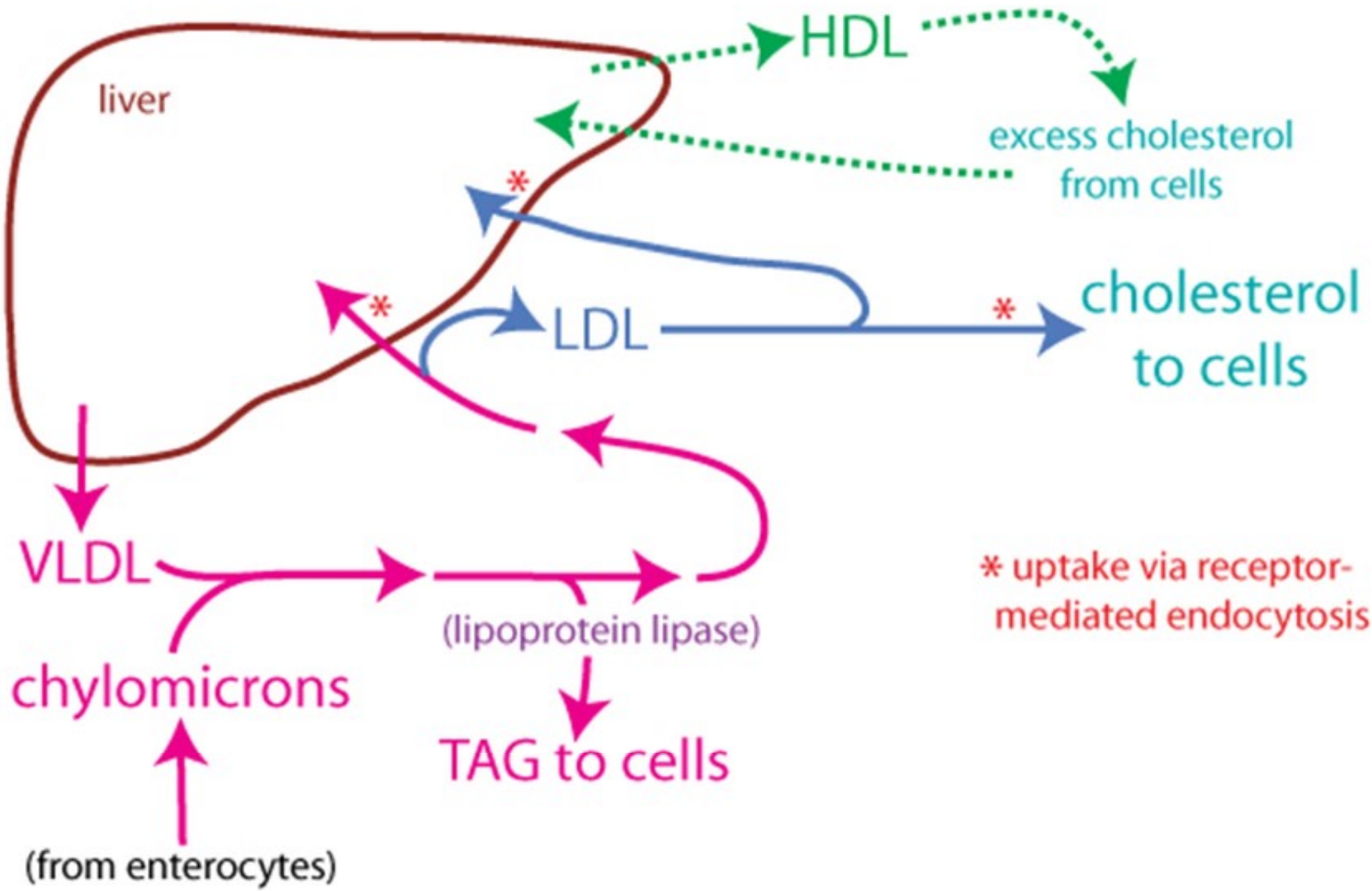


Lipoproteins

All lipids are **hydrophobic** and mostly insoluble in blood, so they require transport within hydrophilic, spherical structures called **lipoproteins**, which possess surface proteins (apoproteins, or apolipoproteins) and inner lipid core.

Lipoprotein particle metabolism can occur via the exogenous or endogenous pathway, depending whether the source of origin is dietary (intestinal) or hepatic.




HDL
liver
excess cholesterol
from cells
*
*
LDL
*
cholesterol
to cells
VLDL
(lipoprotein lipase)
chylomicrons
TAG to cells
(from enterocytes)
* uptake via receptor-
mediated endocytosis

Hyperlipidemia (dyslipidemia) or Hyper-lipoproteinemia

It is increased blood levels of atherogenic lipoproteins especially LDL with increased levels of cholesterol &/or triglycerides that may lead to atherosclerosis, increased risk of coronary heart disease, cerebrovascular disease, pancreatitis, xanthomas and peripheral vascular disease .

Types and Causes of Hyperlipidemia

1. Familial (primary) hyperlipidemia:

This type of hyperlipidemia strongly correlates with family history.

2. Secondary hyperlipidemia: to different medical & environmental conditions:

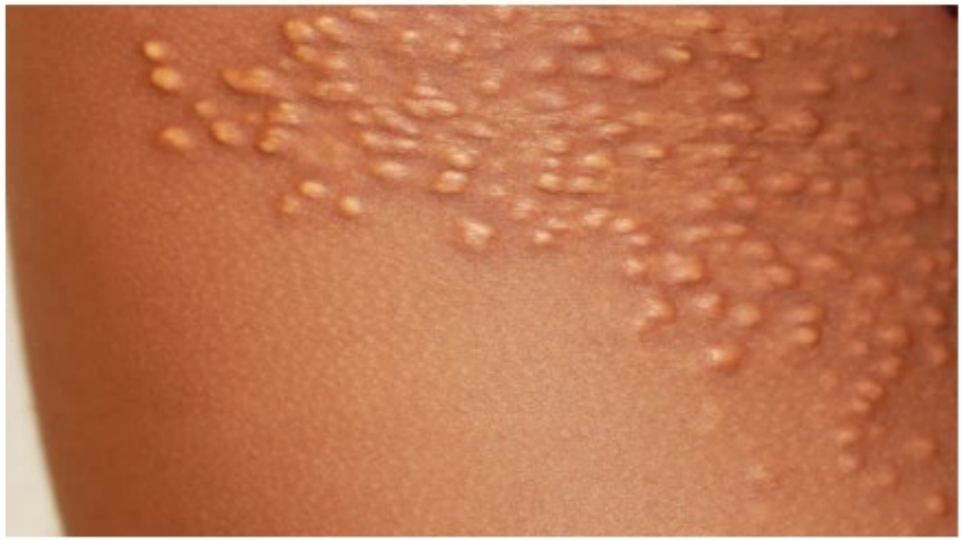
i) Diabetes mellitus

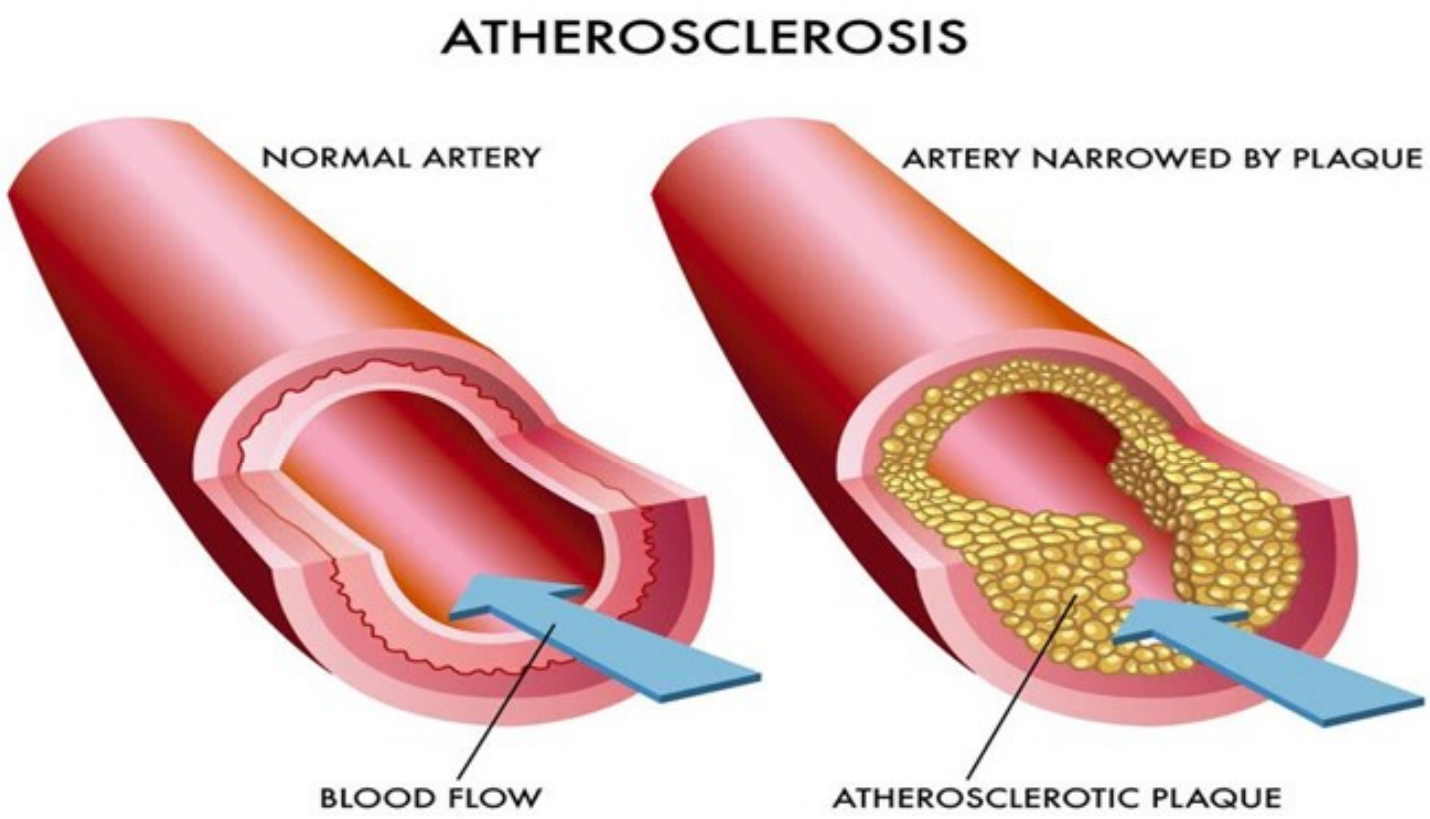
ii) Drug-induced: Beta- blockers, thiazides and oral contraceptives.

iii) Alcoholism.

iv) Obesity.


Xanthomas




ATHEROSCLEROSIS
NORMAL ARTERY
ARTERY NARROWED BY PLAQUE
BLOOD FLOW
ATHEROSCLEROTIC PLAQUE

Treatment of hyperlipoproteinemia

1. Non-drug therapy of hyperlipidemia

1. Diet therapy:

- Low carbohydrate and low saturated fat (animal fat); French is exception (French paradox*).
- high unsaturated fat (vegetable fat e.g., olive oil).
- high protein

2. Stop cigarette smoking and alcohol drinking.

3. Reduce Obesity.

4. Avoid drugs which causes hyperlipidemia.

5- Using antihyperlipidemic drugs.

*The French paradox is the observation of low coronary heart disease death rates despite high intake of dietary cholesterol and saturated fat.

Drug treatment of Hyperlipoproteinemia

1. **Statins (HMG-CoA reductase inhibitors):** lovastatin, fluvastatin, atorvastatin, rosuvastatin, simvastatin and pravastatin.
2. **Bile-acid binding resins:** cholestyramine and colistipole.
3. **Fibric acid derivatives** clofibrate and gemfibrozil.
4. **Niacin and estrogens.**
5. **Dietary and cholesterol absorption inhibitors**: e.g., Ezetimibe
6. **New drugs.**

1. Statins

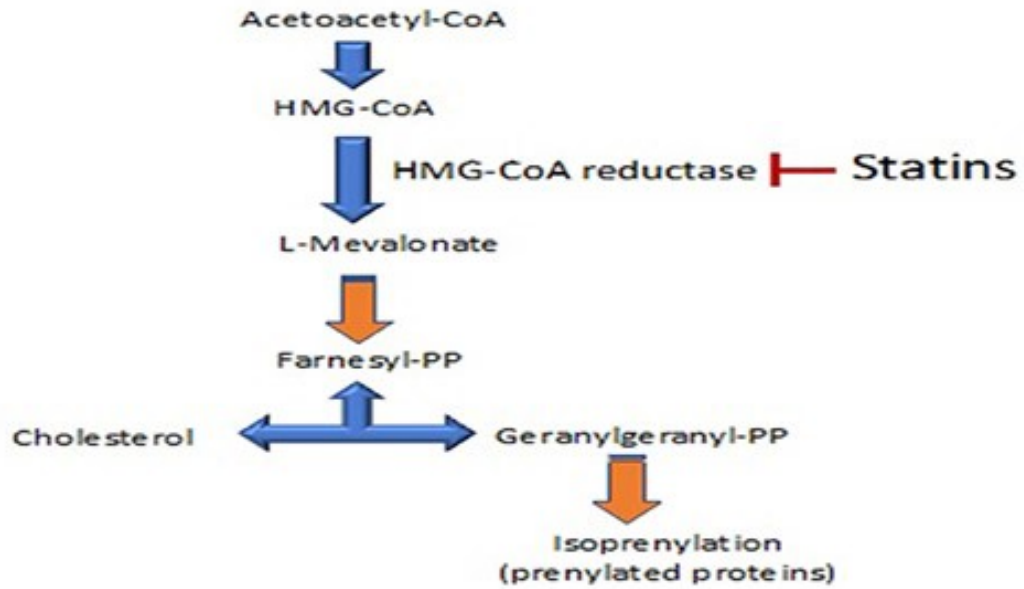
Members: Simvastatin, Lovastatin, Pravastatin and Atorvastatin.

Mechanisms of action

1- HMG-CoA reductase inhibition

❑Statins **inhibit** the rate limiting step responsible for **cholesterol synthesis** in the liver → ↓ cholesterol synthesis → a compensatory increase in hepatic LDL receptors → take up more LDL that the liver needs → ↓ LDL level in the blood (40 %).

-In addition, a modest ↑ HDL (10 %) & ↓ triglycerides (25 %) occur.



❑HMG-CoA reductase inhibition → ↓ production of **prenylated proteins; this inhibition is a double edged sword:**

➢It leads to improvement of endothelial function, modulation of immune function, and other **pleiotropic cardiovascular benefits.**

➢It causes myopathy and insulin resistance with hyperglycemia (diabetes).

2- Other effects (Pleiotropic effects)

Statins have other beneficial non-lipid-lowering actions (pleiotropic) which prevent cardiovascular disease through:

1. **Improve endothelial function.**
2. **Modulate inflammatory responses.**
3. **Maintain plaque stability.**
4. **Prevent thrombus formation.**

3- Prevention of cancers

(esophageal, colorectal, gastric and hepatocellular carcinomas)

Therapeutic Uses of statins

Timing: ***in the evening (at bed time)***: because cholesterol synthesis occurs after midnight

1-Treatment of Familial hypercholesterolemia.

2- Prevention of coronary heart diseases, strocke & atherosclerosis.

3-Anti-inflammatory, anticancer and anti-parasitic activity (Not yet approved).

<u>Advantages:</u> Statins are the Drugs of first choice in treating hyperlipidemia because:

i- They are the best drugs in cardiac protection.

ii - They are the Most effective hypolipidemic agents.

iv- They Reduce both LDL & TGs and increase HDL.

<u>Contraindications:</u>

1-During pregnancy.

2- Hepatic failure

Pharmacokinetics of statins

- Most statins have low oral bioavailability due to an extensive first pass effect at the intestinal and/or hepatic level.
- Such a characteristic can be advantageous, since the **liver is the target organ** for statins.
- **lovastatin** and **simvastatin** are given as inactive lactone **prodrugs**.
- All statins except pravastatin show highly active metabolites.
- The active metabolites are then metabolized and **renally excreted**.
- Atorvastatin shows the longest terminal half-life (11-14 hours).
- Pharmacokinetic interactions with statins are very likely to occur, particularly for those statins that are **CYP3A4 substrates.**

Adverse effects of Statins

1- Myositis and myopathy:

- Manifested by muscle pain, fatigue and ↑CPK (Creatine phosphokinase).
- All statins may cause myopathy and rhabdomyolysis.
- The risk is increased if combined with fibrates or niacin.
- If the patient does not stop the drug, this myopathy → myoglobinuria → renal failure.
- Many mechanisms for statin-induced myopathy have been proposed, among them impaired protein prenylation, mitochondrial dysfunction,, impairment of the insulin receptor/Akt/mTORC pathway and **apoptosis.**

2- Increased risk of diabetes:

Statins are associated with a slightly increased risk of diabetes (2–17%).

3- Hepatic dysfunction: ↑ **liver enzymes.**

Monitoring is needed and stop statins if liver enzymes are 5 folds or more of the normal range.

N.B. statins are concentrated and trapped in the liver .

4- Fetal harm: Statins may cause fetal harm if given during pregnancy.

5- Constipation or diarrhea.

6- Confusion and memory problems: (rare side effect).

7- Drug and food interactions

1- Combining any statins with a fibrate or increases the risks for rhabdomyolysis.

2- Consumption of grapefruit or its juice inhibits the CYP3A4, which are involved in the metabolism of most statins. This increases the levels of the statins and their adverse effects.

3- CYP inhibitors like erythromycin, ketoconazole and verapamil can increase statins toxicity.

2. Bile-Acid Binding sequestrants (Resins)

Members: Cholestyramine & colistipole

Mechanism of action:

❑Because of their large size, resins **administered orally** are not absorbed, They bind bile acids in the intestine and increase their fecal excretion; this results in inhibition of entero-hepatic recycling of bile acids and **increased conversion of cholesterol to bile acids in the liver**.

❑ Moreover, the **intestinal absorption of cholesterol will decrease.**

❑The net loss of bile acids and cholesterol in stool leads to two compensatory changes in hepatic metabolism :

I- **increase in the number of LDL receptors** leading to an increased uptake of LDL from plasma.

2- **increase in the activity of HMG-COA reductase** leading to increased synthesis of cholesterol for conversion to bile acids.

Effects of resins:

Decrease LDL by **20-30%** with no apparent effect on the HDL level.

The efficacy of bile acid binding resins is markedly increased when they are given with inhibitors of HMG-CoA reductase (statins).

Therapeutic uses of resins

1. Treatment of **hypercholesterolemia** and protect against CV diseases.
2. Treatment of bile-acid related **diarrhea** or diarrhea after bowel resection.
3. Treating **Pruritus** in patients with **cholestatic disease** and partial biliary obstruction.
4. Bile reflux gastritis.
5. The inhibition of enterohepatic circulation by cholestyramine makes it an effective drug in the management of:

- hyperthyroidism due to thyroiditis.
- Toxicity by drugs with high enterohepatic recycling like Leflunomide.

- The acid binding resins are available in powdered forms in packets containing **4g for cholestyramine** and 5g of colistipol.

- Most patients will not take more than **two packets twice** a day before breakfast and supper and **mixed with water or juice**.

Adverse Effects

I-GIT symptoms such as nausea, indigestion, abdominal discomfort and **constipation**.

2-They may **interfere with the absorption of fat soluble vitamins (K, A, E, D)** and thereby complicating the management of patients taking warfarin.

3-Resins may **bind to other drugs in the intestine** (digoxin, warfarin and others). As a general rule it is recommended that other drugs taken orally should be ingested at least one hour before or 4 hours after using resins.

Fibric acid derivatives (Fibrates)

Members: Gemfibrozil, bezafibrate and **fenofibrate.**

Mechanism of action and effects:

1- By activation of peroxisome proliferator-activated receptors alpha (***PPARα***) in the nucleus which regulate gene transcription. It increases the activity of lipoprolein lipase in fat cells and increase lipolysis of triglyceride. The major effect of fibrates is to **lower serum triglyceride** levels by **35-50%**.

2-Fibrates also decrease of the hepatic synthesis and secretion of VLDL and increased breakdown of VLDL This lead to (mild decrease or even increase in LDL) and moderate elevation of HDL (15-25%).

3- In clinical trials gemfibrozil was found to reduce the incidence of fatal and non-fatal **myocardial infarction** by 34% in patients with hyperlipidemia.

Adverse Effects

1-Myopathy syndrome with severe muscle cramps, tenderness, stiffness and weakness.

2-GIT disturbances, rash, urticaria and headache.

3-Impotence and anemia.

4- Hepatotoxicity and **gall stones.**

Uses:

Treatment of familial **hypertriglyceridemia** to prevent cardiovascular complications and pancreatitis.

Precautions and contraindications of fibrates

1- Avoid statins with fibrates (the risk of rhabdomyolysis increases)

2- History of cholesterol gall stones.

3-Fibrates should be avoided in hepatic and renal failure.

Niacin (Nicotinic acid)

Niacin is a water soluble vitamin B3 complex needed in dose 11-12 mg per day. It produces anti-hyperlipidemic effects in very high doses (**grams**).

Mechanism of action:

1- Niacin **inhibits VLDL secretion**, and decrease production of LDL **(20-35%).**

2- It **increases** the **clearance** of **VLDL** via the lipoprotien lipase. This pathway contributes to reduction of triglycerides **(35%).**

3- The **catabolic rate for HDL is decreased**. This lead to increase HDL by **35-40%**. **It is the most effective drug on HDL level**.

4- It decreases Lipoprotein a (which implicated in the pathogenesis of fatal CVS diseases).

Adverse Effects

1-Niacin causes a prostaglandin-mediated flushing & itching when given by high doses.

How to overcome this side effects

- Start with **a low dose** & slowly increasing to the therapeutic dose.
- **NSAIDs**: pretreatment with aspirin or ibuprofen 30 minutes before each dose can prevent this problem.
- By co-administration of the prostaglandin receptor antagonist **laropiprant**.

2-Hepatic toxicity.

3-Insulin resistance and severe hyperglycemia.

4- Niacin elevates uric acid levels and may precipitate gouty attacks.

5- Atrial arrhythmias have been reported in elderly patients.

6- Niacin causes birth defects in animals and should not be taken by pregnant women.

Ezetimibe

Mechanism of action

It **blocks intestinal absorption of cholesterol** because it binds to **Niemann-Pick C1-like 1** (NPC1L1) protein on the GIT epithelium (critical mediator of cholesterol absorption) → ↓ cholesterol absorption → ↓ cholesterol levels in the liver which compensated by increase cholesterol synthesis in the liver (overcome by statins).

- the liver compensates by **increased number of hepatic LDL receptors** and shifting LDL from the blood into the liver.
- Ezetimibe is effective even in the absence of dietary cholesterol because it **inhibits reabsorption of cholesterol excreted in the bile.**
- Ezetimibe ***alone*** can reduce LDL-cholesterol by 15-18% and cause mild elevation of HDL.

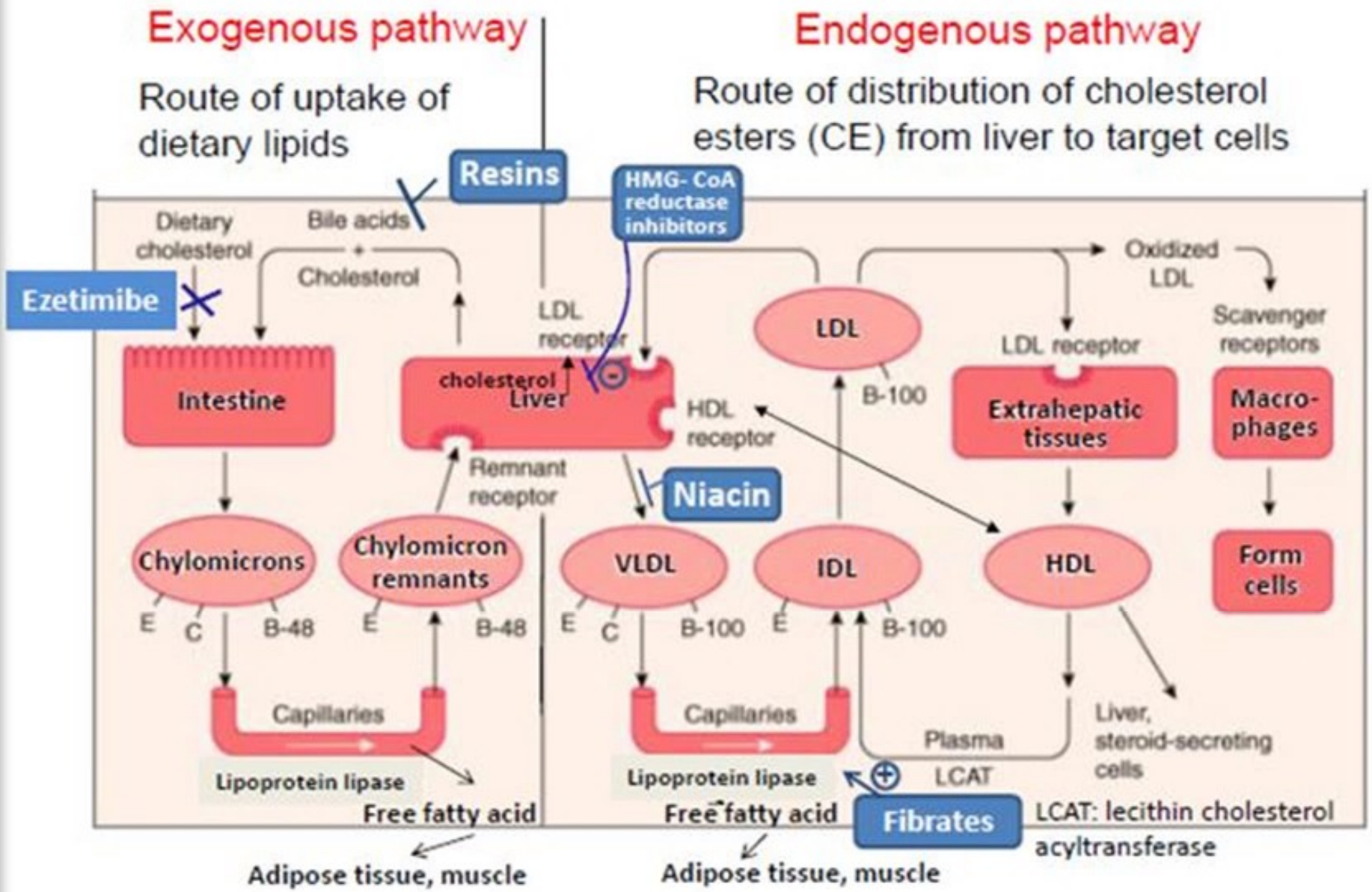
- Ezetimibe with statins (synergism occurs) and LDL-cholesterol decreases by 25% (Ezetimibe) + 40% (Statins).
- It is Metabolized in liver and small intestine to active metabolite.
- Metabolites are excreted in feces and urine.
- Half-life: Long (22 h) because the active metabolite undergoes entero-hepatic recycling. So, given once daily.

Uses: treatment of primary hypercholesterolemia and atherosclerosis

Adverse effects

Headache, diarrhea, myalgia, hypersensitivity reactions.

Lipid-lowering agents



New drugs for hyperlipidemia

1- Ethyl eicosapentaenoic acid or E-EPA

It is a derivative of omega 3. EPA, the active metabolite reduces production of triglycerides in the liver, and to enhance clearance of triglycerides from circulating VLDL particles.

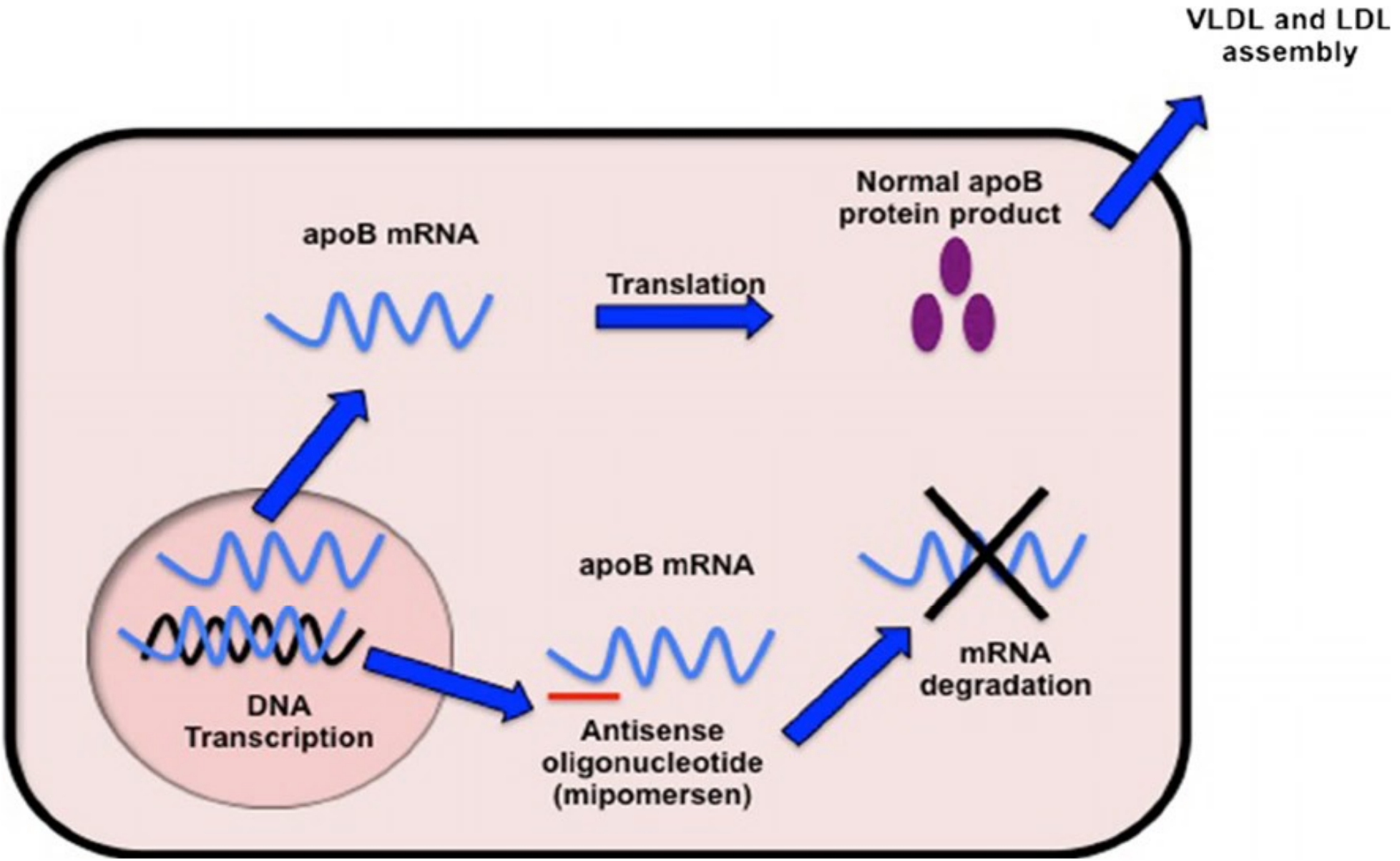
2-Lomitapide

Lomitapide inhibits the microsomal triglyceride transfer protein (MTP or MTTP) which is necessary for VLDL synthesis & secretion in the liver.

3- Mipomersen

Mipomersen binds to the messenger RNA (antisense) coding for apolipoprotein B-100 (ApoB-100), a protein that is the main component of (LDL) and (VLDL).

As a consequence, the RNA is degraded by the enzyme ribonuclease H, and ApoB-100 protien is not translated.


VLDL and LDL assembly
Normal apoB protein product
apoB mRNA
Translation
apoB mRNA
DNA Transcription
Antisense oligonucleotide (mipomersen)
mRNA degradation

4- PCSK9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an **enzyme** that binds to LDL receptors and cause breakdown of these receptors leading to stoppage of LDL removal from the blood, leading to an increase in blood levels of LDL.

The PCSK9 inhibitors (**alirocumab** and **evolocumab**) block the PCSK9 enzyme, resulting in more LDL receptors available to remove LDL from the blood, which produces in a decrease in LDL blood levels.

THANK YOU!