# Pharmacology

# Antihyperlipidemic drugs (2)

**Fathalla A Khedr**

**Associate professor of Medicinal Chemistry**
**Pharm Med Chem & Drug Design Department**

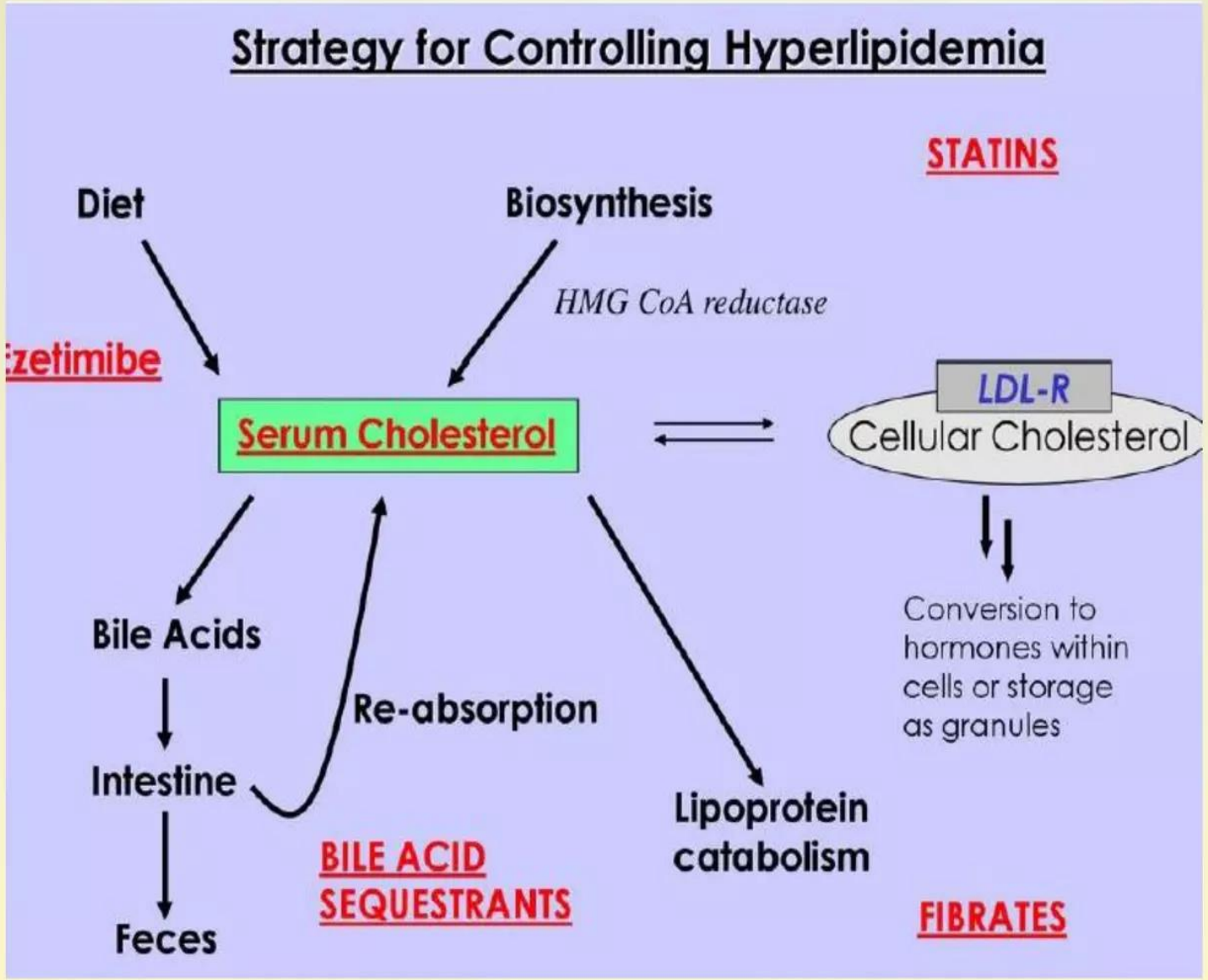
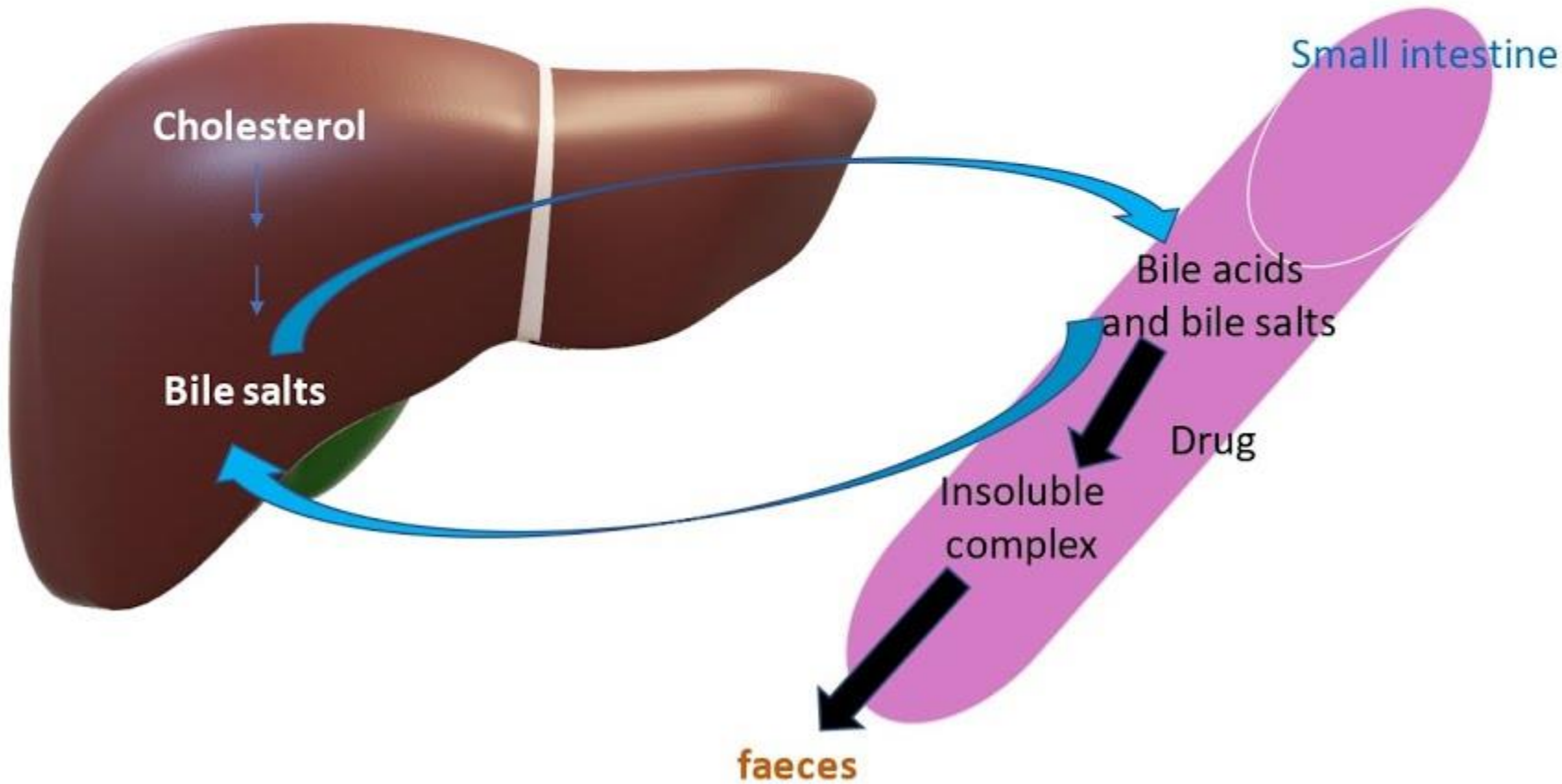


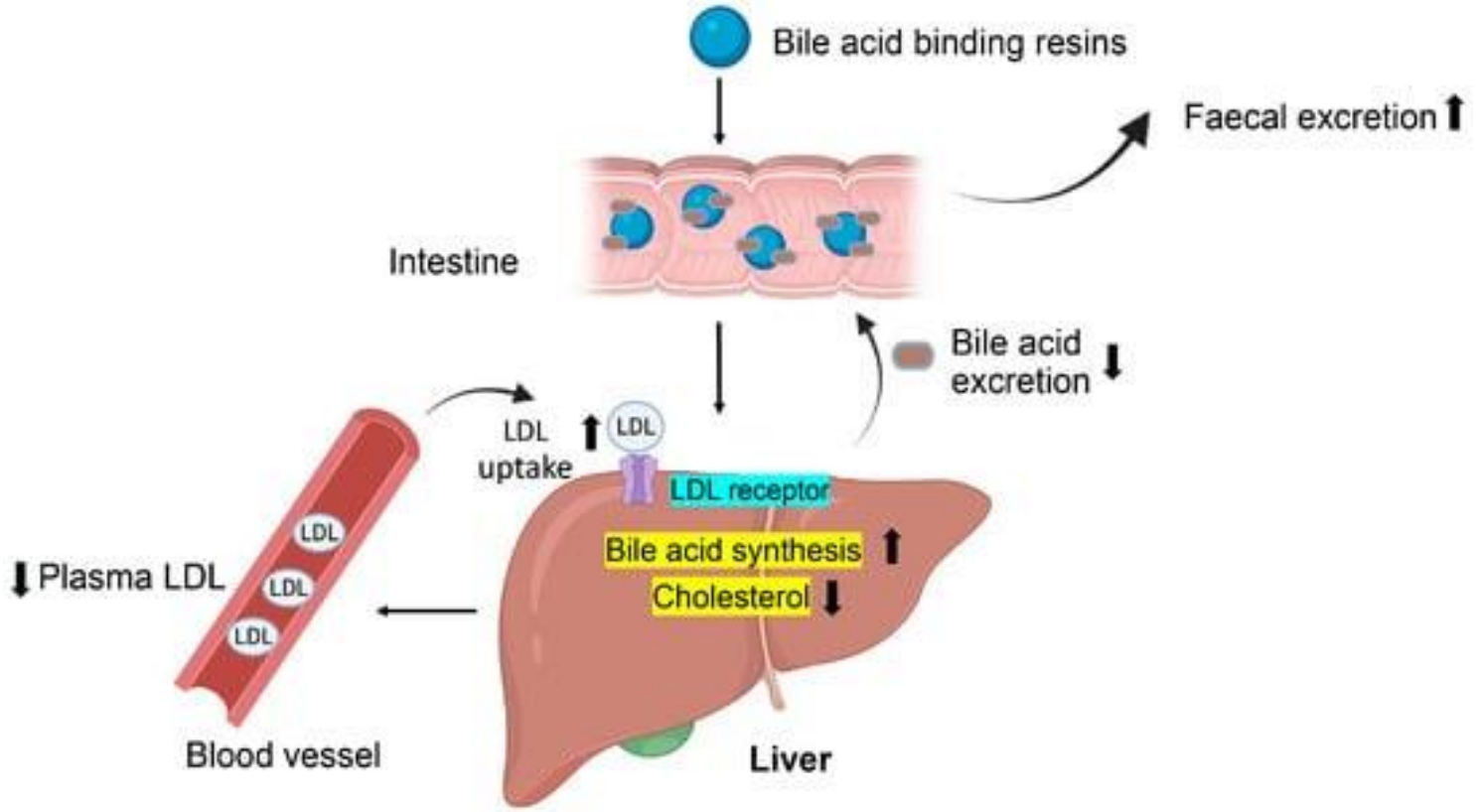

**Figure 1. Mechanism of actions of antihyperlipidemic agents.**

# 2. Bile acid sequestrants (Resins):

- Cholestyramine, Colestipol



**Mechanism :** A large, nonabsorbable polymer cationic resin that binds bile acids in the intestine and thereby interrupts enterohepatic bile acid circulation. The ↑ excretion of bile acids results in ↑ conversion of cholesterol to bile acids in the liver. This, in turn, results in upregulation of hepatic LDL receptors and hence ↑ clearance of LDL from the plasma.



## Uses:

1- Type **IIa** hypercholesterolemia

2- Diarrhea due to bile acid malabsorption (bile acid induce diarrhea).

3- Pruritus' due to obstructive jaundice

## Side Effects:

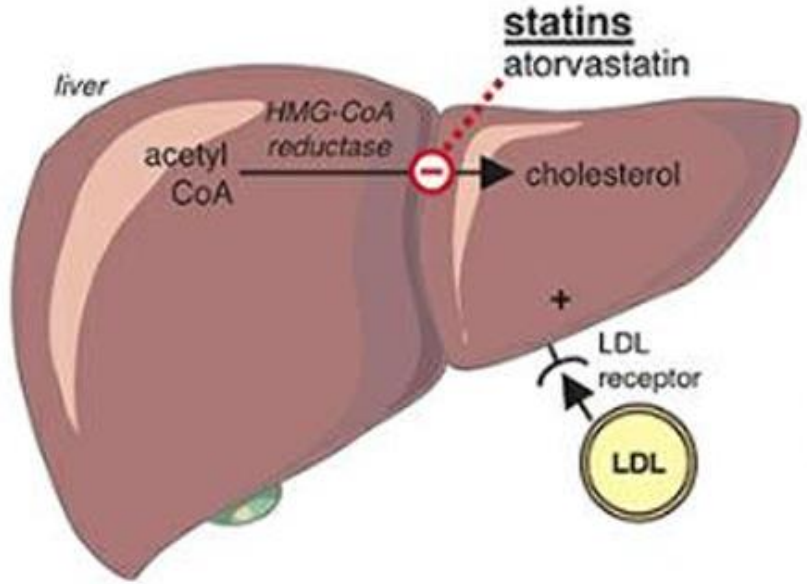
1- GIT upset Unpleasant to take (bitter, sandy, gritty), bloating, indigestion, nausea, constipation. High doses: steatorrhea,

2- Reduces absorption of fat soluble vitamins (A, D, E, and K).

# 3- HMG-CoA reductase inhibitors (statins)

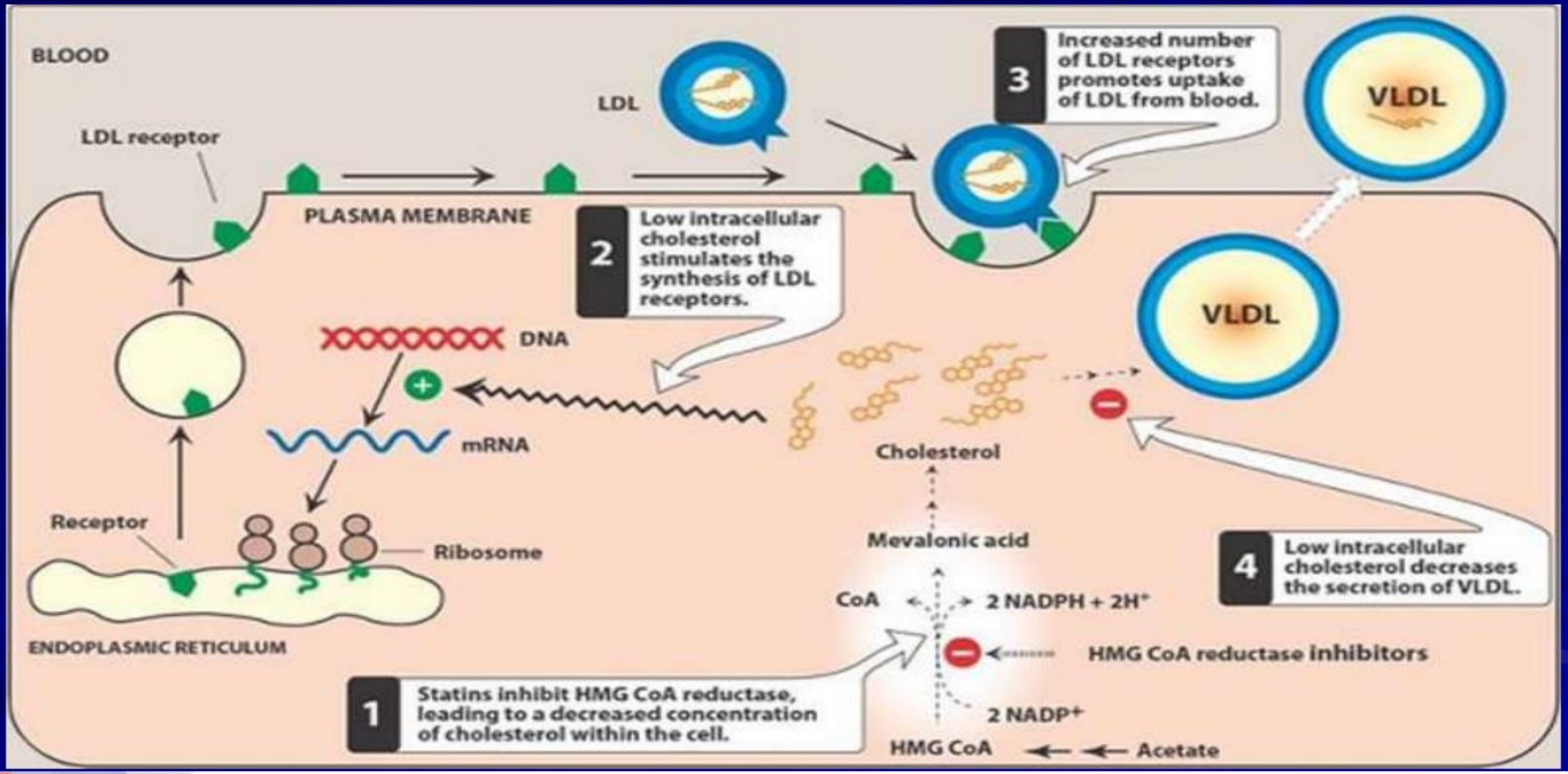
ATORVASTATIN, PRAVASTATIN, SIMVASTATIN, FLUVASTATIN, LOVASTATIN , ROSUVASTATIN

**Mechanism :** are HMG-CoA reductase inhibitors which is a rate-limiting enzyme for cholesterol synthesis. Statins thus blocks endogenous cholesterol synthesis, this decrease in liver cholesterol will activate SREBP (sterol-regulated, membrane-bound transcription factors) processing → forcing hepatocytes to ↑ **LDL** receptors displayed on liver cell membranes → The newly produced LDL receptors remove LDL from the blood and deliver it to the interior of the cell where the LDL is digested, and its released cholesterol becomes available for metabolic purposes.




Inhibition of endogenous cholesterol synthesis by the liver leads to upregulation of LDL receptors on the surface of the liver and increased clearance of LDL from the bloodstream.

# Mechanism of Action of Statins



**Clinical Uses:** Drug therapy of choice to reduce hypercholesterolemia and achieve LDL cholesterol goals in patients at risk for or with coronary artery disease (CHD).









# Adverse Effects

**H:** Hepatocyte dysfunction leading to elevation of serum transaminases. Therapy should b stopped If liver enzymes rise 3 folds the upper normal value.

**M:** Myopathy, myositis and rhabdomyolysis in both cardiac and muscle leading to elev level of CPK enzyme.

**G:** GIT upset

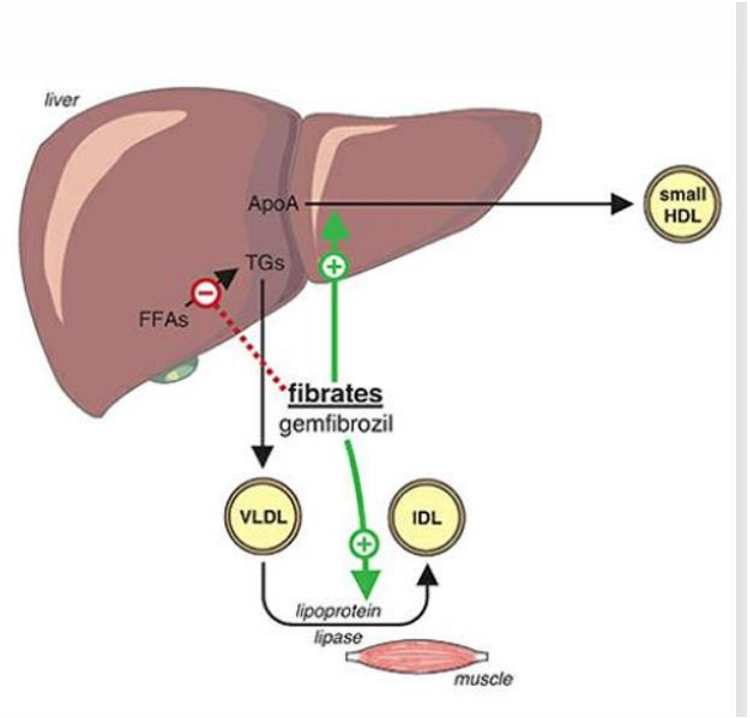
**COA:** cataract (lenticular opacity)

**Reductase;** renal dysfunction

# 4- Fibric Acid Derivatives: Clofibrate, FENOFIBRATE, BEZAFIBRATE and GEMFIBROZIL

**Mechanism:** A fibric acid derivative that binds to and activates nuclear transcription regulator peroxisome proliferator-activated receptor-α (PPAR- α), expressed primarily in the liver and skeletal muscle. PPAR-α functions as a transcription factor that regulates the expression of genes involved in lipid metabolism. Activated PPAR-α enhances the transcription of Lipoprotein Lipase (LPL), an enzyme responsible for hydrolyzing triglycerides in chylomicrons and VLDL particles into free fatty acids. This leads to: Increased clearance of triglyceride-rich lipoproteins from the bloodstream and reduction in plasma triglyceride levels.

Clinical Uses: Hypertriglyceridemia.



# Adverse Effects

1- **GIT upset** (nausea and vomiting)

2- Gallstone

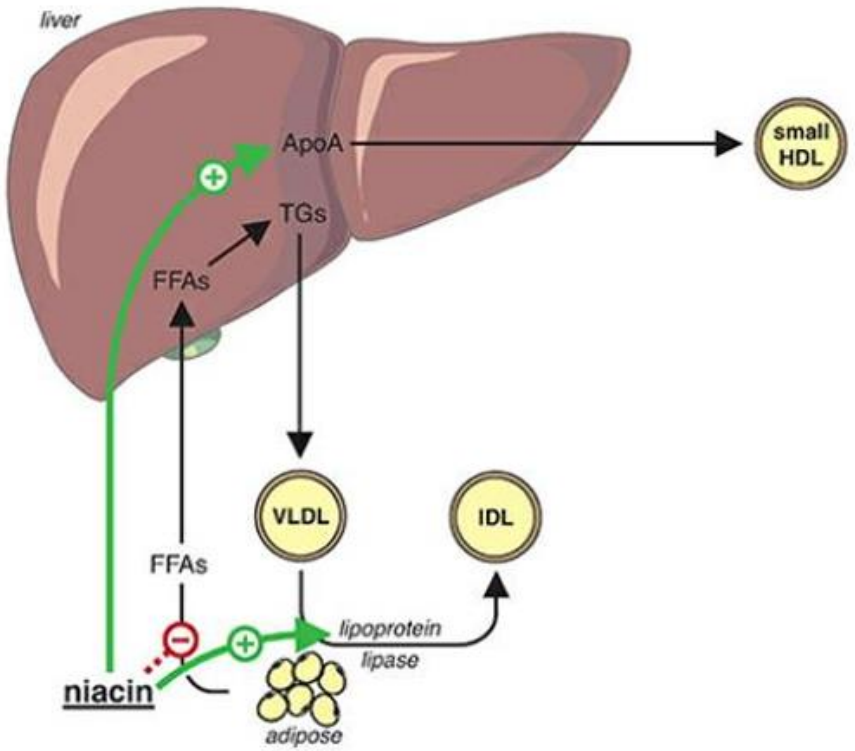
**3- Hepatic dysfunction** and elevation of serum transaminases.

4- **increase the risk of myopathy** if used in combination with statins.

# 5-NIACIN (vitamin B3)

**Mechanism :** It inhibits lipolysis in adipose tissue → Less free fatty acids reach the liver → Reduced VLDL and LDL production and TG synthesis.

## Clinical Uses: Hypertriglyceridemia.




## Adverse Effects

1- Flushing (prostaglandin mediated) is common wh therapy is initiated, or the dose increased. Can be prevent by taking an aspirin beforehand and by using sustaine release preparations.

2- GI upset

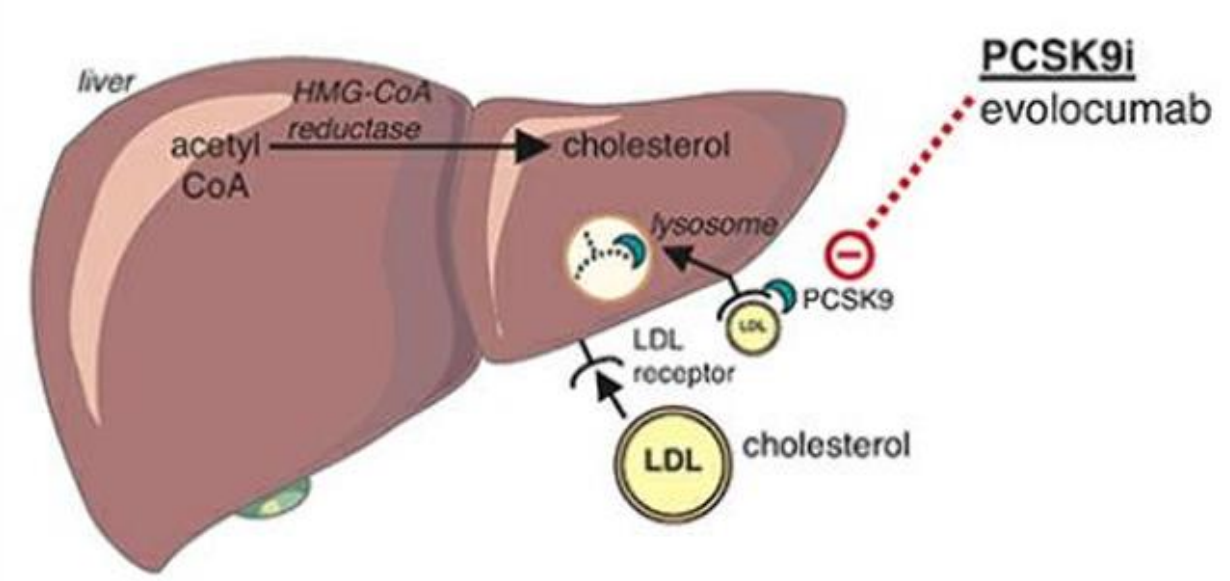
3- myopathy

4- glucose intolerance

5- hyperuricemia

# 6 -PCSK9 EVOLOCUMAB , ALIROCUMAB

**Mechanism :** This monoclonal antibody class of drugs inhibits the PCSK9 enzyme, which plays a major role in the breakdown of hepatic LDL receptors. Inhibition of PCSK9 increases the number of LDL receptors available leading to a profound reduction in circulating LDL particles. By preventing LDL receptor destruction, PCSK9i as adjunct to statin therapy can reduce LDL-C by 50-60% above that achieved by statin therapy alone.



# Clinical Uses: Hypercholesterolemia.



# Summary

| | LDL-cholesterol | TGs |
|---|---|---|
| Cholestyramine - Ezetimibe | ●●● | |
| HMG Co-A reductase inhibitors | ●●● | |
| Fibric acid derivatives | | ♣♣♣ |
| Niacin | ● | ♣♣ |
| PCSK9 inhibitors | ●●● | |