



# **Anti Hyperlipidemic Drugs**

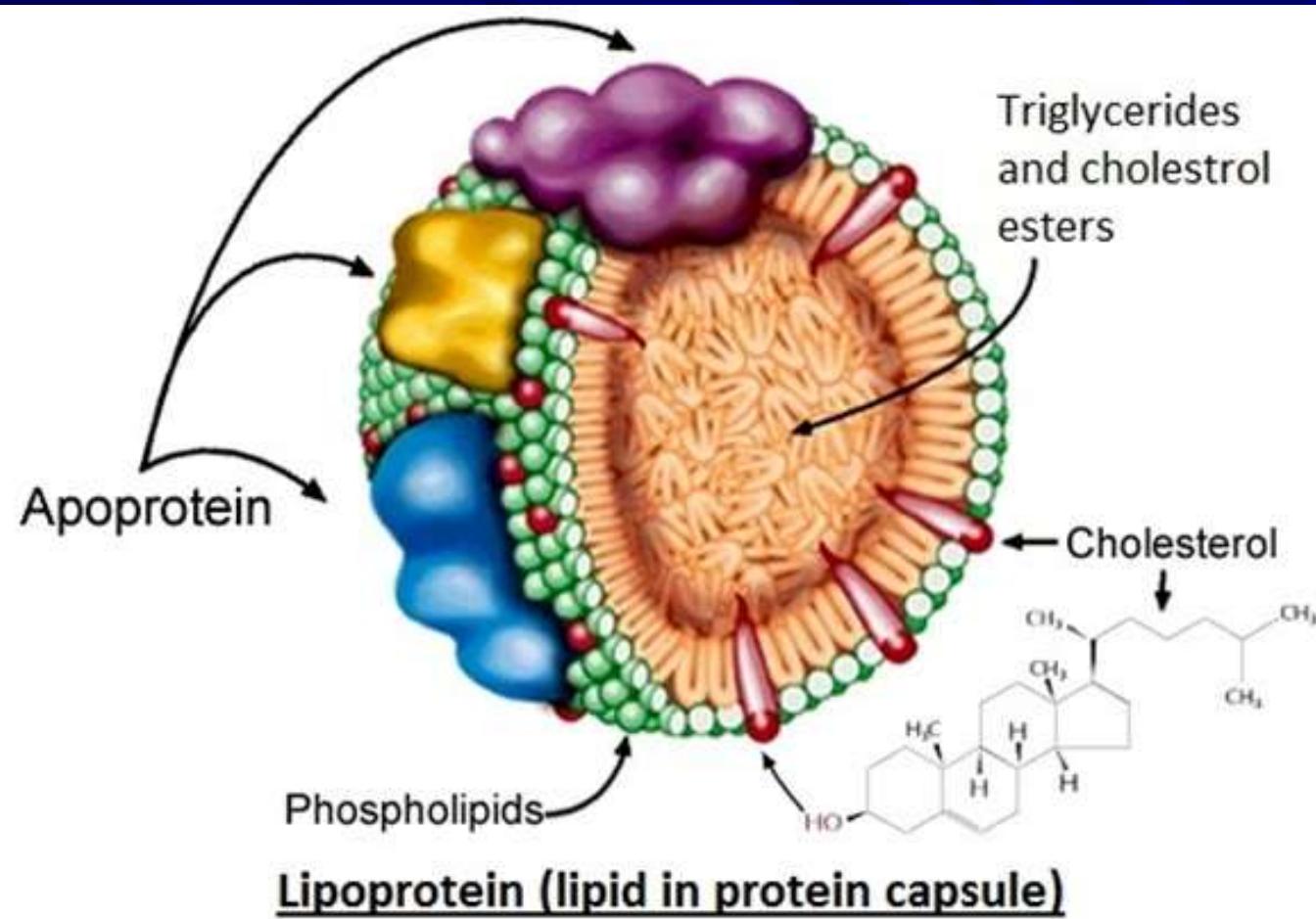
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## **Lipoproteins**

Macromolecular complexes in the blood that transport lipids

## **Apolipoproteins**

Proteins on the surface of lipoproteins; they play critical roles in the regulation of lipoprotein metabolism and uptake into cells



## **Chylomicrons**

Formed in the intestine and carry triglycerides of dietary origin, unesterified cholesterol, and cholestrylo esters. They transit the thoracic duct to the bloodstream

## **Low-density lipoprotein (LDL)**

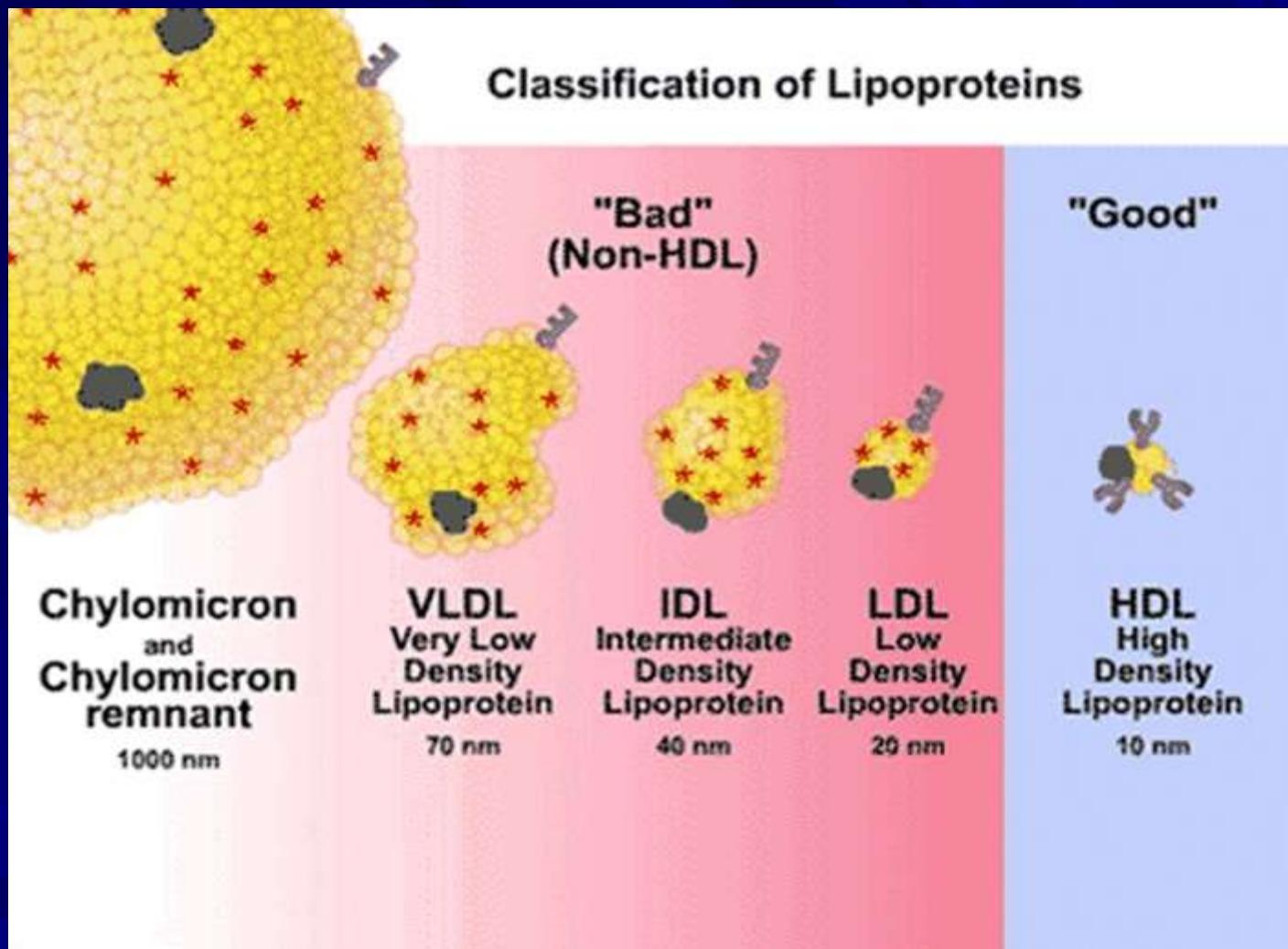
Cholesterol-rich lipoprotein whose regulated uptake by hepatocytes and other cells requires functional LDL receptors; an elevated LDL concentration is associated with atherosclerosis

## **High-density lipoprotein (HDL)**

Cholesterol-rich lipoprotein that transports cholesterol from the tissues to the liver; a low concentration is associated with atherosclerosis

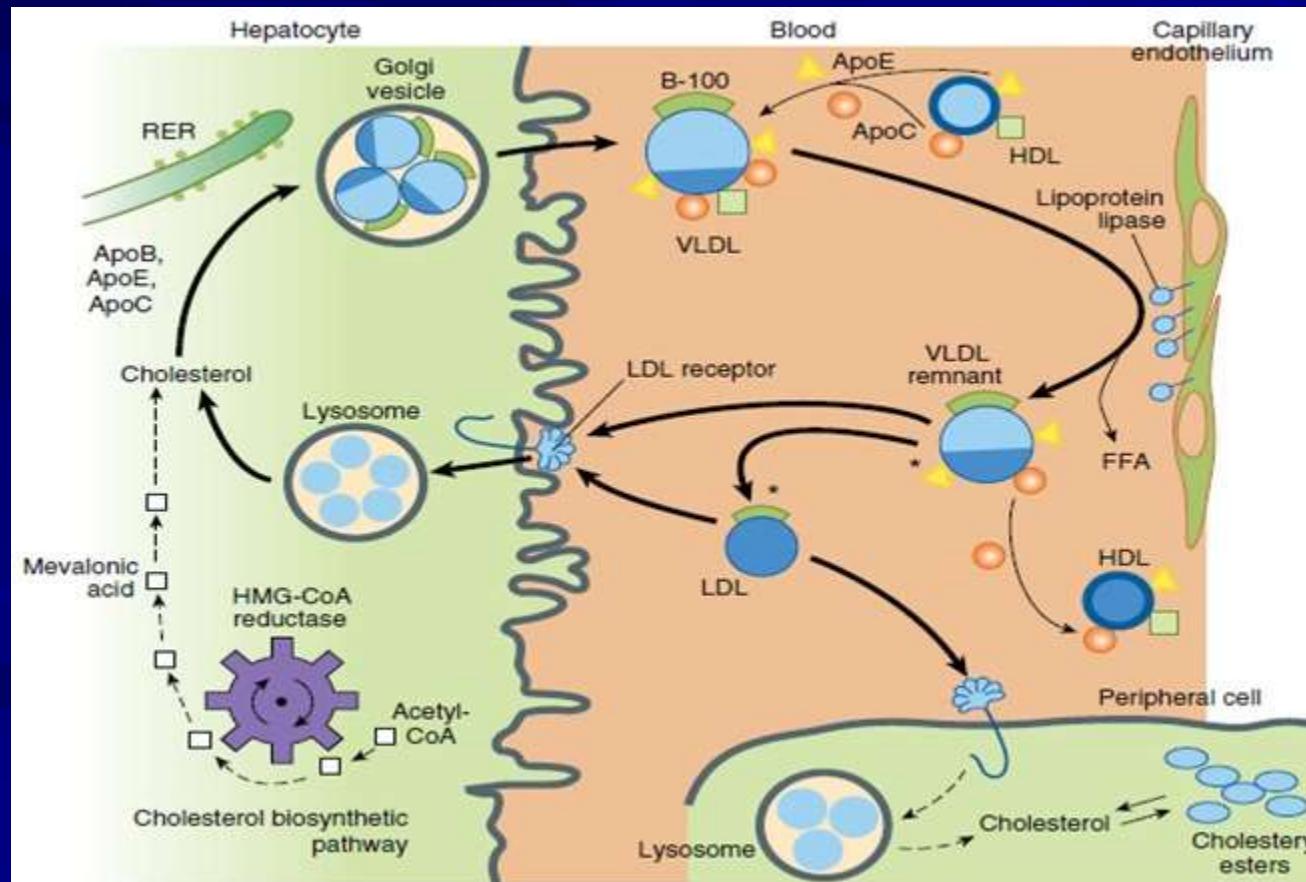
## **Very-low-density lipoprotein (VLDL)**

Triglyceride- and cholesterol-rich lipoprotein secreted by the liver that transports triglycerides to the periphery; precursor of LDL



# Metabolism of Lipoproteins of Hepatic Origin;

triangles indicate apo E; circles and squares represent C apolipoproteins. FFA, free fatty acid; RER, rough endoplasmic reticulum



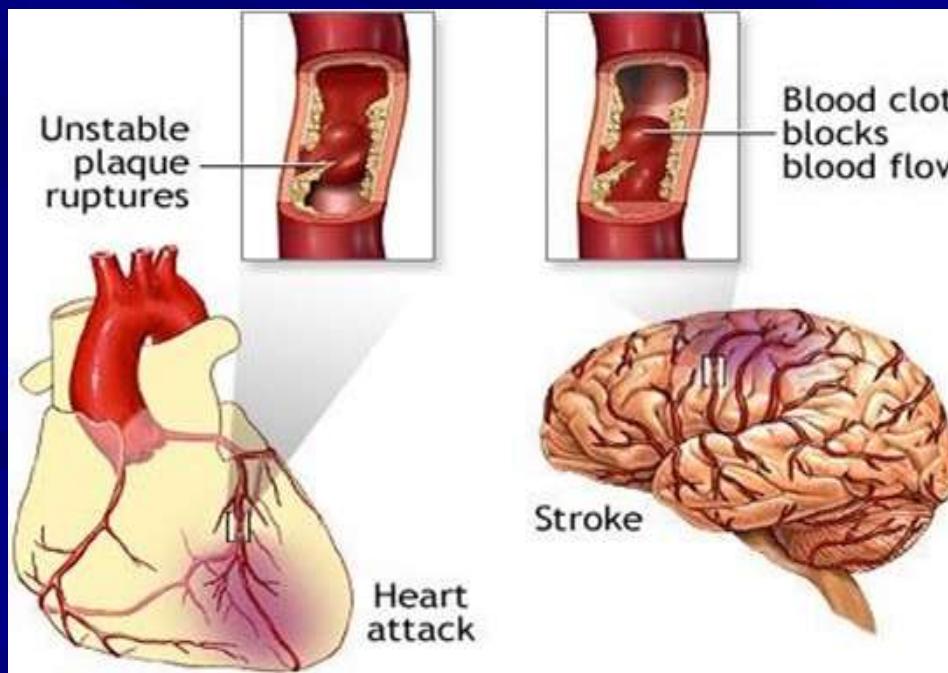
## Metabolism of Lipoproteins of Hepatic Origin

- Nascent VLDL are secreted via the Golgi apparatus. They acquire additional apo C lipoproteins and apo E from HDL.
- Very-low-density lipoproteins (VLDL) are converted to VLDL remnants (IDL) by lipolysis via lipoprotein lipase in the vessels of peripheral tissues.
- C apolipoproteins and a portion of the apo E are given back to high-density lipoproteins (HDL).
- Some of the VLDL remnants are converted to LDL by further loss of triglycerides and loss of apo E.
- A major pathway for LDL degradation involves the endocytosis of LDL by LDL receptors in the liver and the peripheral tissues, for which apo B-100 is the ligand.

**Note:** Lipoprotein lipase (LPL) An enzyme found primarily on the surface of endothelial cells that releases free fatty acids from triglycerides in lipoproteins; the free fatty acids are taken up into cells

# Lipoprotein Disorders

- Disorders of lipid metabolism are manifest by elevation of the plasma concentrations of the various lipid and lipoprotein fractions (total and LDL cholesterol, VLDL, triglycerides, chylomicrons) and they result in cardiovascular disease and atherosclerosis (deposition of fats at walls of arteries, forming plaque)



## **Hyperlipoproteinemias or Hyperlipidemias.**

Metabolic disorders that involve elevations in any lipoprotein species

### **Hyperlipemia**

denotes increased levels of triglycerides.

**The major clinical sequelae of hyperlipidemias are:**

- Acute pancreatitis
- Atherosclerosis.

## **Lipoprotein Disorders**

- Detected by measuring lipids in serum after a 10-hour fast.
- Risk of heart disease increases with concentrations of the atherogenic lipoproteins and is modified by other risk factors.
- Risk of heart disease is inversely related to levels of HDL.

## **Lipoprotein Disorders**

- Primary hyperlipoproteinemias
- Secondary hyperlipoproteinemia.

# The primary hyperlipoproteinemias and their treatment.

Disorder	Manifestations	Diet + Single Drug <sup>1</sup>	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase or cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management (omega-3 fatty acids, niacin, or fibrate)	Niacin plus fibrate
Familial hypertriglyceridemia- Severe	VLDL, chylomicrons increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
	VLDL increased; chylomicrons may be increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Omega-3 fatty acids, niacin, fibrate, or reductase inhibitor	Two or three of the individual drugs
	LDL predominantly increased	Niacin, reductase inhibitor, or ezetimibe	Two or three of the individual drugs
	VLDL, LDL increased	Omega-3 fatty acids, niacin, or reductase inhibitor	Niacin or fibrate plus reductase inhibitor <sup>2</sup>
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin, or either plus reductase inhibitor
Familial hypercholesterolemia	LDL increased	Reductase inhibitor, resin, niacin, or ezetimibe	Two or three of the individual drugs
	LDL increased	Niacin, atorvastatin, rosuvastatin, or ezetimibe	Niacin plus reductase inhibitor plus ezetimibe
Familial ligand-defective apo B	LDL increased	Niacin, reductase inhibitor, or ezetimibe	Niacin plus reductase inhibitor or ezetimibe
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin	

## Secondary causes of hyperlipoproteinemia.

Hypertriglyceridemia	Hypercholesterolemia
Diabetes mellitus	Hypothyroidism
Alcohol ingestion	Early nephrosis
Severe nephrosis	Resolving lipemia
Estrogens	Immunoglobulin-lipoprotein complex disorders
Uremia	Anorexia nervosa
Corticosteroid excess	Cholestasis
Myxedema	Hypopituitarism
Glycogen storage disease	Corticosteroid excess
Hypopituitarism	
Acromegaly	
Immunoglobulin-lipoprotein complex disorders	
Lipodystrophy	
Protease inhibitors	

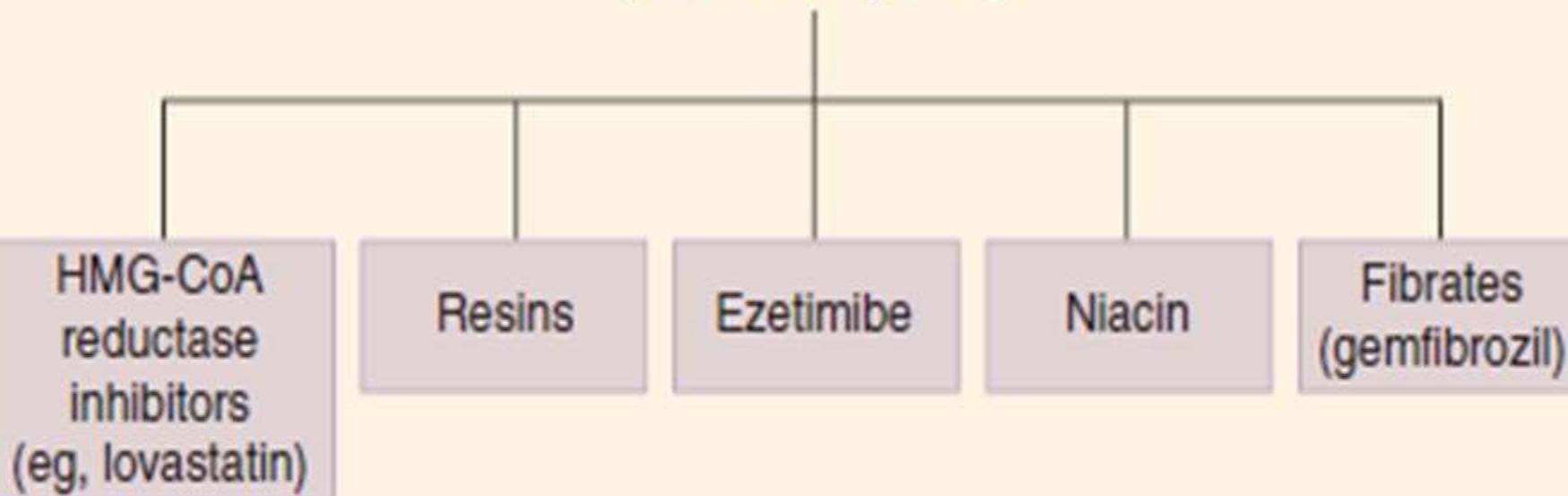
# **Anti-hyperlipidemic Drugs are Mainly Classified into 5 groups:**

1. HMG-CoA Reductase Inhibitors  
Atorvastatin, Fluvastatin, Lovastatin, Pravastatin and Simvastatin.
2. Fibrates  
Fenofibrate, Gemfibrozil and Clofibrate
3. Anion-exchange resins (bile acid sequestrants)  
Colesevelam, Colestipol and Cholestyramine
4. Nicotinic acid  
Niacin.
5. Cholesterol absorption inhibitors  
Ezetimibe.

## **Other Drugs**

- Alpha-tocopherol acetate (vitamin E)
- Omega-3 marine triglycerides (Maxepa)
- Orlistat

## Lipid-lowering drugs



## Drug Therapy:

The primary goal of therapy is to:

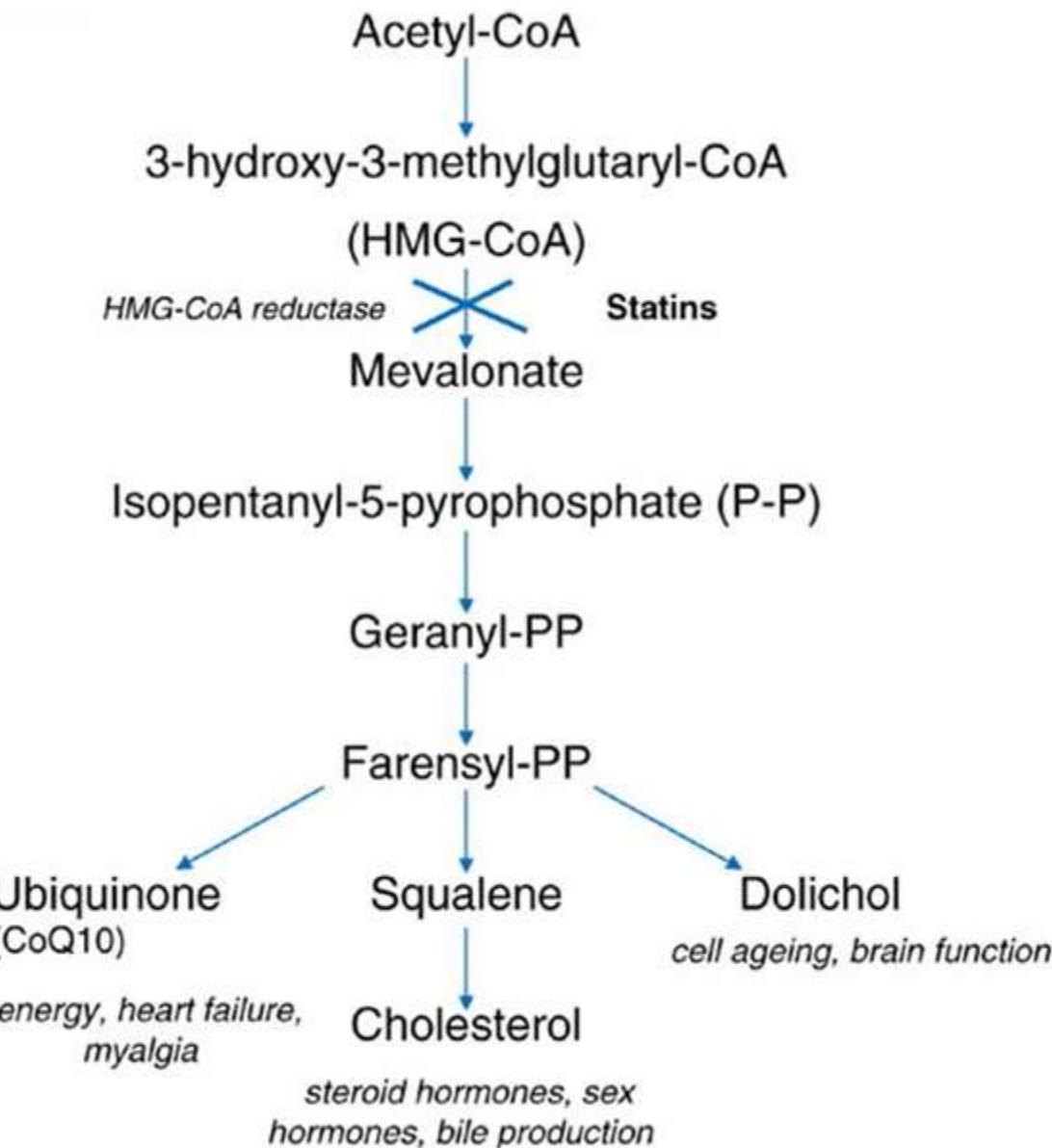
- Decrease levels of LDL
- Increase in HDL

# HMG-CoA Reductase Inhibitors (HMGs or Statins)

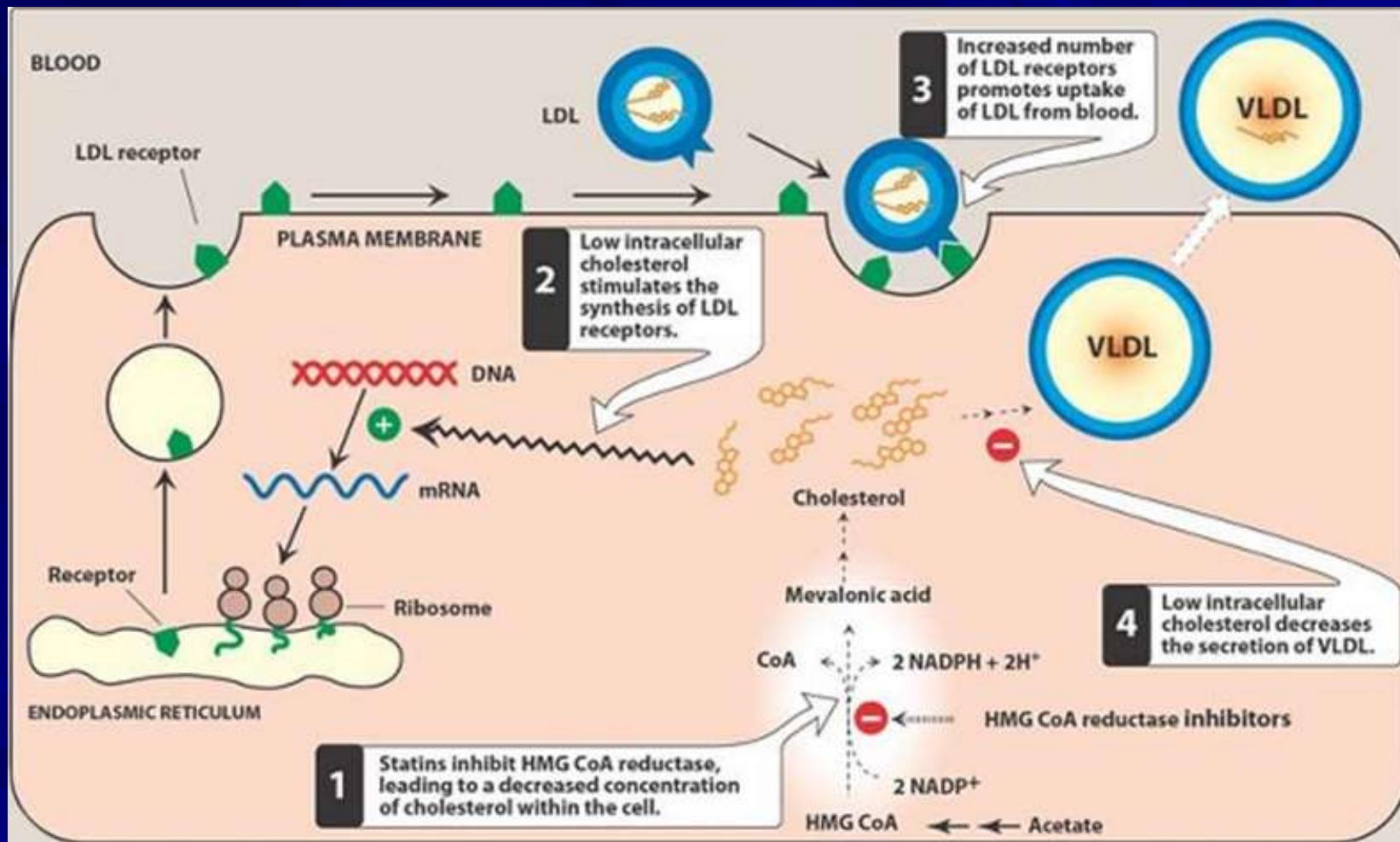
- Lovastatin
- Simvastatin
- Pravastatin
- Atorvastatin
- Fluvastatin
- Rosuvastatin

# Mechanism of Action of HMGs or Statins

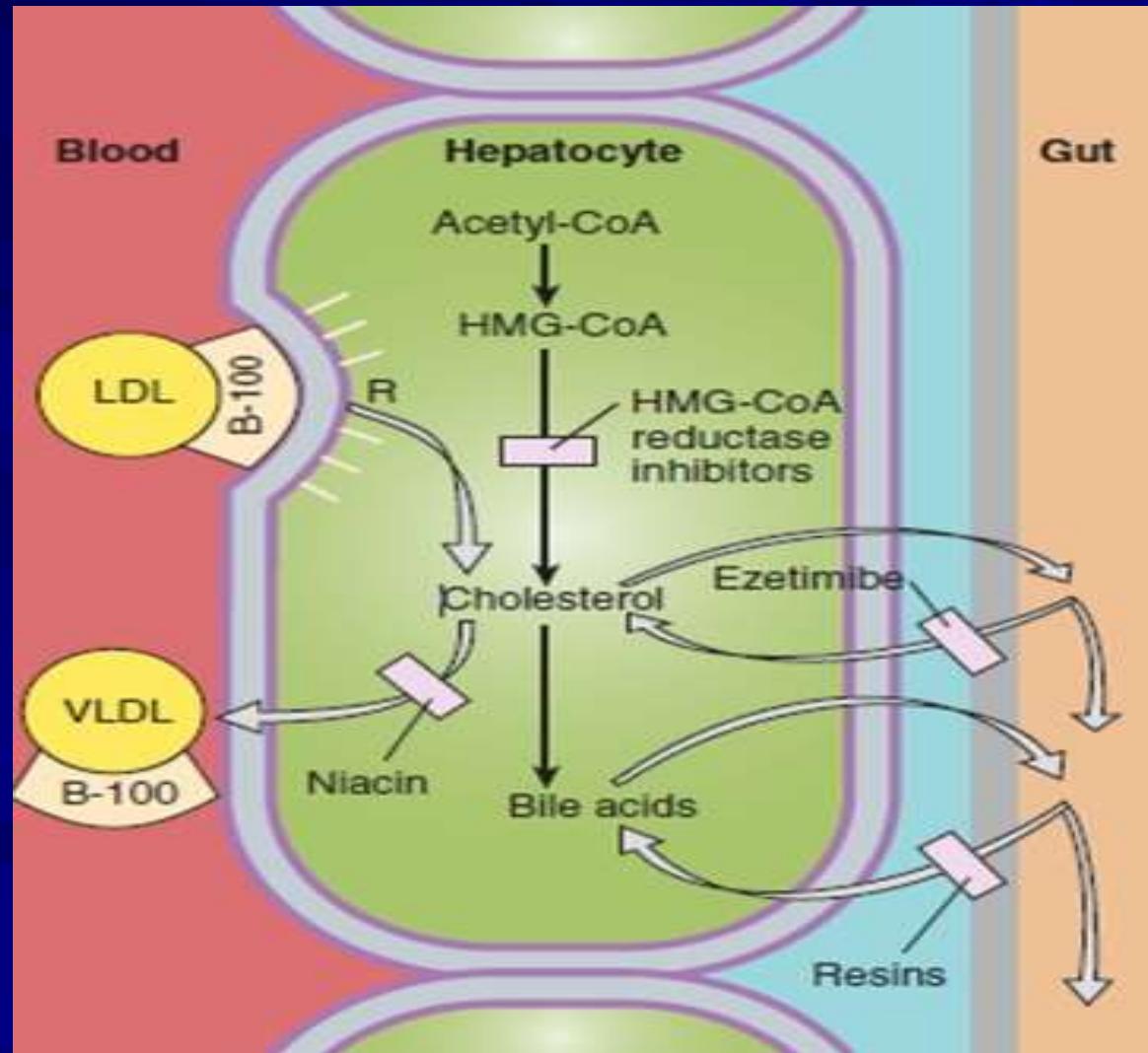
- Most potent LDL reducers
- They are structural analogs of HMG-CoA
- Competitively inhibit HMG-CoA reductase enzyme
- They block the rate-limiting step in hepatic cholesterol synthesis (conversion of hydroxy methylglutaryl coenzyme A (**HMG-CoA**) to mevalonate by HMG-CoA reductase)
- Low intracellular cholesterol stimulate the synthesis of LDL receptors
- Promote uptake of LDL from the blood
- Low intracellular cholesterol decrease secretion of VLDL to the blood
- They have direct anti-atherosclerotic effects, and have been shown to prevent bone loss.



# Mechanism of Action of Statins



# Sites of Action of Antihyperlipidemias.



## Therapeutic Uses:

- These drugs are effective in lowering LDL cholesterol levels especially when used in combination with other cholesterol lowering drugs.
- They reduce the risk of coronary events and mortality in patients with ischemic heart disease, and they also reduce the risk of ischemic stroke.

- Rosuvastatin, atorvastatin, and simvastatin have greater maximal efficacy than the other statins while Fluvastatin has less maximal efficacy
- ↓Triglycerides and ↑HDL cholesterol in patients with triglycerides levels that are higher than 250 mg/dL and with reduced HDL cholesterol levels.

## Pharmacokinetics

- Lovastatin and simvastatin are prodrugs that are hydrolyzed in the gastrointestinal tract to the active derivatives
- Pravastatin, Atorvastatin, fluvastatin and rosuvastatin are active as given
- Absorption varies from 40% to 75% but Fluvastatin completely absorbed.
- Most of the absorbed dose is excreted in the bile; 5–20% is excreted in the urine.
- Plasma Half lives of these drugs range from 1 to 3 hours, atorvastatin (14 hours), pitavastatin (12 hours) and rosuvastatin (19 hours).

- Because of a circadian rhythm to LDL-receptor synthesis & the cholesterol synthesis also occurs predominantly at night, reductase inhibitors-except atorvastatin and rosuvastatin-should be given in the evening if a single daily dose is used.

## Adverse Effect of Statins

1. Transient, and minor abnormality of liver function tests (Mild elevations of serum aminotransferases)
2. Increase in creatine kinase (released from skeletal muscle) in 10% of patients
3. Myopathy and rhabdomyolysis (disintegration or dissolution of muscle and elevation of muscle enzymes (creatine kinase, CPK)

NOTE: In patients with renal insufficiency, Plasma creatine kinase levels should be determined regularly.

## Drug Interactions:

- The HMG CoA reductase inhibitors are metabolized by the cytochrome P450 system; drugs or foods (eg, grapefruit juice) that inhibit cytochrome P450 activity increase the risk of hepatotoxicity and myopathy.
- The HMG CoA reductase inhibitors may also increase warfarin levels. Thus, it is important to evaluate INR
- Cyclosporine, itraconazole, erythromycin and gemfibrozil or niacin. Plasma creatine kinase levels should be determined regularly in patients taking drugs.

## Contraindications:

- Pregnancy (teratogenic)
- Nursing mothers.
- Children or teenagers

# Fibric Acid Derivatives (Fibrates)

- Bezafibrate
- Ciprofibrate
- Fenofibrate
- Gemfibrozil

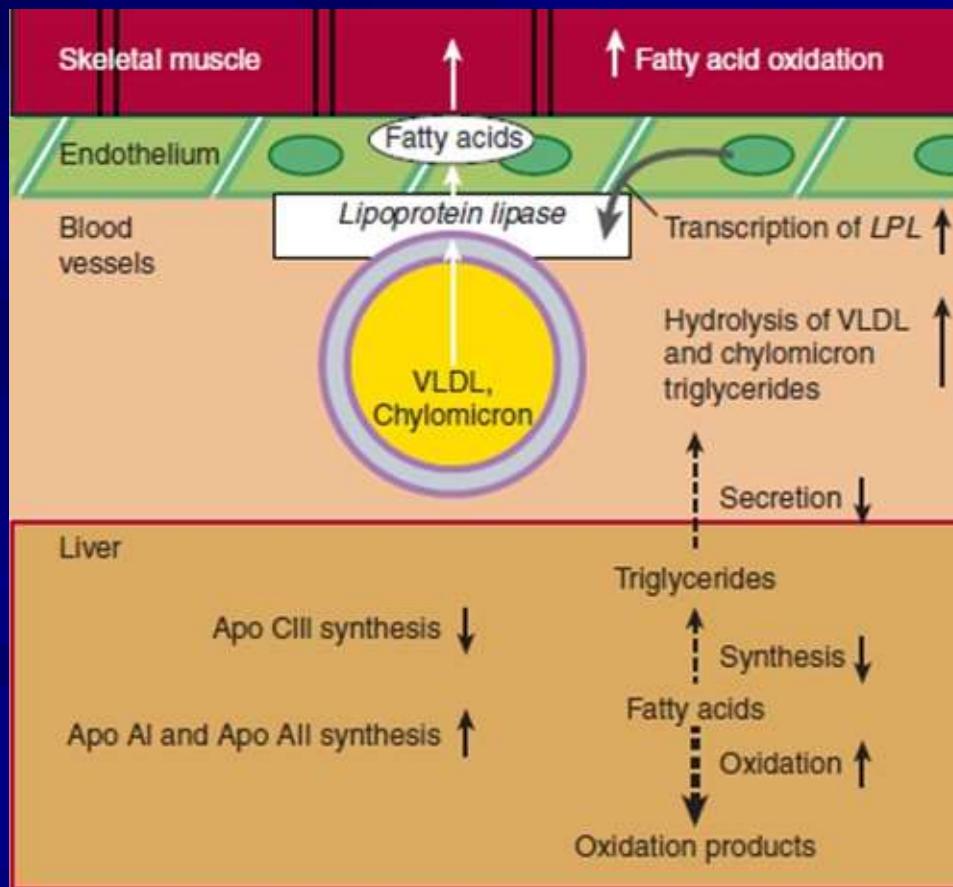
## Mechanism of Action

- Agonists at PPAR- $\alpha$  (peroxisome proliferator-activated receptor- $\alpha$  )  $\rightarrow$  expression of genes responsible for increased activity of plasma lipoprotein lipase enzyme  $\rightarrow$  **hydrolysis of VLDL and chylomicrons** $\rightarrow$   $\downarrow$  serum TGs
- $\uparrow$  apo A-I and apo A-II
- $\downarrow$  apo C-III, an inhibitor of lipolysis.
- A major effect is an increase in oxidation of fatty acids in liver and striated muscle
- They increase lipolysis of lipoprotein triglyceride via LPL
- Increase clearance of LDL by liver &  $\uparrow$  HDL.

**Note:** Proliferator-activated receptor-alpha (PPAR- $\alpha$ ) is Member of a family of nuclear transcription regulators that participate in the regulation of metabolic processes; target of the fibrate drugs and omega-3 fatty acids

## Hepatic and peripheral effects of fibrates.

These effects are mediated by activation of peroxisome proliferator-activated receptor- $\alpha$ , which modulates the expression of several proteins.



## Therapeutic Uses

- Hypertriglyceridemias in which VLDL predominate
- Dysbetalipoproteinemia.
- Hypertriglyceridemia that results from treatment with viral protease inhibitors

## **Pharmacokinetic of Fibrat Acid Derivatives:**

- Well absorbed from the gastrointestinal tract
- Extensively bound to plasma proteins
- Excreted mainly by the kidney as unchanged drug or metabolites.

## **Contraindication**

- Where hepatic or renal function is severely impaired (but gemfibrozil has been used in uraemic and nephrotic patients without aggravating deterioration in kidney function)
- Pregnant or lactating women

## Adveres Effect of Fibric Acid Derivatives

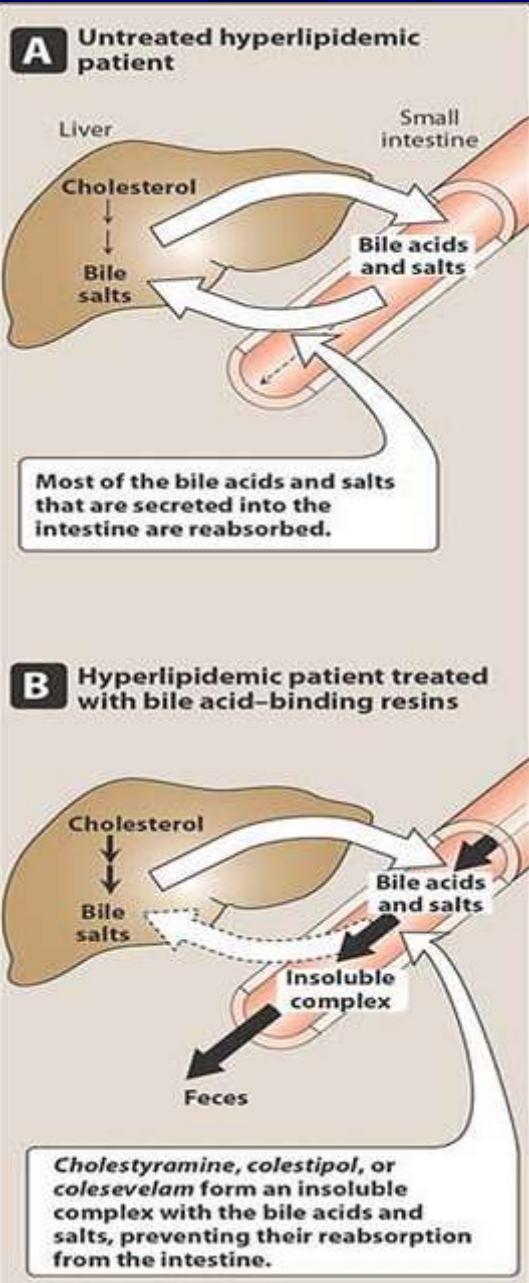
- Gastrointestinal effects, rash
- Myopathy, arrhythmias, hypokalemia,
- Increase in aminotransferases or alkaline phosphatase
- Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.
- Fibric acid derivatives may induce a Myopathy and rhabdomyolysis **the risk is greater in:**
  - Patients with poor renal Function
  - In patients taking a statin.
- Fibrates enhance the effect of co-administered oral Anticoagulants.

## Anion-exchange Resins (Bile Acid Sequestrants):

- Cholestyramine
- Colesevelam
- Colestipol

## **Mechanism of Action:**

- Anion exchange resins bind bile acids in the intestine forming complex → loss of bile acids in the stools → ↑ conversion of cholesterol into bile acids in the liver.
- Decreased concentration of intrahepatic cholesterol → compensatory increase in LDL receptors → ↑ hepatic uptake of circulating LDL → ↓ serum LDL cholesterol levels.



## **Therapeutic uses of Anion-exchange resins (Bile Acid Sequestrants):**

- Hypercholesterolemia
- Reduce pruritus in patients with cholestasis (biliary obstruction and bile salt accumulation).

## **Pharmacokinetics:**

Orally given but neither absorbed nor metabolically altered by intestine, totally excreted in feces.

## **Adverse Effect of Anion – Exchange Resins (Bile Acid Sequestrants)**

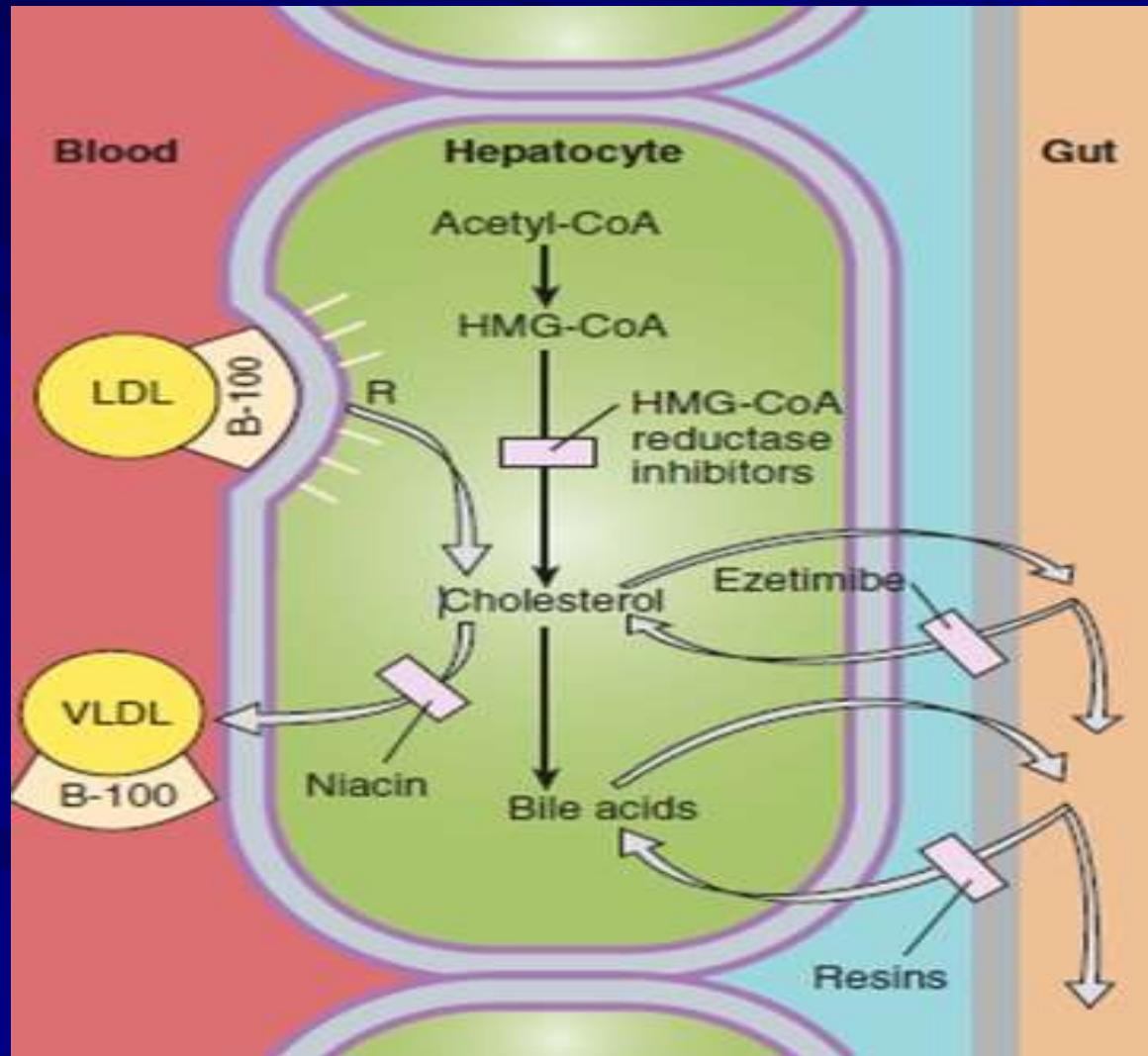
- Gastrointestinal effects: bloating, constipation, and an unpleasant gritty taste.
- Impaired absorptions: Absorption of vitamins (eg, vitamin K, dietary folates) and drugs (eg, thiazide diuretics, warfarin, pravastatin and fluvastatin) is impaired by the resins

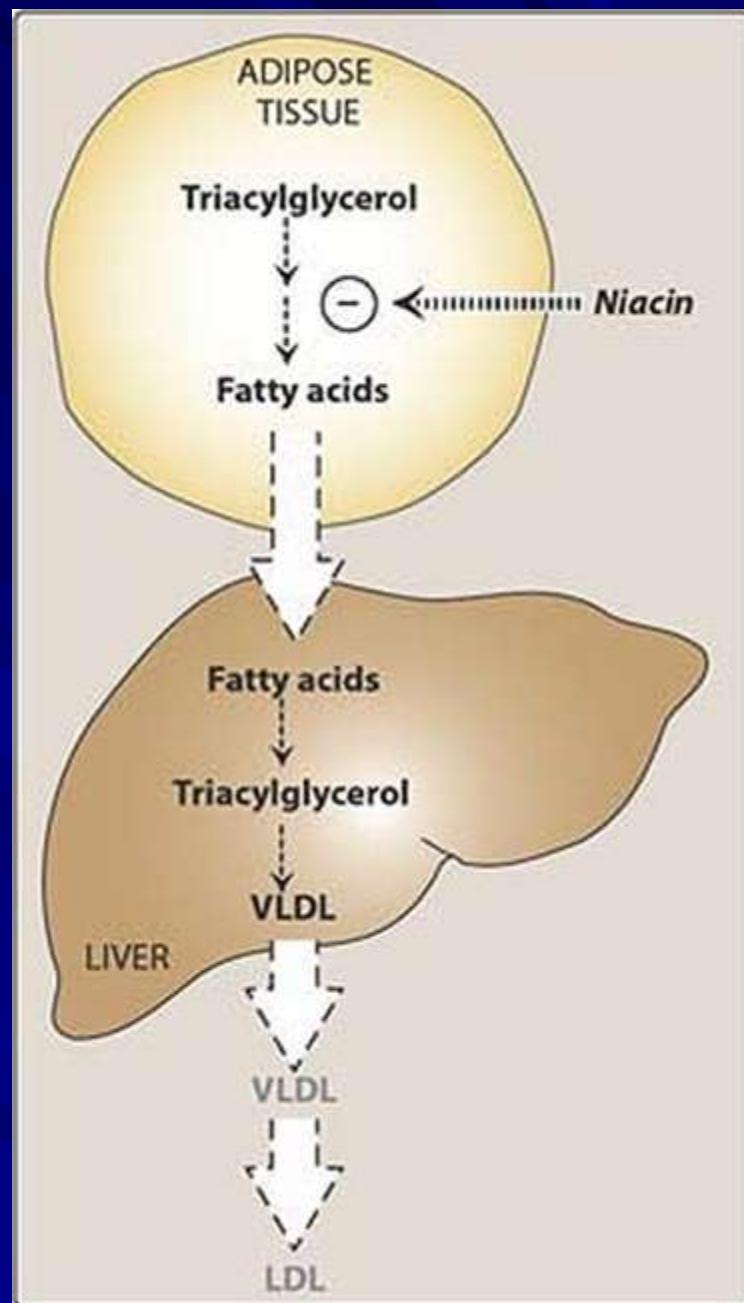
# Niacin (Nicotinic Acid)

## Mechanism of Action:

- Through multiple actions, niacin (but not nicotinamide) ↓ LDL cholesterol, triglycerides, and VLDL and ↑ HDL cholesterol.
- In the liver, ↓VLDL synthesis, which in turn ↓ LDL levels
- Inhibits the intracellular lipase of adipose tissue via receptor-mediated signaling and thus ↓ plasma fatty acid and triglyceride levels. Consequently, LDL formation is ↓ and ↓ LDL cholesterol.
- ↑ Clearance of VLDL by the lipoprotein lipase associated with capillary endothelial cells ↓ in plasma triglyceride
- Niacin reduces the catabolic rate for HDL.
- ↓ circulating fibrinogen a, ↑ tissue plasminogen activator.
- ↓ Endothelial dysfunction → ↓ thrombosis

# Sites of Action of Antihyperlipidemias.







# Niacin (Nicotinic Acid)

## Therapeutic Uses:

- Niacin lowers plasma levels of both cholesterol and triacylglycerol.
- Particularly useful in the treatment of familial hyperlipidemias.
- Niacin is used to treat other severe hypercholesterolemias in combination with other antihyperlipidemic agents.
- Raising plasma HDL levels, which is the most common indication

## Pharmacokinetics:

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

**Note:** Nicotinamide alone does not decrease plasma lipid levels.

## Adverse Effects:

1. Cutaneous flush (most common side effects) accompanied by an uncomfortable feeling of warmth) and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated. The sustained-release formulation of niacin, which is taken once daily at bedtime, reduces bothersome initial adverse effects.
2. Nausea and abdominal pain.
3. Hyperuricemia and gout (Niacin inhibits tubular secretion of uric acid)
4. Impaired glucose tolerance
5. Hepatotoxicity

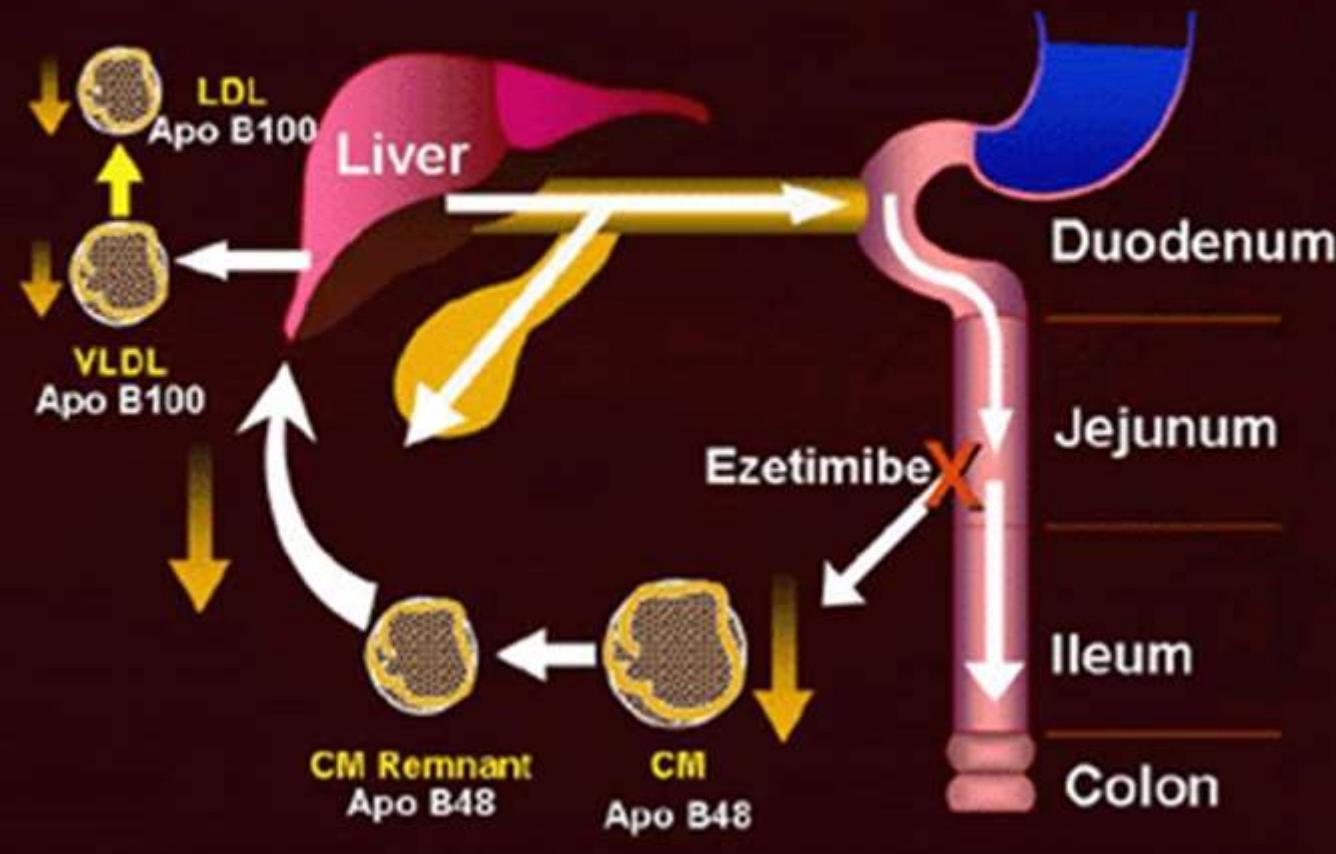


# Cholesterol Absorption Inhibitors

## Ezetimibe

- Prodrug , converted in the liver to the active glucuronide form.
- This active metabolite inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine → ↓ in the delivery of intestinal cholesterol to the liver → ↓ hepatic cholesterol stores → A compensatory ↑ in the synthesis of LDL receptors ,↑ the removal of LDL lipoproteins from the blood (↑ clearance of cholesterol from the blood).
- When combined with an HMG-CoA reductase inhibitor, it is even more effective

## Ezetimibe: Mechanism of Action



## Pharmacokinetic of Ezetimibe

- Metabolized in the small intestine and liver via glucuronide conjugation (a Phase II reaction), with subsequent biliary and renal excretion.
- Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma, with a half-life of approximately 22 hours.
- Ezetimibe has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E. Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.

**Note:** A formulation of ezetimibe and simvastatin has been shown to lower **LDL** levels more effectively than the statin alone.

## Clinical Use of Ezetimibe

- Hypercholesterolemia
- Phytosterolemia (a rare genetic disorder that results from impaired export of phytosterols (plant sterol))

## Adverse Effects of Ezetimibe

- When combined with HMG-CoA reductase inhibitors, it may increase the risk of hepatic toxicity.
- Serum concentrations of the glucuronide form are increased by fibrates and reduced by cholestyramine.

## Combination Drug Therapy

- Maximum effect with minimum toxicity & to achieve the desired effect on the various lipoproteins (LDL, VLDL, and HDL).
- Certain drug combinations provide advantages, others present specific challenges
- Resins interfere with the absorption of certain HMG-CoA reductase inhibitors (pravastatin, cerivastatin, atorvastatin and fluvastatin), these must be given at least 1 h before or 4 h after the resins.
- The combination of reductase inhibitors with either fibrates or niacin → **myopathy**