Antihyperlipidemic Drugs

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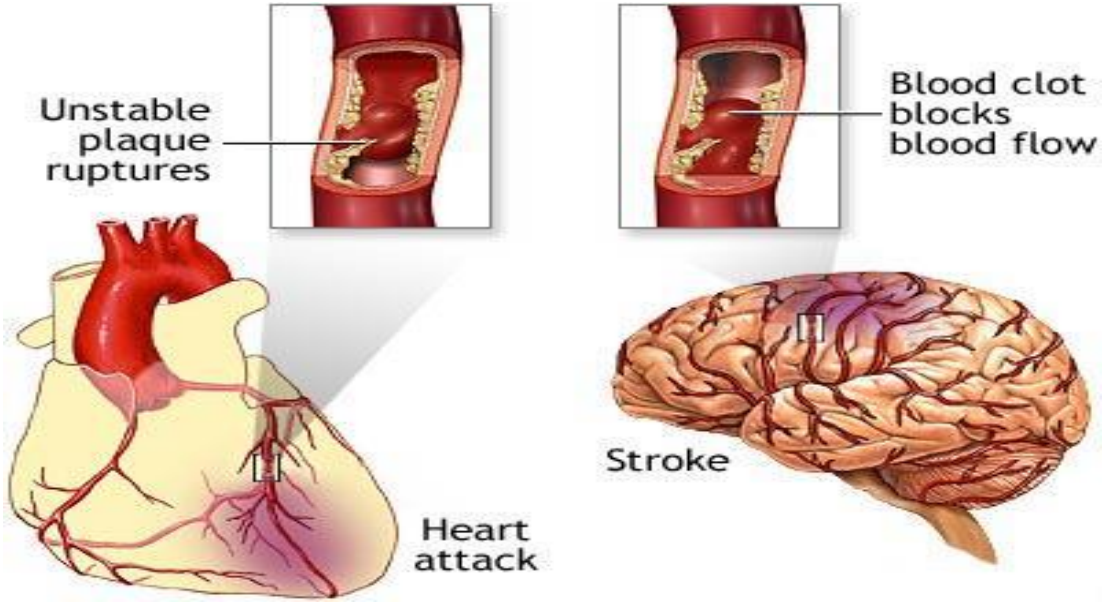
- **Lipid disorders**

  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)

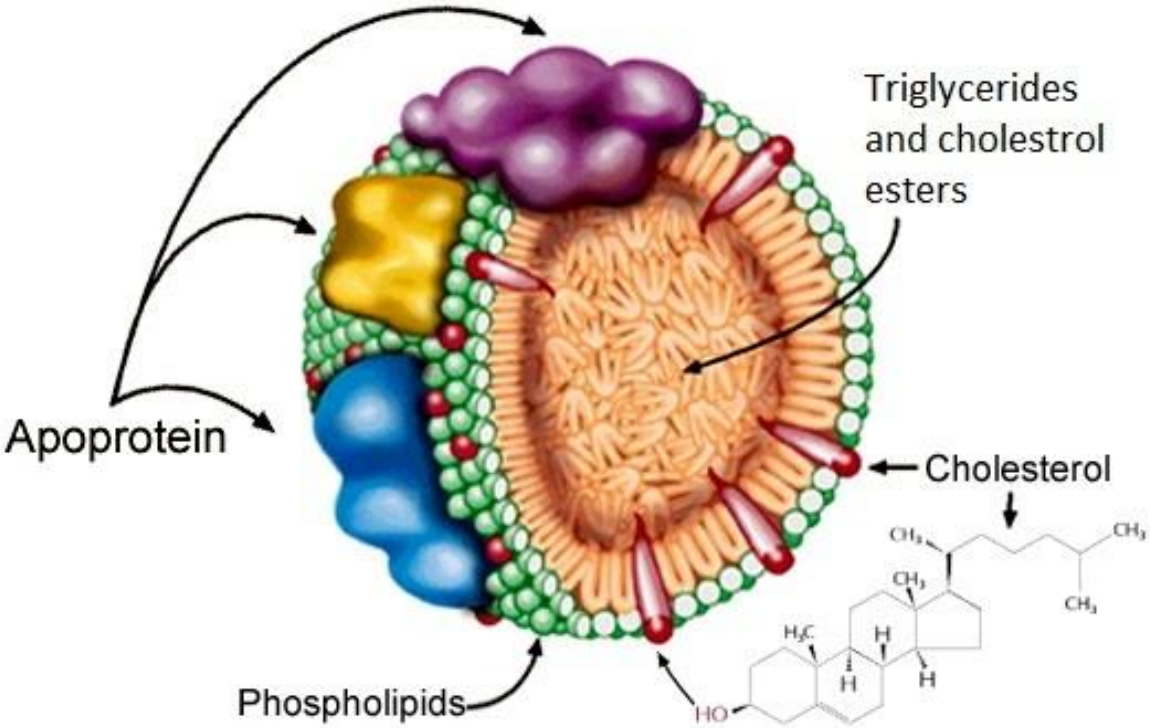


Dyslipidemia / Hyperlipidemias

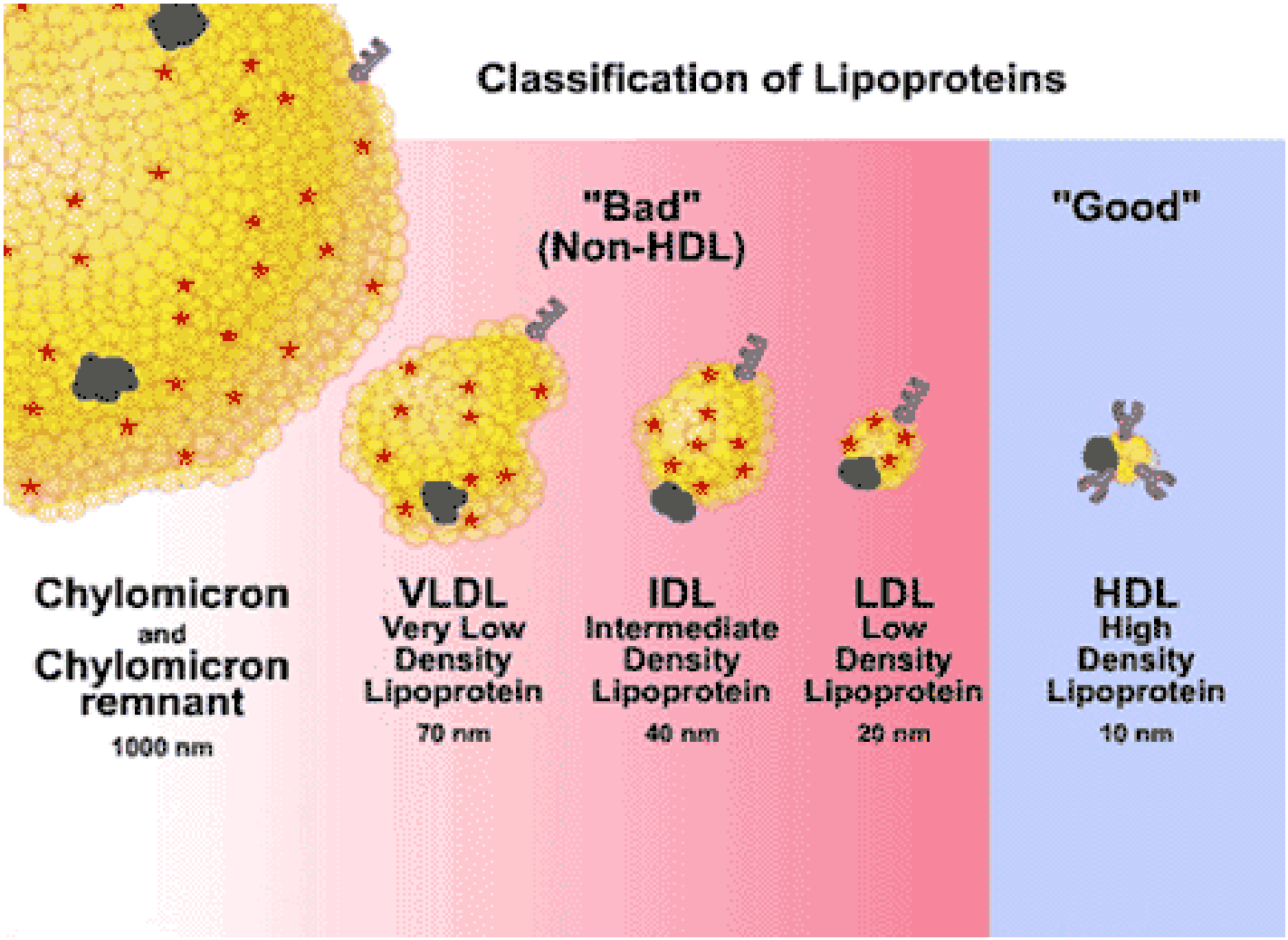
Plasma lipids are transported in complexes called lipoproteins

Hyperlipidemia / Hyperlipoprotinemias : Metabolic disorders that involves increase in any lipoproteins

Hyperlipemia denotes increased levels of TGs



Lipoprotein (lipid in protein capsule)


Classification of Lipoproteins
"Bad"
(Non-HDL)
"Good"
Chylomicron
and
Chylomicron
remnant
1000 nm
VLDL
Very Low
Density
Lipoprotein
70 nm
IDL
Intermediate
Density
Lipoprotein
40 nm
LDL
Low
Density
Lipoprotein
20 nm
HDL
High
Density
Lipoprotein
10 nm

The story of lipids

- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).
- LDL then carries fat and cholesterol to the body's cells.
- High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.

The story of lipids (cont.)

- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.
- HDL cholesterol is able to go and remove cholesterol from the atheroma.
- Atherogenic cholesterol → LDL, VLDL, IDL

Complications of Dyslipidemia / Hyperlipidemias

- **Atherosclerosis**
- **Atherosclerosis associated conditions such as:**
  - Coronary Heart Disease
  - Ischemic cerebrovascular disease
  - Peripheral vascular disease
- **Acute pancreatitis** (seen in marked hyperlipemia)

Type of hyperlipidemia

- Primary hyperlipidemia
- Secondary hyperlipidemia

- **CLASSIFICATION- based on the pattern of lipoprotein**
- **Familial Chylomicronemia (I)**:increased Chylomicrons due to deficiency of lipoprotein lipase or its cofactor
- **Familial Hypercholesterolemia (IIA):** levels of LDL tend to increase with normal VLDL.
- **Familial Combined (mixed)Hyperlipidemiaa (IIB):** elevated levels of VLDL, LDL.
- **Familial Dysbetalipoproteinemia (III):** Increased IDL resulting increased TG and cholesterol levels.
- **Familial Hypertriglyceridemia (VI):** Increase VLDL production with normal or decreased LDL.
- **Familial mixed hypertriglyceridemia (V):** Serum VLDL and chylomicrons are increased

Secondary hyperlipidaemias results from:

- Liver disease
- Biliary disease
- Obesity
- Hypothyroidism
- Diabetes,
- Diet
- Alcohol excess
- Renal disease (nephrotic syndrome)
- D**rugs**, HIV protease inhibitors, thiazide diuretics, oral contraceptive steroids

The most severe hyperlipidaemias usually occur In patients with concurrent conditions, e.g. Diabetes Mellitus with one of the primary hyperlipidaemias

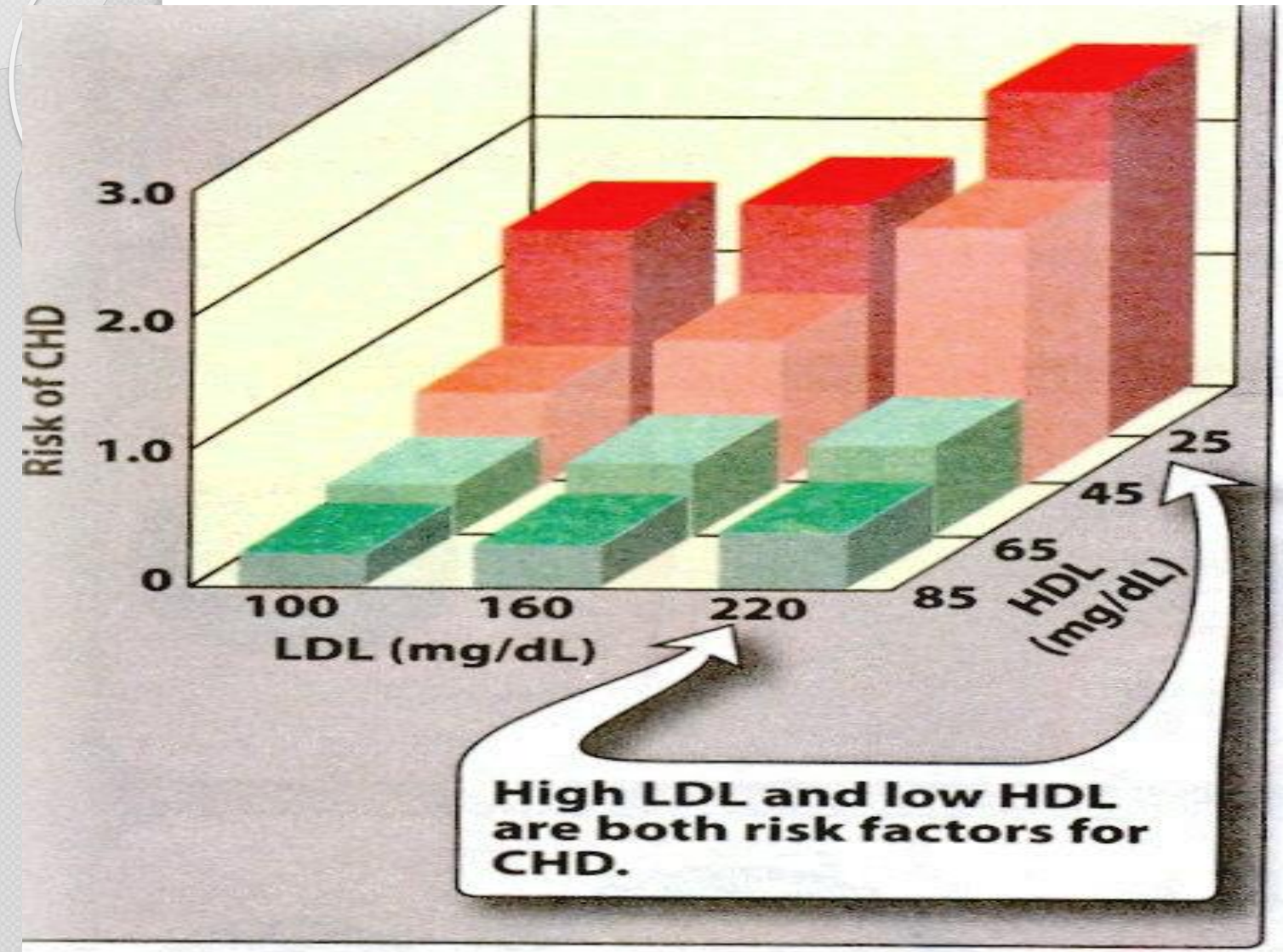


Figure 21.3
Effect of circulating LDL and HDL on the risk of coronary heart disease

Drug therapy: the primary goal of therapy is to:

- Decrease levels of LDL
- Increase in HDL


LDL
HDL

Treatment strategies: Prevention &Drugs

Prevention

- Dietary modifications
  - Reduce total intake of cholesterol and saturated & trans fats.
  - Reduce total calories including carbohydrates.
  - Add Fish oils (Omega – 3 fatty acids).

- Exercise
- Reduce alcohol intake.
- Decrease / Quit cigarette smoking
- Weight reduction
- Antioxidants----- Vit. C + fruits + vegetables

  Folic acid , Vit B-complex

Dietary sources of Cholesterol

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

2. Drugs

Targets of drug therapy:

- To ↓ production of lipoproteins
- ↑ catabolism of lipoproteins in plasma
- ↑ removal of cholesterol from body

Table 35–1. National Cholesterol Education Program: Adult Treatment Guidelines (2001).

	Desirable	Borderline to High[1]	High
Total cholesterol	< 200 (5.2)[2]	200–239[2] (5.2–6.2)	> 240 (6.2)[2]
LDL cholesterol	< 130 (3.4)[3]	130–159 (3.4–4.1)	> 160 (4.1)
HDL cholesterol			> 60 (1.55)
Men	> 40 (1.04)		
Women	> 50 (1.30)		
Triglycerides	< 120 (1.4)	120–199 (1.4–2.3)	> 200 (2.3)

[1] Consider as high if coronary disease or more than 2 risk factors are present.

[2] mg/dL (mmol/L).

[3] Optimal level is < 100 (2.6).

Anti-hyperlipidemic drugs are mainly classified into 5 types :

1. **HMG CoA REDUCTASE INHIBITORS:**

   E.g.: Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin.

2. **FIBRATES:**

   E.g.: Fenofibrate, Gemfibrozil, Clofibrate

3. **Anion –exchange resins(BILE ACID SEQUESTRANTS):**

   E.g.: Colesevelam, Colestipol, Cholestyramine

4. **Nicotinic acid:**

   E.g: NIACIN.

5. **CHOLESTEROL ABSORPTION INHIBITORS:**

   E.g.: Ezetimibe.

6. **OTHER DRUGS**

   E.g: Alpha-tocopherol acetate (vitamin E)

   Omega-3 marine triglycerides (Maxepa)

   Orlistat

HMG-CoA Reductase Inhibitors (HMGs or statins)

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

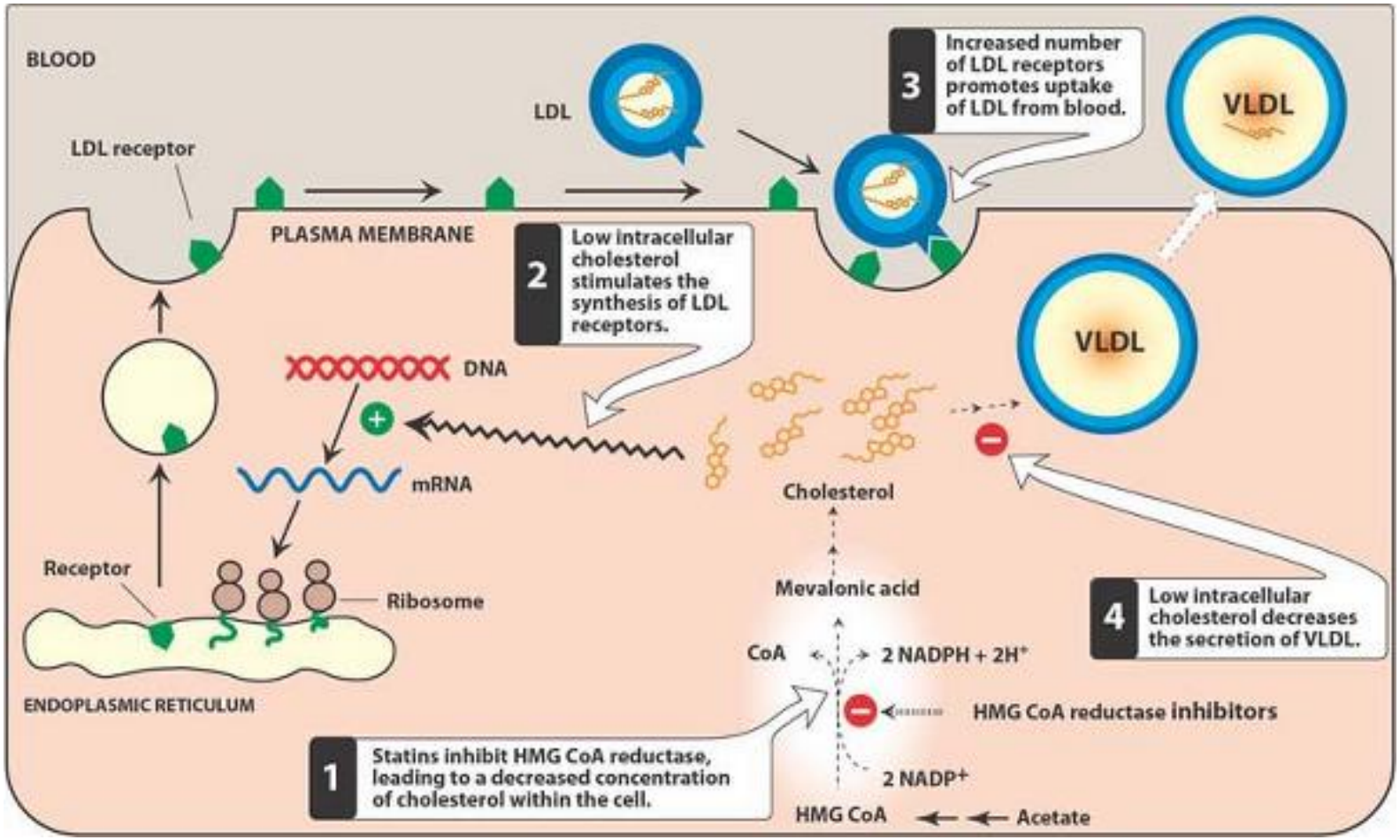
- Most effective in reducing LDL
- Decreased oxidative stress and vascular inflammation
- Stability of atherosclerotic lesions

HMG-CoA Reductase Inhibitors (HMGs or statins)

- Block the rate-limiting enzyme for endogenous cholesterol synthesis, hydroxy-methylglutaryl Coenzyme A *(HMG CoA)* reductase.
- Increased synthesis of LDL-receptors (upregulation) in the liver
- Increased clearance of LDL from the circulation

Note: Plasma total cholesterol and LDL-cholesterol fall to attain a maximum effect 1 month after therapy.

Mechanism of action of statins



- **Therapeutic uses:** These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.
- These drugs are often given in combination with other antihyperlipidemic drugs

Pharmacokinetics:

- Pravastatin and fluvastatin are almost completely absorbed after oral administration.
- oral doses of lovastatin and simvastatin are from 30 to 50 percent absorbed.
- pravastatin and fluvastatin are active, whereas lovastatin and simvastatin must be hydrolyzed to their acid forms.
- Excretion takes place through the bile and feces
- some urinary elimination also occurs.
- Their half-lives range from 1.5 to 2 hours.

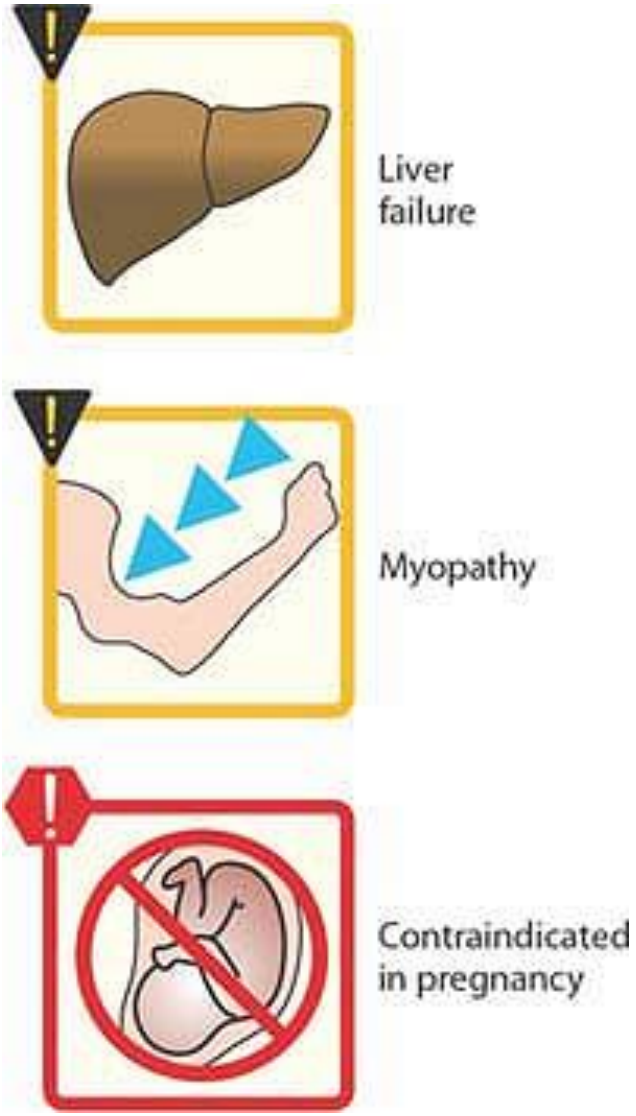
Because of a circadian rhythm to LDL-receptor synthesis, statins are a little more effective if given in the evening rather than in the morning

Adverse effect of statins

1. Transient, and minor abnormality of liver function tests
2. Myopathy and rhabdomyolysis (disintegration or dissolution of muscle and elevation of muscle enzymes (creatine hosphokinase, CPK):

- In patients with renal insufficiency
- In patients taking drugs such as cyclosporine, itraconazole, erythromycin, gemfibrozil, or niacin. Plasma creatine kinase levels should be determined regularly.

Adverse effect of statins



- **Drug interactions:** The HMG CoA reductase inhibitors may also increase warfarin levels. Thus, it is important to evaluate INR
- **Contraindications:** These drugs are contraindicated during pregnancy and in nursing mothers. They should not be used in children or teenagers.

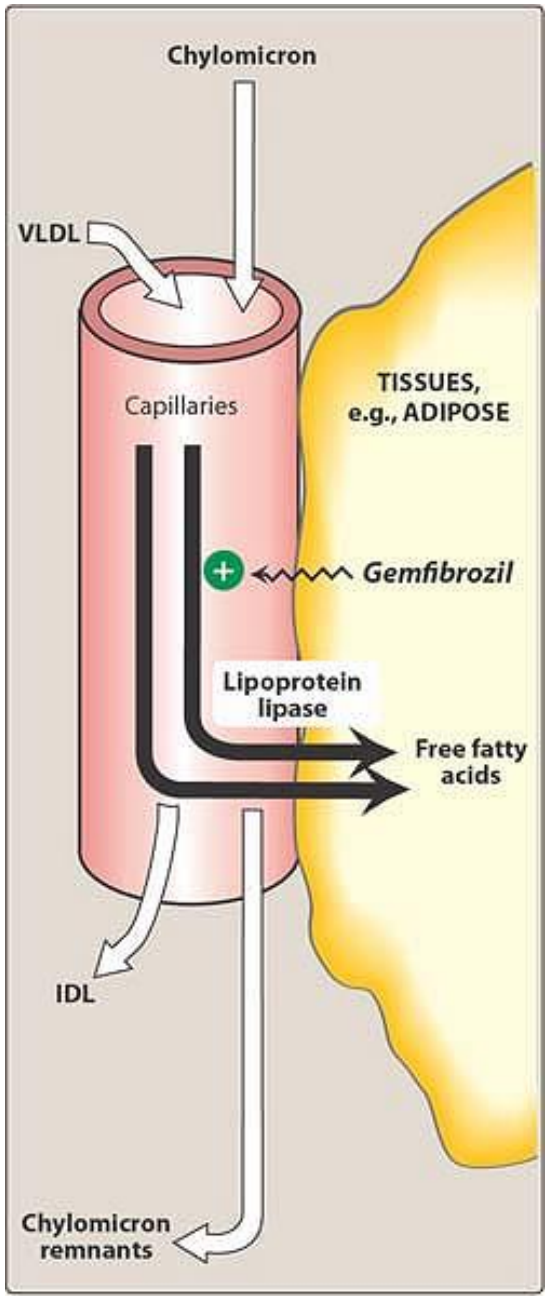
FIBRIC ACID DERIVATIVES (FIBRATES)

- Bezafibrate
- Ciprofibrate
- Fenofibrate
- Gemfibrozil

Mechanism of action

Agonists at **PPAR**(peroxisome proliferator-activated receptor) → expression of genes responsible for increased activity of plasma lipoprotein lipase enzyme → **hydrolysis of VLDL and chylomicrons**→ ↓ serum TGs

Increase clearance of LDL by liver & ↑ HDL.


Chylomicron
VLDL
Capillaries
TISSUES,
e.g., ADIPOSE
Gemfibrozil
Lipoprotein
lipase
Free fatty
acids
IDL
Chylomicron
remnants

Therapeutic uses

Hypertriglyceridemia (the most effective in reduction TGs) - combined hyperlipidemia (type III) if statins are contraindicated

Pharmacokinetic of Fibric 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

Adverse effect of fibric acid derivatives

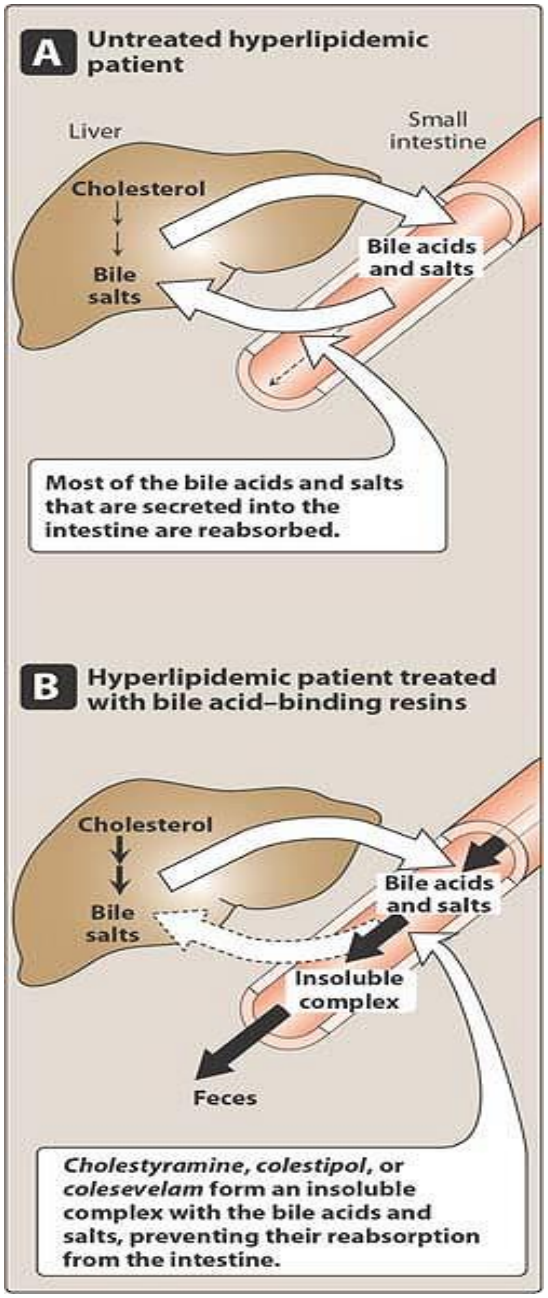
- Gastrointestinal effects
- Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.
- Fibric acid derivatives may induce a Myopathy and rhabdomyolysis the risk is greater in:
- Patients with poor renal Function
- In patients taking 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*.


A
Untreated hyperlipidemic patient
Liver
Small intestine
Cholesterol
Bile salts
Bile acids and salts
Most of the bile acids and salts that are secreted into the intestine are reabsorbed.
B
Hyperlipidemic patient treated with bile acid–binding resins
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
Cholestyramine, colestipol, or colesevelam form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

Therapeutic uses:

1. In treatment of type IIA and IIB hyperlipidemias (along with statins when response to statins is inadequate or they are contraindicated).
2. Useful for Pruritus in biliary obstruction (↑ bile acids).

Pharmacokinetics:

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

Adverse effect of Anion – exchange resins (BILE ACID SEQUESTRANTS)

1. Gastrointestinal effects: constipation(most common), nausea, and flatulence, anorexia, diarrhea, these effects are dose-related.
2. Impaired absorptions: At high doses, cholestyramine and colestipol impair the absorption of the fat-soluble vitamins (A, D, E, and K).

Note: Colesevelam has fewer gastrointestinal side effects and not Impaired absorptions

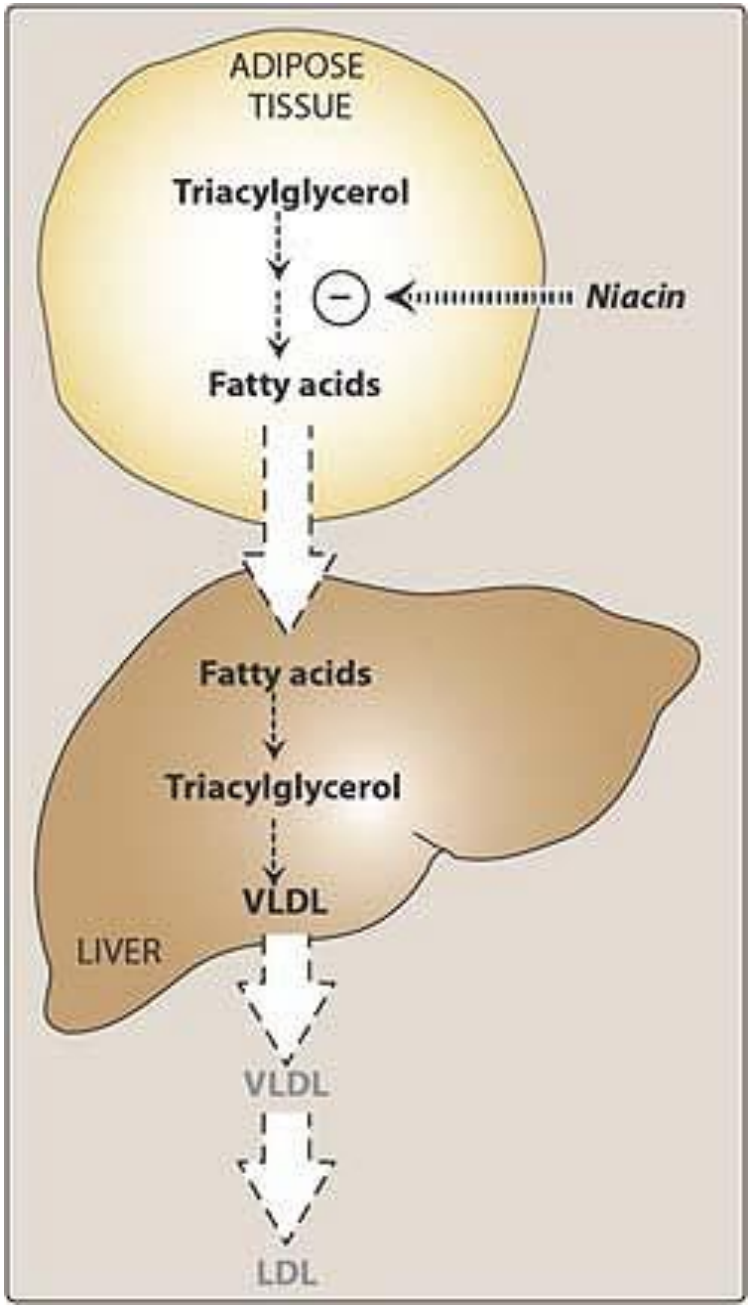
Drug interactions:

Tetracycline, warfarin, digoxin, thiazide diuretics, phenobarbitone and thyroid hormones should be taken 1 h-2h before or 4 h-6h after colestyramine to avoid impairment of their absorption (Because the drug binds anions)

Niacin (nicotinic acid)

Mechanism of action:

- It is a potent ***inhibitor of lipolysis*** in adipose tissues → ↓ **mobilization of FFAs** (major precursor of TGs) to the liver → ↓ **VLDL** (after few hours).
- Since LDL is derived from VLDL so ↓ VLDL → ↓ **LDL** (after few hours).
- **↑ HDL levels** (*the most potent antihyperlipidemic).*
- ↓ **endothelial dysfunction** →↓ thrombosis.


ADIPOSE TISSUE
Triacylglycerol
Niacin
Fatty acids
Fatty acids
Triacylglycerol
VLDL
LIVER
VLDL
LDL

Niacin (nicotinic acid)

Therapeutic uses:

Niacin lowers plasma levels of both cholesterol and triacylglycerol. Therefore, it is particularly useful in the treatment of familial hyperlipidemias. Niacin is also used to treat other severe hypercholesterolemias, often in combination with other antihyperlipidemic agents. In addition, it is the most potent antihyperlipidemic agent for raising plasma HDL levels, which is the most common indication for its clinical use.

Pharmacokinetics:

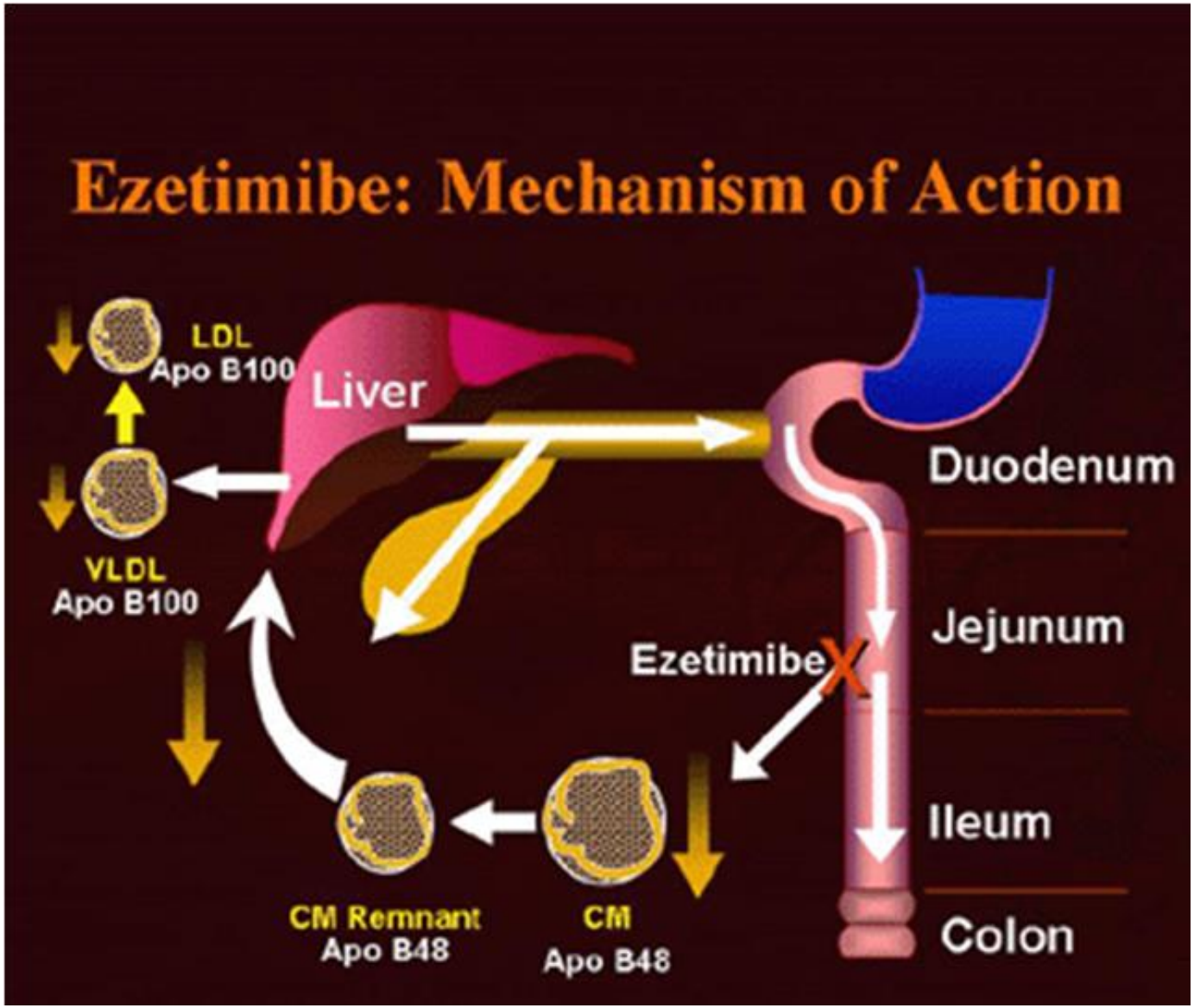
Niacin is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide-adenine dinucleotide (NAD^+). Niacin, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Nicotinamide alone does not decrease plasma lipid 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**
- Selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine → ↓ in the delivery of intestinal cholesterol to the liver → ↓ of hepatic cholesterol stores → ↑ clearance of cholesterol from the blood.
- Ezetimibe lowers LDL cholesterol and triacylglycerols
- Increases HDL cholesterol.


Ezetimibe: Mechanism of Action
LDL
Apo B100
Liver
Duodenum
VLDL
Apo B100
Jejunum
Ezetimibe
X
Ileum
CM Remnant
Apo B48
CM
Apo B48
Colon

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

Combination drug therapy

- **Bile acid resins** can be safely combined with **statins** or **nicotinic acid** (↓ LDL, VLDL cholesterol levels respectively).
- **Ezetimibe + statins** → **synergistic** effects.
- Fibrates and statins are **CI** → myopathy**.**
- Nicotinic acid and statins (must be **cautiously** used) → **myopathy.**

Alpha-tocopherol acetate (vitamin E)

Has no effect on lipid levels but is a powerful antioxidant. Considerable evidence points to oxidation of LDL as an essential step in the development of atheroma, and therefore interest has centred on the role of either endogenous or therapeutic vitamin E in prevention of atheroma.

Omega-3 marine triglycerides (Maxepa) contain

the triglyceride precursors of two polyunsaturated fatty acids derived from oily fish. They have no place in treating hypercholesterolaemia.

Some patients with moderate to severe hypertriglyceridaemia may respond to oral use, although LDLcholesterol may rise.

Orlistat, a weight-reducing agent,

it is pancreatic lipase inhibitor

- lowers the Glycaemia of diabetes mellitus to a degree that Accords with the weight loss, and improves Hyperlipidaemia
- There is a risk of steatorrhoea and malabsorption of Fat-soluble vitamins A, D and E, K.

References

1. Dr. Najlaa Saadi Ismael, lecture notes
2. Dr. M. Khurram Mahmood, lecture notes
3. Lipincott's Pharmacology, 5th edition