AGENTS USED IN HYPERLIPIDEMIA

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INTRODUCTION

- Coronary heart disease (CHD) is the cause of about half of all deaths in the United States.
- The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol.
- Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes.
- Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids).

Causes of hyperlipidemias

- **Genetic factors:** Single gene defect in lipoprotein metabolism;

1. familial hypertriglyceridaemia
2. familial hypercholesterolaemia

- **Individual's Lifestyle:**

1. lack exercise,
2. consumption of diet containing excess saturated fatty acids)

Classification of Hyperlipoproteinemia

1. Primary:

A. Group I: Hypercholesterolemia

- Increase LDL
- Increased risk of CHD

Treatment: Statins, Cholestyramine

B. Group II: Hypertriglyceridemia

- Increase VLDL
- Increase risk of pancreatitis & CHD

Treatment: Fibrates

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	
Isotretinoin	
Protease inhibitors	

Lipoproteins

➢Lipids are transported in blood as macromolecular complexes called **lipoproteins**

- **high cholesterol** ⟶ High risk factor of CHD
- **Increase LDL** ⟶ High risk factor of CHD
- **Low levels of HDL** ⟶ Low risk factor for CHD
- **Increase triglyceride** ⟶ High Risk factor in pancreatitis & in CHD

Optimal lipoprotiens blood parameters

- Lipoprotein disorders are detected by measuring lipids in serum after a 10-hour fast

	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	< 150 (1.7)	150–199 (1.7–2.3)	> 200 (2.3)

Treatment of hyperlipidaemia

A. General Measures:

- **Diet:**
  - **Avoiding animal fat (saturated oils)**
  - **Increasing polyunsaturated or monounsaturated oils or fats**
  - **Use of anti-oxidants vitamins as vitamin C & E supplemented with fresh fruits & vegetables**
  - **Weight reduction**
  - **Exercise**
- **Risk factors correction as DM, Hypertension, smoking and drugs**

B. Drugs:

- The decision to use drug therapy is based on the specific metabolic defect and its potential for causing atherosclerosis or pancreatitis
- Diet should be continued to achieve the full potential of the drug regimen
- Drugs should be avoided in pregnant and lactating women and those likely to become pregnant.
- All drugs that alter plasma lipoprotein concentrations may require adjustment of doses of warfarin and indandione anticoagulants.

HMG COA REDUCTASE INHIBITORS (STATINS)

Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin MEVACOR
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR

FIBRATES

Gemfibrozil LOPID
Fenofibrate TRICOR, LOFIBRA, TRIGLIDE

NIACIN

Niacin NIASPAN, SLO-NIACIN

CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe ZETIA

BILE ACID SEQUESTRANTS

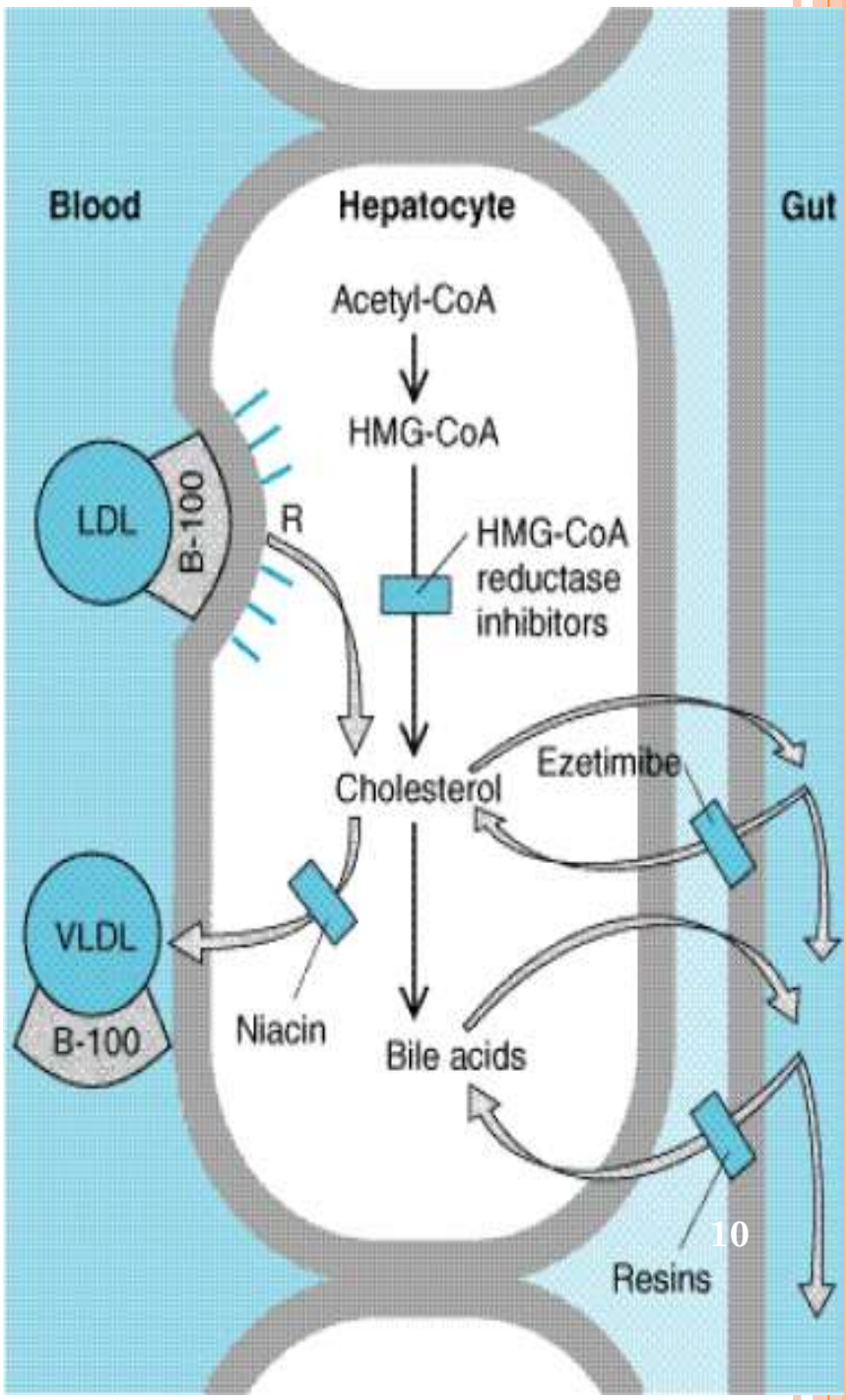
Colesevelam WELCHOL
Colestipol COLESTID
Cholestyramine QUESTRAN, PREVALITE

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, various OTC preparations

- Children with familial hypercholesterolemia may be treated with a resin or reductase inhibitor, usually after 7 or 8 years of age

- The decision to treat a child should be based on the level of LDL, other risk factors, the family history, and the child's age. Drugs are rarely indicated before age 16.

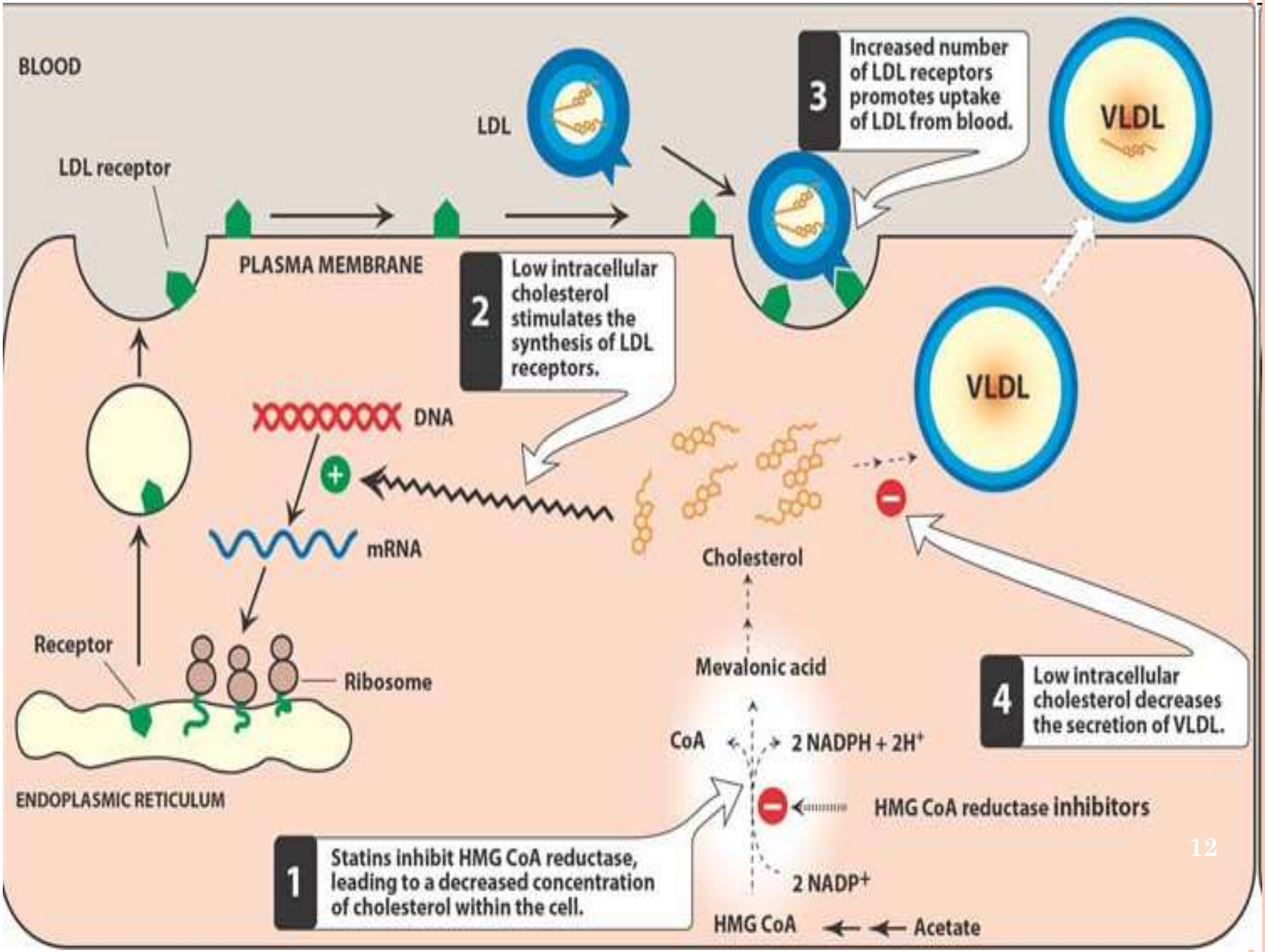


1. COMPETITIVE INHIBITORS OF HMG-COA REDUCTASE (REDUCTASE INHIBITORS; "STATINS")

➢These compounds are structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A

➢**Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin,** and **rosuvastatin**

- They inhibit first step of cholesterol synthesis
- They act by **inhibiting HMG CoA reductase**
- Decrease concentration of cholesterol within cell
- Increase number of LDL receptors
- Promote uptake of LDL from blood
- First-line & more effective treatment for lowering LDL
- They are given as single oral dose usually in the evening


BLOOD
LDL
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
LDL receptor
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Therapeutic uses:

1. Hypercholesterolemia to reduce high LDL alone or with others

2. After AMI:

Statins are administered immediately after AMI irrespective of blood lipid levels because they cause plaque stabilization, improve coronary endothelial function, inhibit platelet thrombus formation, anti-inflammatory activity

3. Patients at high risk of coronary heart disease with or without hypercholesterolemia

Adverse Effects

1. **Liver:** Liver function disorders (elevated levels of transaminase)
2. **Muscle:** skeletal muscle weakness & pain (common). Myopathy & even rhabdomyolysis occur rarely. Measure plasma creatine phosphokinase (CPK) levels

Drug interaction: increase warfarin levels

Thus, it is important to evaluate INR times (standardized prothrombin time) frequently

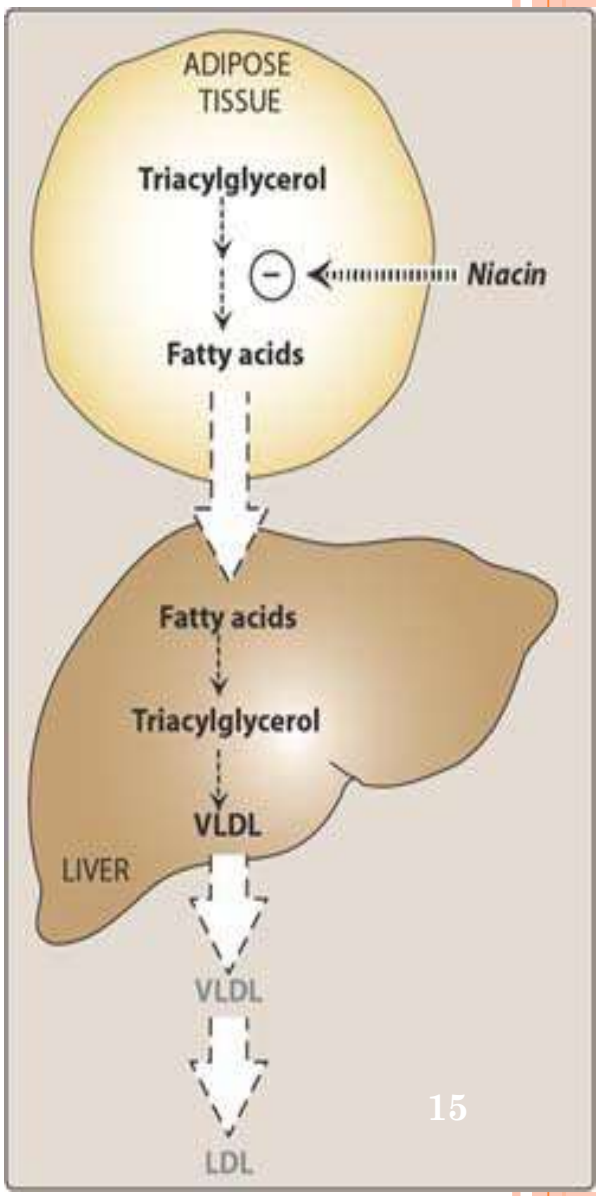
Contraindications

1. **Pregnancy**
2. **Lactating women**
3. **Children and teenagers**

2. Nicotinic acid (Niacin)

➢Decreases VLDL & LDL (both triglyceride & cholesterol) & most potent agent to increases HDL

- •Reduces lipolysis in adipose tissues
- •Decrease lipid supply to liver
- •Decrease hepatic lipid synthesis
- •Decreasing VLDL & LDL
- •Niacin can be used in combination with statins
- •Is useful in familial hyperlipidemias



Adverse effect

1. Flushing, pruritis (most common); these prostaglandin-mediated reactions can be prevented by taking **aspirin** prior to niacin therapy

2. Liver dysfunction

2. Hyperglycaemia

4. Hyperuricaemia

5. Nausea & vomiting

3. Fibric acid derivatives

- **Fenofibrate, Gemfibrozil, Clofibrate**

- These agents function primarily as ligands for the nuclear transcription receptor, peroxisome proliferator-activated receptor-alpha (PPAR-).
- They increase lipolysis of lipoprotein triglyceride via Lipoprotein lipase (LPL).
- Intracellular lipolysis in adipose tissue is decreased.
- Levels of VLDL decrease, as a result of decreased secretion by the liver.
- Only modest reductions of LDL occur
- They are useful in **hypertriglyceridemia and mixed hyperlipidemia**

Adverse effects

1. Mild GI disturbances (dyspepsia, abd pain)

2. Myositis, muscle weakness or tenderness, myopathy, rhabdomyolysis

3. Gallstones (increase biliary cholesterol excretion)

Contraindications:

1.pregnancy,

2.lactation,

3. patients with severe hepatic & renal dysfunction & gallbladder disease

4. BILE ACID SEQUESTRANTS (RESINS)

- **Cholestyramine, colestipol, and colesevelam**
- 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 preventing the bile acids from returning to the liver by the enterohepatic circulation.

- Thus lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids

- Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL

Therapeutic uses:

1. drugs of choice (often in combination with diet or niacin) in treating hyperlipidemias

2. Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction.

Adverse effects

1. Unpleasant taste & GI disturbances (constipation, diarrhea, flatulence, steatorrhea)

2. Interference with drug absorption as digoxin, thiazides, warfarin, aspirin

5. Cholesterol absorption inhibitors

- **Ezetimibe** selectively inhibits intestinal 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 clearance of cholesterol from the blood.
- Ezetimibe lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol by 1.3 percent.
- Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation

- Useful in hypercholesterolemia when a statin alone is inadequate

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓