

# Chapter 8. Anti-Hyperlipidemic Drugs

## Syllabus:

**Anti-hyperlipidemic agents:** Clofibrate, Lovastatin, Cholesteramine and Cholestipol

## 8.1. HYPERLIPIDEMIA

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

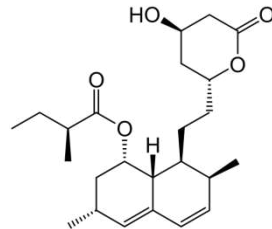
## 8.2. ANTI HYPERLIPIDEMIA

1. **HMG CoA reductase inhibitors (statins):** Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin.
2. **Anion exchange resins (bile acid sequestrants):** Cholestyramine, Colestipol, Colesevelam.
3. **Fibrates (activate lipoprotein lipase):** Clofibrate, Gemfibrozil, Fenofibrate, Bezafibrate.
4. **Nicotinic acid (inhibit lipolysis and triglyceride synthesis):** Niacin.
5. **Other:**
  - Cholesterol absorption inhibitors:** ezetimibe.
  - Alpha-topherol acetate (vitamin E), Gugulipid.
  - Orlistat (weight reducing agent).

### 1. HMG CoA Reductase Inhibitors (Statins):

- ✓ **MOA:** Statins competitively inhibit conversion of 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) to mevalonate (rate limiting step in Cholesterol synthesis) by an enzyme HMG CoA reductase, results in compensatory increase in LDL receptors expression on liver cells, this increases receptor mediated uptake and metabolism of LDL.
- ✓ Different statins differ in their potency and maximal efficacy in reducing LDL-CH (20-50 %), and also decrease the TG level (10-30%) and increase HDL (5-10%)
- ✓ **Use:** First choice for Primary Hyperlipidemia with raised LDL (Type IIa, IIb & V), also used in secondary hyperlipidemia and atherosclerotic CVS disorders (Angina, MI).

### 1) Lovastatin



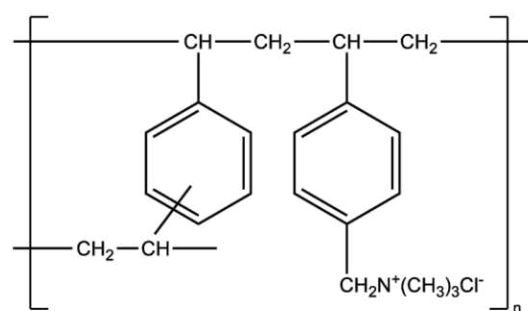
(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate

- ✓ HMG Co-A Reductase Inhibitor
- ✓ It is lipophilic in nature and given orally in the precursor lactone form. And reduce the LDL up to 30-35 %

### 2. Bile acid sequestrants

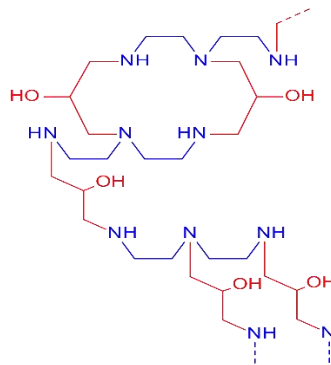
- ✓ **MOA: Cholestyramine** and **Colestipol** are basic ion exchange resins supplied in chloride form. Neither digested nor absorbed in gut, but it binds bile acids in the intestine interrupting their enterohepatic circulation. Faecal excretion of bile salts and CH is increased and this indirectly leads to enhanced hepatic metabolism of CH to bile acids.
- ✓ **Used** to retard atherosclerosis, but less preferred due to unpalatability and poor patient acceptability.

#### 1) Cholestyramine



typical structure of main polymeric groups

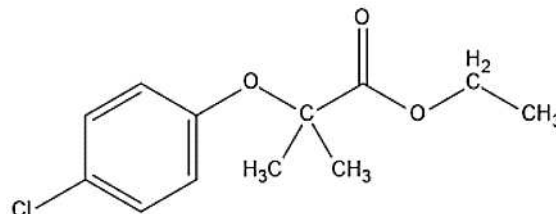
**2) Colestipol:** Copolymer of bis(2-aminoethyl)amine and 2-(chloromethyl)oxirane



**3. Fibrates**

Fibrates primarily activate **lipoprotein lipase** enzyme that causes degradation of VLDL resulting in reduction of TGs. This effect is exerted through **peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ )** that is a gene transcription regulating LDL receptor expression in liver, fat and muscles. Activation of PPAR $\alpha$  enhances lipoprotein lipase synthesis and fatty acid oxidation. Fibrates decrease hepatic TG synthesis and free fatty acids.

**1) Clofibrate:** due to its less effect to prevent atherosclerosis, it is out of use.



ethyl 2-(4-chlorophenoxy)-2-methylpropanoate

Uses of Fibrates:

- ✓ Uses in hyperlipidemia raised with TG level- Type III Primary hyperlipidemia
- ✓ Also effective in Type IV and V
- ✓ Preferred antihyperlipidemic drug for type-II diabetes
- ✓ Also decrease the atherosclerotic events

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