Antihyperlipidemic Drugs

**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)

**Type of hyperlipidemia**
1. Primary hyperlipidemia
2. Secondary hyperlipidemia

**CLASSIFICATION** based on the pattern of lipoprotein on electrophoresis or Itracentrifugation.

**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)Hyperlipidemia (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), **Drugs** (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
Drug therapy: the primary goal of therapy is to:
- Decrease levels of LDL
- Increase in HDL

Anti-hyperlipidemic drugs are mainly classified into 5 types:
- **HMG CoA REDUCTASE INHIBITORS**: E.g. Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin.
- **FIBRATES**: E.g. Fenofibrate, Gemfibrozil, Clofibrate
- **Anion –exchange resins(BILE ACID SEQUESTRANTS)**: E.g. Colesevelam, Colestipol, Cholestyramine
- **Nicotinic acid**: E.g. NIACIN.
- **CHOLESTEROL ABSORPTION INHIBITORS**: E.g. Ezetimibe.
- **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. (They are most potent LDL reducers)

**Mechanism of action of 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.

**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 of statins: 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.

Note: 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 effects

1. Transient, and minor abnormality of liver function tests
2. Myopathy and rhabdomyolysis (disintegration or dissolution of muscle and elevation of muscle enzymes (creatine phosphokinase, CPK), the risk is greater in:
   - 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.

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. ↑ clearance of LDL by liver & ↑ HDL.

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

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

Contraindication
1. Where hepatic or renal function is severely impaired (but gemfibrozil has been used in uraemic and nephrotic patients without aggravating deterioration in kidney function)
2. pregnant or lactating women

Adverse effects
1. Gastrointestinal effects
2. Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.
3. Myopathy and rhabdomyolysis the risk is greater in:
   • Patients with poor renal Function
   • In patients taking a statin.
4. Fibrates enhance the effect of co-administered oral Anticoagulants.
Anion – exchange resins (BILE ACID SEQUESTRANTS): Cholestyramine, Colestipol, Colesevelam

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:
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 effects:
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 absorption of the fat-soluble vitamins (A, D, E, and K).

Drug interactions: Tetracycline, warfarin, digoxin, thiazide diuretics, phenobarbitone and thyroid hormones should be taken 1 h-2h before or 4 h-6h after cholestyramine 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
- ↓ Endothelial dysfunction → ↓ thrombosis.

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.

Pharmacokinetic
- 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.
OTHER DRUGS:

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 LDL cholesterol 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 Hyperlipidemia. There is a risk of steatorrhoea and malabsorption of Fat-soluble vitamins A, D and E.
Antihyperlipidemic Drugs

Acetyl-CoA

3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)

\[ \text{HMG-CoA reductase} \]

Mevalonate

Isopentenyl-5-pyrophosphate (P-P)

Geranyl-PP

Farensyl-PP

Ubiquinone (CoQ10)

energy, heart failure, myalgia

Squalene

Dolichol

cell ageing, brain function

Cholesterol

steroid hormones, sex hormones, bile production

---

BLOOD

LDL receptor

PLASMA MEMBRANE

Low intracellular cholesterol stimulates the synthesis of LDL receptors.

Increased number of LDL receptors promotes uptake of LDL from blood.

Increased cholesterol decreases the secretion of VLDL.

Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
Antihyperlipidemic Drugs

Dr. Najlaa Saadi

A Untreated hyperlipidemic patient
- Liver
- Cholesterol
- Bile acids and salts
- Triacylglycerol
- Fatty acids
- Niacin

Most of the bile acids and salts that are secreted into the intestine are reabsorbed.

B Hyperlipidemic patient treated with bile acid–binding resins
- Liver
- VLDL
- LDL

Cholestyramine, colestipol, or coleser/colestam form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

Ezetimibe: Mechanism of Action

(10-10)