Antihyperlipidemic Drugs

- Plasma lipids are transported in complexes called lipoproteins. Metabolic disorders that involve elevations in any lipoprotein species are termed **hyperlipoproteinemias** or **hyperlipidemias.**
- **Atherosclerosis (ATCS)** is a disorder in which lipid deposits on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow. ATCS is a major contributor in the development of heart disease.
- Triglycerides (TG) and cholesterides are insoluble in water and must be bound to a lipid-containing protein (**lipoprotein**) for transportation throughout the body.
- Although several lipoproteins are found in the blood, we will focus on the low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and the high-density lipoproteins (HDL).

  - **Very-Low-Density Lipoproteins** VLDL are secreted by liver and export TGs to peripheral tissues.
  - **Low-density lipoproteins** (LDL) transport cholesterol to the peripheral cells. When the cells have all the cholesterol they need, the excess cholesterol is discarded into the blood. This can result in an excess of cholesterol, which can penetrate the walls of the arteries, resulting in atherosclerotic plaque formation. Elevation of the LDL increases the risk for heart disease.
  - **High-density lipoproteins** (HDL) take cholesterol from the peripheral cells and bring it to the liver, where it is metabolised and excreted. The higher the HDL, the lower the risk for development of ATCS. Therefore, it is desirable to see an increase in the HDL (the "good" lipoprotein) because of the protective nature of its properties against the development of atherosclerosis and a decrease in the LDL.

Hyperlipidaemia can be diagnosed by lipoprotein profile, which is a laboratory tests used to measure the blood lipid and can provide valuable information on the important cholesterol levels, such as:

1- Total cholesterol
2- LDL (the harmful lipoprotein)
3- HDL (the protective lipoprotein)
4- Triglycerides

Drugs for Hyperlipidemia

1- HMG-CoA reductase inhibitors
2- Bile acid sequestrants
3- Fibric acid derivatives
4- Niacin
5- Cholesterol absorption inhibitor.

1- HMG CoA reductase inhibitors

HMG-CoA (3- hydroxy-3-methyglutaryl coenzyme A) reductase is an enzyme that is a **catalyst** (a substance that accelerates a chemical reaction without itself undergoing a

change) in the manufacture of cholesterol. These drugs appear to have one of two activities, namely, inhibiting the manufacture of cholesterol or promoting the breakdown of cholesterol. This drug activity lowers the blood levels of cholesterol and serum triglycerides and increases blood levels of HDLs. Examples of these drugs are Fluvastatin (Lescol), lovastatin (Mevacor), and simvastatin (Zocor). They are first line treatment for patients with elevated risk of ASCVD (atherosclerotic cardiovascular diseases) to reduce the occurrence of ASCVD events.

Therapeutic uses:
These drugs, along with a diet restricted in saturated fat and cholesterol, are used to treat hyperlipidaemia when diet and other nonpharmacologic treatments alone have not resulted in lowered cholesterol levels.

Adverse effects
- Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy or if a patient has symptoms consistent with liver dysfunction as hepatic insufficiency can cause drug accumulation.
- Myopathy and rhabdomyolysis (disintegration of skeletal muscle) have been reported.
- The HMG CoA reductase inhibitors may also increase the effect of warfarin. Thus, it is important to evaluate the international normalised ratio (INR) when initiating a statin or changing the dosage.
- These drugs are contraindicated during pregnancy, lactation, and active liver disease.

2- Bile Acid Sequestrants
Cholestyramine, colestipol, and colesevelam are 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 lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol containing LDL-C particles, leading to a decrease in plasma LDL-C.

Therapeutic uses
The bile acid sequestrants are used as adjunctive therapy for the reduction of elevated serum cholesterol in patients with hypercholesterolemia who do not have an adequate response to a diet and exercise program.

Adverse effects
1- A common side effects is constipation. Constipation may be severe and may occasionally result in faecal impaction. Haemorrhoids may be aggravated.
2- Additional adverse reactions include vitamin A and D deficiencies,
3- Bleeding tendencies (including gastrointestinal bleeding) caused by a depletion of vitamin K , nausea, abdominal pain, and distention.

3- Fibric Acid Derivatives

Fibric acid derivatives work in a variety of ways.

1- Clofibrate (Atromid-S), acts to stimulate the liver to increase breakdown of very–low-density lipoproteins (VLDL) to low density lipoproteins (LDL), decreasing liver synthesis of VLDL and inhibiting cholesterol formation.
2- Fenofibrate (Tricor) acts by reducing VLDL and stimulating the catabolism of TG-rich lipoproteins, resulting in a decrease in plasma TG and cholesterol.
3- Gemfibrozil (Lopid) increases the excretion of cholesterol in the feces and reduces the production of triglycerides by the liver, thus lowering serum lipid levels.

Therapeutic uses:

1- Clofibrate and gemfibrozil are used to treat individuals with very high serum triglyceride levels who present a risk of abdominal pain and pancreatitis and who do not experience a response to diet modifications. Clofibrate is not used for the treatment of other types of hyperlipidaemia and is not thought to be effective for prevention of coronary heart disease.
2- Fenofibrate (Tricor) is used as adjunctive treatment for the reduction of LDL, total cholesterol, and triglycerides in patients with hyperlipidaemia.

Adverse effects

- Include nausea, vomiting, gastrointestinal upset, and diarrhoea.
- Clofibrate, fenofibrate, and gemfibrozil may increase cholesterol excretion into the bile, leading to cholelithiasis (stones in the gallbladder) or cholecystitis (inflammation of the gallbladder). If cholelithiasis is found, use of the drug is discontinued.
- Fenofibrate may also result in abnormal liver function tests, respiratory problems, back pain, and headache.
- Gemfibrozil may cause dyspepsia, skin rash, vertigo, and headache.

4- Niacin (nicotinic acid)

Niacin reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day. Niacin can be used in combination with statins, and fixed-dose combinations of long-acting niacin with lovastatin and simvastatin are available.

Note: the addition of niacin to statin therapy has not been shown to reduce the risk of ASCVD events.

Mechanism of action

At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for TG synthesis. Reduced liver TG levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

Adverse effects

- The most common adverse effects of niacin are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated.

- Some patients also experience nausea and abdominal pain. Slow titration of the dosage or use of the sustained-release formulation of niacin reduces bothersome initial adverse effects.
- Niacin inhibits tubular secretion of uric acid and, thus, predisposes patients to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

5- Cholesterol absorption inhibitor

- Ezetimibe selectively inhibits 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-C by approximately 18% to 23%. Due its modest LDL-C lowering, ezetimibe is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk, or in statin-intolerant patients.
- Adverse effects are uncommon with the use of ezetimibe.

Actions of the antihyperlipidemic drugs were summarised and demonstrated in table 1.

Table 1: Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

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

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.