Antihyperlipidemic Drugs

- Hyperlipidemias.
- Hyperlipoproteinemias.
- Hyperlipemia.
- Hypercholesterolemia.
- Direct relationship with acute pancreatitis and atherosclerosis
Lipoprotein Particles

Structure
Treatment Goals

• Reduction of LDL-C is the primary goal of cholesterol-lowering therapy.
• Lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL-C and increases in HDL-C.
• Most patients are unable to achieve significant LDL-C reductions with lifestyle modifications alone, and drug therapy may be required.
• Treatment with HMG CoA reductase inhibitors (statins) is the primary treatment option for hypercholesterolemia.
• Diet and exercise are the primary modes of treating hypertriglyceridemia.

• If indicated, *niacin* and fibric acid derivatives are the most efficacious in lowering triglycerides.

• Omega-3 fatty acids (fish oil) in adequate doses may also be beneficial.

• Triglyceride reduction is a secondary benefit of the statins, with the primary benefit being reduction of LDL-C.
Strategy For Controlling Hyperlipidemia

Diet

Ezetimibe

Bile Acids

Intestine

Feces

Bile Acid SEQUESTRANTS

Serum Cholesterol

HMG CoA reductase

Biosynthesis

STATINS

LDL-R

Conversion to hormones within cells or storage as granules

FIBRATES

Re-absorption

Lipoprotein catabolism
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HMG CoA reductase inhibitors (Statins)

- Competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis.

- Pitavastatin, rosuvastatin, and atorvastatin are the most potent LDL cholesterol–lowering statins, followed by simvastatin, pravastatin, and then lovastatin and fluvastatin.

- The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients.
1. Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.

2. Low intracellular cholesterol stimulates the synthesis of LDL receptors.

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

4. Low intracellular cholesterol decreases the secretion of VLDL.

BLOOD

PLASMA MEMBRANE

LDL receptor

Receptor

Ribosome

ENDOPLASMIC RETICULUM

VLDL

HMG CoA reductase inhibitors

HMG CoA

Acetate

Cholesterol

Mevalonic acid

CoA

2 NADPH + 2H⁺

2 NADP⁺
• These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias.
• All statins are metabolized in the liver, with some metabolites retaining activity.
• Excretion takes place principally through bile and feces, but some urinary elimination also occurs.
• Elevated liver enzymes may occur with statin therapy. Liver function should be evaluated prior to treatment.
Adverse Effect

• Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare have been reported.)
Niacin (Nicotinic Acid)

- Niacin can reduce 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 grams/day.
- Niacin can be used in combination with statins.
- Inhibits lipolysis at gram level.
Niacin

• 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**.
Adverse Effect

• The most common side 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 usage of the sustained-release formulation of niacin reduces bothersome initial adverse effects.

• Niacin inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout.

• Impaired glucose tolerance and hepatotoxicity have also been reported.

• The drug should be avoided in hepatic disease.
Fibrates

- Fenofibrate and gemfibrozil are derivatives of fibric acid that
  - Lower serum triglycerides
  - Increase HDL levels.
- The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism.
- PPARs function as ligand-activated transcription factors.
- Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated.
- The fibrates are used in the treatment of hypertriglyceridemias
• Leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase and decreasing apolipoprotein (apo) CII concentration.

• Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.

• Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII.
Pharmacokinetics

- Gemfibrozil and fenofibrate are completely absorbed after oral administration.
- Fenofibrate is a prodrug, which is converted to the active moiety fenofibric acid.
- Both drugs undergo extensive biotransformation
- Excreted in the urine as glucuronide conjugates.
Bile acid–binding resins

- Bile acid sequestrants (resins) have significant LDL cholesterol-lowering effects, although the benefits are less than those observed with statins.
- 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 lowering the bile acid concentration.
• This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile.
• Intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL-C.
• This increased uptake is mediated by an up-regulation of cell surface LDL receptors.
Pharmacokinetics

• Bile acid sequestrants are **insoluble** in water and have **large molecular weights**.

• After **oral** administration, they are neither absorbed nor metabolically altered by the intestine.

• Instead, they are **totally excreted in feces**.
Adverse effects

- GI disturbances, such as constipation, nausea, and flatulence.
- **Colesevelam** has fewer GI side effects than other bile acid resin.
- These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K).
- Interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone).
- Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins.
- Contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL).
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 cholesterol by approximately 17%.
• Ezetimibe is often used as an adjunct to statin therapy or in statin-intolerant patients, due to its modest LDL-lowering effects.
• Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation.
• Biliary and renal excretion.
• Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.
• Adverse effects are uncommon with use of ezetimibe.
Omega-3 fatty acids

- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering.
- Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver.
- The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna and salmon.
- Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C.
- Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone.
• **Icosapent ethyl** is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C. Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL).

• The most common side effects of omega-3 PUFAs include GI effects *(abdominal pain, nausea, diarrhea)* and a fishy aftertaste.

• Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets.
Combination Drug Therapy

Simvastatin and ezetimibe,
Simvastatin and niacin

• It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels.

• The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL-C levels.