Antihyperlipidemic Drugs

1) Niacin (1H half-life)

- Nicotinic Acid or Vitamin B3, functions only after conversion to NAD or NADP+ Nicotinamide.
- Has hypolipidemic effects only in large doses.
- Increases plasminogen activator, Reduces fibrinogen levels, Affects all lipid parameters: Decreases LDL-C production(20-30%), Lowers triglycerides (35-45%), Best agent to increase HDL-C(35-40%).

***MOA**:

-inhibits the lipolysis of triglycerides by inhibiting adipocyte adenylyl cyclase, inhibit a rate –limiting enzyme of triglyceride synthesis, diacylglycerol acetyltransferase 2 , Inhibits intracellular lipase in adipose tissues.

- Reduction of triglyceride synthesis reduces hepatic VLDL and consequently LDL.

*** Toxicity: acanthosis nigricans** (black hyperpigmentation of the skin) , Elevations in transaminases and possible hepatotoxicity, Insulin resistance and hyperglycemia, Hyperuricemia and gout, Cardiac arrhythmias, Amblyopia, blurring of vision.

- Harmless cutaneous vasodilation and sensation of warmth, can be prevented by NSAIDS.

2) Fibrates or Fibric Acid Derivatives or "PPARs Activators"

(Clofibrate, Gemfobrozil, Fenofibrate, Bezafibrate)

- Drugs of choice in severe hypertriglyceridemia.

*** MOA:**

- Activate PPAR- α (Peroxisome Proliferator Activated Receptor- α) which:
stimulates fatty acid oxidation, increases LPL synthesis, and reduces expression of apo C-III, and increases apoA-I and apoA-II expression.
- Increase lipolysis of lipoprotein triglyceride via LPL, Decrease levels of VLDL and LDL, Moderately increase HDL, have anticoagulant and fibrinolytic activities.

***Toxicity:**

- Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, anemia, myalgia, fatigue, myopathy and rhabdomyolysis.
- Elevated transaminases or alkaline phosphatase .
- Interacts with statins, levels of both drugs will increase, Risk of cholesterol gallstones.
- Used with caution in renal failure.

3) Bile Acid –Binding Resins

(Colestipol, Chlestyramine, Colesevelam)

- The safest drugs

***MOA:**

- These are large polymeric anionic- exchange resins, insoluble in water, which bind the negatively charged bile acids in the intestinal lumen and prevent their reabsorption leading to depletion of bile acid pool and increased hepatic synthesis.
- This leads to increased LDL clearance and lowers LDL-C levels, may increase triglyceride levels.

*** Indications:**

- Lower LDL as much as 25%, but will cause GI side effects. -Relieve pruritus in cholestasis.

***Toxicity:**

- Gritty sensation, Constipation and bloating, Heartburn, Malabsorption of Vitamin K, Gall stones
-Impaired absorption of many drugs(digitalis, propranolol, thiazides, warfarin, folic acid, statins, aspirin….etc).

4) Competitive Inhibitors of HMG-CoA Reductase "Statins"

(Mevastatin , Simvastatin , Lovastatin , Pravastatin , Fluvastatin , Atorvastatin, Rosuvastatin).

-Most commonly prescribed drugs worldwide, Most effective in lowering LDL.

***MOA:**

-Competitively inhibit the early rate- limiting enzyme in de novo synthesis of cholesterol (3- hydroxy-3methylglutaryl coenzyme A reductase). This results in increased expression of the LDL receptor gene.
-Higher doses can reduce triglyceride levels caused by elevated VLDL levels.
-Some (**simvastatin** and **rosuvastatin**) can raise HDL-C levels.
-Decrease oxidative stress and vascular inflammation by enhancing NO production, Reduce platelet aggregation.

***Toxicity:**

- Toxicity is dose-related, associated with advanced age, hepatic or renal dysfunction, small body size, associated diseases, hypothyroidism and concomitant drugs.
-Elevation of transaminases, intermittent and not associated with strong evidence of liver failure, elevation of creatine kinase (CK) activity.
-Rhabdomyolysis, causing myoglobinuria and renal injury and failure or even death. It is extremely rare (less than one in 10,000 people).
- Lupus-like disorder and peripheral neuropathy.

***Pharmacogenetics of Statins:** metabolized by the CYP enzyme system, which is a subject to individual genetic differences. These differences will be exhibited for their: Therapeutic Response and Side Effects.

5) Inhibitors of Sterol Absorption (Ezetimibe)

- Action is complementary to statins(60% reuction in LDL-C)

***MOA:**

-Inhibitor of NPC1L1, a specific transport process in jejunal brush border.

-Reduces cholesterol delivery to the liver by the chylomicron remnants.

-Reduces cholesterol absorption and reabsorption by 54%, precipitating a compensatory increase in cholesterol synthesis.

***Side effects:** allergic reactions, reversible impairment of liver function tests and myopathy

6) Inhibitors of Cholesteryl Ester Transfer Protein

(Torcetrapib: withdrawn **, Anacetrapib, Dalcetrapib)**

-Can increase HDL levels by 45-106% in humans.

***MOA**:

- Inhibits CETP which is a plasma glycoprotein synthesized by the liver that mediates the transfer of cholesteryl esters from HDL to triglyceriderich lipoproteins and LDL in exchange for a molecule of triglyceride.