Lipid Lowering Drugs

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Atherosclerosis

• A form of arteriosclerosis characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.

• The nomenclature comes from the Greek words athero (meaning gruel or paste) and sclerosis (hardness).
Atherosclerosis

artery with cholesterol buildup
Atherosclerosis

Cell Types
- Smooth muscle cell
- Endothelial cells
- Fibroblasts
- Macrophages
- "foam cells"
- T-lymphocytes
- Mast cells
Normal and atheromatous coronary artery

Normal coronary artery

Atherosclerotic coronary artery

Atheroma

Fibrous cap
Non- Modifiable Risk Factors

Age
   – Atherosclerosis begins in the young, but does not precipitate organ injury until later in life

Gender
   – Men more prone than women, but by age 60- 70 about equal frequency

Family History
   – Genetic differences
Modifiable Risk Factors (potentially controllable)

- Hyperlipidemia
- Hypertension
- Cigarette smoking
- Diabetes Mellitus
- Elevated Homocysteine
- Factors that affect hemostasis and thrombosis
- Infections: Herpes virus; Chlamydia pneumoniae
- Obesity, sedentary lifestyle, stress

Among all these factors, elevated serum cholesterol levels are unique in the ability to drive atherosclerosis in the absence of other risk factors
Atherosclerosis

Genetics

• Familial hypercholesterolemia (FH) - Deficiency/mutation of LDL receptors
Atherosclerosis

What are the mechanisms leading to atherosclerosis lesions?

• Two major sources of cholesterol in the body

  – endogenous production (liver, 1g/day)
  – food (animal sources) numbers mean.

LDL Cholesterol levels:
  – Less than 100 Optimal
  – 100 - 129 Near optimal/above optimal
  – 130 - 159 Borderline high
  – 160 - 189 High
  – 190 and above Very high
Mechanisms leading to atherosclerosis lesions?

- Cholesterol and fats are poorly soluble in blood and therefore are transported via lipoproteins.

- Lipoproteins- classified by the type and ratio of protein and fats they contain which determines their size and density.
  - Chylomicrons
  - VLDL
  - IDL
  - LDL
  - HDL
How does high cholesterol lead to atherosclerosis?
Prevention

Lifestyle

• Diet – low in fat/cholesterol, increased fruits/vegetables (vitamins alone have not shown a protective effect)

• Physical activity can increases HDL (higher HDL cholesterol is linked with a lower risk of heart disease), and also help control weight, diabetes and high blood pressure

• Decreasing body weight increases HDL

• Smoking

• Stress
Drugs which lower Cholesterol

- Statins (simvastatin, atorvostatin, pravastatin) decrease LDL by 30-50%. Block HMG CoA reductase.
- Increase expression of LDL receptor in the liver, further decreasing circulating LDL.
LIPID-LOWERING DRUGS: Statins

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors. The reductase catalyses the conversion of HMG-CoA to mevalonic acid; blocks the synthesis of CHO in the liver:

decrease hepatic CHO synthesis: lowers total and LDL

increase in synthesis of CHO receptors
+ increased clearance of LDL

Several studies demonstrated positive effects on morbidity and mortality.
Relatively few side-effects...
However, adverse effects: myopathy (incr in pts given combined therapy with nicotinic acid or fibrates. Should not be given during pregnancy.
### Promising pharmacodynamic actions:

- Improved endothelial function
- Reduced vascular inflammation and platelet aggregability
- Antithrombotic action
- Stabilisation of atherosclerotic plaques
- Increased neovascularisation of ischaemic tissue
- Enhanced fibrinolysis
- Immune suppression
- Osteoclast apoptosis and increased synthetic activity in osteoblasts
LIPID-LOWERING DRUGS: Statins

Pharmacokinetics
- well absorbed when given orally
- extracted by the liver (target tissue), undergo extensive presystemic biotransformation

Simvastatin is an inactive pro-drug
LIPID-LOWERING DRUGS: Statins

Clinical uses

- **Secondary prevention** of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease (angina, transient ischemic attacks) following acute myocardial infarction or stroke.

- **Primary prevention** of arterial disease in patients who are at high risk because of elevated serum CHO concentration, especially if there are other risk factors for atherosclerosis.

- **Atorvastatin** lowers serum CHO in patients with homozygous familiar hypercholesterolemia.
LIPID-LOWERING DRUGS: Statins

• Pleiotropic actions.
  Improve endothelial function, upregulate eNOS. Anti-inflammatory, reduce odds of plaque rupture.
LIPID-LOWERING DRUGS: Statins

Adverse effects:
- mild gastrointestinal disturbances
- increased plasma activities in liver enzymes
- severe myositis (rhabdomyolysis) and angio-oedema (rare)
LIPID-LOWERING DRUGS: Fibrates

- stimulate the β-oxidative degradation of fatty acids
- liberate free fatty acids for storage in fat or for metabolism in striated muscle
- Activate PPAR-alpha (peroxisome proliferator-activated receptors) and increase expression of genes facilitating lipid metabolism.

Less effective than statins in decreasing LDL. More effective at increasing HDL and lowering triglycerides.

- reduce hepatic VLDL production and increase hepatic LDL uptake.
- Produce a modest decrease in LDL (~ 10%) and increase in HDL (~ 10%).
- But, a marked decrease in TGs (~ 30%)
- Drugs of choice in severe hypertriglycerideridemia.
LIPID-LOWERING DRUGS: Fibrates

Other effects:
- improve glucose tolerance
- inhibit vascular smooth muscle inflammation

fenofibrate  clofibrate
gemfibrozil  ciprofibrate
LIPID-LOWERING DRUGS: Fibrates

Adverse effects:

- In patients with renal impairment myositis (rhabdomyolysis) myoglobulinuria, acute renal failure

- Combination of statins and fibrates increases risk of rhabdomyolysis by 10+ fold. Can improve insulin resistance

- Mild GIT symptoms
Fibrates

Toxicity:

• Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, and anemia.

• **Myalgia, fatigue, myopathy and rhabdomyolysis.** *(Breakdown of muscle fibers resulting in the release of muscle fiber contents (myoglobin) into the blood stream)*.

• Risk of cholesterol gallstones.

• Interacts with statins, levels of both drugs will increase.

• Used with caution in renal failure.

• Elevated transaminases or alkaline phosphatase.
Treatment

Other Drugs which lower Cholesterol

• Probucol lowers LDL (5-15%) and HDL (can be variable). Also a potent antioxidant.
• Binding agents – increase bile excretion (cholestyramine & cholestipol)
• Nicotinic acid (niacin) Increases HDL, decreases triglycerides and LDL (can be combined with statins!)
Inhibits lipolysis of adipose tissue
Niacin

• Nicotinic Acid or Vitamin B3, one of the oldest drugs.
• Water-soluble B-complex vitamin, functions only after conversion to NAD or NADP+ Nicotinamide.
• Niacin has hypolipidemic effects in large doses.
• Affects all lipid parameters:
  – Best agent to increase HDL-C (35-40%).
  – Lowers triglycerides (35-45%).
  – Decreases LDL-C production (20-30%).
• Reduces fibrinogen levels.
• Increases plasminogen activator,
Niacin

Mechanism of Action:

- In adipose tissue, inhibits the lipolysis of triglycerides by inhibiting adipocyte adenylyl cyclase, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis.

- May also inhibit a rate–limiting enzyme of triglyceride synthesis, diacylglycerol acetyltransferase 2.

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

- Inhibits intracellular lipase in adipose tissues leading to decreased FFA flux to the liver.

- Completely absorbed, peaks within 1hr, half-life is about 1 hr, so need to be given by twice or thrice daily administration.
Niacin

**Toxicity:**

- Harmless cutaneous vasodilation and sensation of warmth.
- Pruritus, rashes, dry skin or mucus membranes (*acanthosis nigricans*).
- Nausea, vomiting, abdominal discomfort, diarrhea.
- Elevations in transaminases and possible hepatotoxicity.
- Insulin resistance and hyperglycemia.
- Hyperuricemia and gout.
- Cardiac arrhythmias.
- Amblyopia, blurring of vision.
Acanthosis Nigricans
Bile Acid – Binding Resins

• Colestipol.
• Chlestyramine.
• Colesevelam.

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.

• Consequently, hepatic cholesterol content is decreased, stimulating the production of LDL receptors. This leads to increased LDL clearance and lowers LDL-C levels.

• However, this effect is partially offset by the enhanced cholesterol synthesis caused by upregulation of HMG-CoA reductase.

• May increase triglyceride levels.
Bile Acid – Binding Resins

Indications:

• Lower LDL as much as 25%, but will cause GI side effects.

• Relieve pruritus in cholestasis.

• Digitalis toxicity, can bind digitoxin and enhance its excretion.
Bile Acid – Binding Resins

Toxicity:

Probably the safest drugs, since they are not absorbed from the intestine because of their large size. Maximal doses are effective but cause side effects.

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