ANTIHYPERTENSION DRUGS

Lipids are transported in the blood by being incorporated within lipoproteins.
Lipoproteins are macromolecular disc like complexes of lipids and specific proteins called apoproteins. These apoproteins are crucial in the regulation of lipoprotein metabolism (they act as enzymes, cofactors or cell receptor ligands). Distinct classes of lipoproteins are found depending on the variation in lipid and apoprotein composition.
Chylomicrons and their remnant contain apoprotein B48 which is formed in the intestine. Apoprotein B100 is synthesized in the liver and are found in (VLDL, IDL, LDL and lipoprotein a).
Lipoproteins that convey lipids into the artery wall.
Plasma cholesterol and triglyceride are clinically important because they are major treatable risk factors for atherosclerosis and cardiovascular diseases. Hypertriglyceridemia also predispose to acute pancreatitis.

Adult treatment guidelines

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<th>Desirable</th>
<th>Borderline</th>
<th>High</th>
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<tbody>
<tr>
<td><strong>Tc</strong></td>
<td>&lt;200(5.2)</td>
<td>200-239(5.2-6.2)</td>
<td>&gt;240(6.2)</td>
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<tr>
<td><strong>LDL</strong></td>
<td>&lt;130(3.4)</td>
<td>130-159(3.4-4.1)</td>
<td>&gt;160(4.1)</td>
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<td><strong>HDL</strong></td>
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<tr>
<td>Men</td>
<td>&gt;40(1.04)</td>
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<tr>
<td>Women</td>
<td>&gt;50(1.3)</td>
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<tr>
<td><strong>TG</strong></td>
<td>&lt;150(1.7)</td>
<td>150-199(1.7-2.3)</td>
<td>&gt;200(2.3)</td>
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Optimal levels of LDL is <100 and to 60-70 in patients with CAD. High risk patients should aim levels: HDL >38, fasting TG < 180 and Tc < 150 mg/dl. Levels of Tc, TG, and HDL should be obtained after 12 hours fasting. To permit calculation of LDL:

\[ \text{LDL} = \text{Tc} - \text{HDL} - \left( \frac{\text{TG}}{2.3 \text{ mmol/l}} \right) \]

Lipid levels in mg/dl can be converted to mmol/l by dividing by 38 for cholesterol and 88 for TG.

* This formula becomes unreliable when TG exceeds 4 mmol/l (350 mg/dl)

Lipoprotein Disorders:
Primary lipid abnormalities may be diagnosed after exclusion of secondary lipid disorders. The numerical Fredrickson classification (type I-V) is no longer in use instead primary lipid disorders are classified according to the predominant lipid problem

- Hypercholesterolemia
- Hypertriglyceridemia
- Mixed hyperlipidemia

Causes of secondary hyperlipidemia:
1) Secondary hypercholesterolemia (common causes)
   - hypothyroidism, pregnancy, cholestatic liver disease, drugs(diuretics, steroids, androgens), nephritic syndrome (early nephrosis)
2) Secondary Hypertriglyceridemia (common causes): DM (type2), chronic renal disease(uremia, severe nephrosis), abdominal obesity, excess alcohol, hepatocellular disease and drugs(β-blockers, corticosteroids, estrogens).
Management:
Lipid lowering therapies have a key role in the secondary and primary prevention of CVS disease. Assessment of absolute risk, treatment of all modifiable risk factors and optimization of lifestyle factors especially diet and exercise are central to the management.

Non pharmacological treatment:
1- Reduce intake of saturated fat to less than 7-10% of total energy.
2- Reduce intake of cholesterol to less than 250mg/day.
3- Reduce sources of saturated fat and cholesterol by low fat dietary products and low glycemic index carbohydrates.
4- Consumption of vegetable, fruits, legumes & fish.
5- Supplementary intake of fish oil (contain n3 FA) & dietary fibers.
6- Achieve ideal body weight and increase activity and exercise.
7- Reduce or stop alcohol intake, also stop smoking.

Pharmacological treatment:
Predominant hypercholesterolemia:
1) Statins (HMG CoA reductase inhibitors).
2) Nicotinic acid (vit.B3) Niacin.
3) Cholesterol absorption inhibitors (Ezetimibe)
4) Bile acid sequestrating resins.
*start with statin (Ezetimibe if intolerant)
So: statin ± Ezetimibe ± Resin or Niacin.

Predominant Hypertriglyceridemia:
1) Fibrates.
2) Highly polyunsaturated n=3 fatty acids.
* start with fibrates (fish oil if intolerant)
So: fibrates ± fish oil ± Niacin.

**Mixed hyperlipidemia:**
Combination therapy is often required
- Statin + fish oil is safer and effective when TG are not so high.
- Fibrates + cholesterol absorption inhibitors
- Statin + Niacin
- Statin + Fibrates
- In the last two combinations the risk of myopathy is greater.

**Drugs:**
3-hydroxy-3-methylglutaryl (HMG) Coenzyme A (CoA) reductase inhibitors commonly known as Statins.
In order of potency as LDL lowering agents these are:
Rosuvastatin and Atorvastatin → Simvastatin → Pravastatin → Lovastatin → Fluvastatin.
*Pravastatin & Fluvastatin are active as such Lovastatin & Simvastatin are hydrolysed to the active drug.*

**Mechanism of action:**
These drugs inhibit cholesterol synthesis by competing effectively to inhibit the HMG CoA reductase the rate limiting step in the cholesterol synthesis thus depleting the intracellular supply of cholesterol. This depletion leads to increased activity and number of LDL receptors which increase the clearance of LDL and it's precursor IDL and causing secondary reduction in LDL synthesis. As a result Statins reduce LDL by up to 60% reduce TG up to 40% and ↑HDL up to 10%.
The therapeutic benefits also include plaque stabilization.
Improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.

- The population who may benefit from statins is large and are ‘rationed’ according to the following priorities:
– 1st choice: for pts following MI or with angina, even for pts with ‘normal’ total cholesterol levels
– 2nd choice: patients with a 30% ten year risk of cardiovascular disease (e.g. hypertension/diabetes) with a total cholesterol > 5mM

• Jan 2006 – NICE: recommends statins for primary prevention in patients with CV risk >20%
• Statins should be considered for all patients at high risk of cardiovascular disease irrespective of cholesterol?
• The combination of: Statin + aspirin + b-blocker + ACE: independently and additively reduce risk in secondary prevention with a 75% reduction in risk.

Adverse effects: these drugs are well tolerated & safe. Side effects are rare. These include:
  • Liver function test abnormalities which returns to normal after stopping the drug.
  • Muscle: Myalgia, increased CK Myositis & infrequently rhabdomyolysis.

Drug interactions:
Fibrates and Niacin when combined with Statins →↑ the incidence of myopathy.
Statins →↑ Warfarin levels. Also interactions with ciclosporin, itraconazol, fibrates and protease inhibitors

Contraindications:
  ❖ Pregnancy and lactation
  ❖ They shouldn't be used in children.

Nicotinic acid (Niacin):

Mechanism of action:
In pharmacological doses (in grams) Niacin reduces peripheral
FA release (by inhibiting lipolysis in adipose tissue) into the circulation which the liver utilizes for TG synthesis. This TG is required for VLDL synthesis in the liver also LDL is derived from VLDL in the plasma. Therefore a reduction in the VLDL production leads to ↓LDL levels; the result therefore is ↓Tc and TG while HDL is increased. Niacin also ↑ the secretion of tissue plasminogens activator and ↓ levels of plasma fibrinogen. These effects of Niacin reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

**Adverse effects:**

- a- Flushing (intense cutaneous flush) and pruritis which is reduced or prevented by administration of aspirin prior to Niacin because it's prostaglandin mediated.
- b- Other side effects include: gastric irritation, abnormal liver function test, exacerbation of Gout & hyperglycemia.

**Fibrates:** are fatty acid derivative Fenofibrate and Gemfibrozil. Fenofibrate is a prodrug and is more effective than Gemfibrozil.

**Mechanism of action:**

Fibrates stimulate Peroxisome proliferator activated receptor alpha (PPAR)-α which controls the expression of gene products that mediate the metabolism of TG & HDL. As a result synthesis of FA, TG & VLDL is reduced while lipoprotein lipase activity which catabolizes TG is enhanced, in addition the promoter regions of genes such as apolipoprotein I and ATP binding cassette A1, are up regulated leading to ↑HDL, consequently Fibrates reduce TG up to 50%, and ↑HDL by 20% but LDL changes are variable.
Adverse effects:
Exhibit a similar profile & frequency of side effects as Statins including Myalgia, Myositis and abnormal liver function test. Fibrates cause mild GIT disturbances & ↑risk of cholelithiasis and prolong the action of anticoagulants.

**Cholesterol absorption inhibitors:**
**Ezetimibe:**

**Mechanism of action:**
These inhibit the intestinal mucosa transporter NPC₁L₁ that absorbs dietary and biliary cholesterol. The resultant depletion of hepatic cholesterol up regulates hepatic LDL receptor activity. This mechanism is synergistic with statins, LDL is reduced by 17%, TG is reduced by 6% While HDL is increased by 1.3%

**Bile acid sequestrating Resins:**
**Cholestyramine-Colestipol and Colesevelam:**

**Mechanism of action:**
These are anion exchange resins that bind negatively charged bile acids & bile salts in the small intestine. The complex is excreted in feces & therefore preventing the bile acids from returning to the liver through the enterohepatic circulation. As a result the liver increases its de novo bile acid synthesis from hepatic cholesterol. The resultant depletion of hepatic cholesterol up regulates LDL receptor activity and reduces LDL in a manner similar to statins (and also synergistic to statins). These drugs cause substantial decrease in LDL and modest increase in HDL but minimal effects on TG.
Cholestyramine is also used to relieve pruritis due to accumulation of bile acids in patients with biliary obstruction.

**Adverse effects:**
A) GIT disturbance such as constipation, nausea & flatulance  
B) Impairment of absorption of fat soluble vitamins (A,E,D,K).  
C) Interference with absorption of many drugs therefore these
drugs should be given at least 2 hours before resin.

**Highly poly unsaturated long chain (n=3) fatty acids**
*(Fish oil)(omega fatty acids)*

Eicosapentanoic acid (EPA) and Docosahexanoic acid (DHA) comprise 30% of the fatty acids in fish oil. EPA & DHA are potent inhibitors of VLDL TG formation.

Intake of 2gm of n3 fatty acid (equal to 6gm of most forms of fish oil) per day lower TG in a dose dependant manner. Up to 50% reduction of TG can be achieved with 15gm fish oil per day. Changes in LDL & HDL are variable. Fish oil also inhibit platelet aggregation and have been shown to decrease mortality from CHD (coronary heart disease).

Fish oil is safe and well tolerated.