Drugs for Dyslipidemia

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Imbalances in lipid components

- High total cholesterol
- High LDL cholesterol
- Low HDL cholesterol
- High triglycerides

Significant risk factor for cardiovascular diseases
Heart disease – 1st leading cause of death in US*
Stroke – 3rd leading cause of death in US*

* 2005 statistics, Am Heart Association

Heart disease – 11th leading cause of death in US*
Stroke – 33rd leading cause of death in US*

* 2005 statistics, Am Heart Association
Drugs for Dyslipidemia

Dyslipidemia

Other risk factors of CV diseases
- High blood pressure
- Tobacco use
- Diabetes
- Physical inactivity
- Poor nutrition

Lipids

Molecules mainly of hydrogen and carbon atoms
Linked by neutral covalent bonds
Nonpolar, insoluble in water
4 subclasses
Lipids

- Fatty acids
  - Saturated, monounsaturated, polyunsaturated
- Triacylglycerols
  - Also known as triglycerides (fat)
  - Majority lipids in this form
- Phospholipids
  - Similar to triacylglycerols except one hydroxyl group of glycerol is attached to a phosphate group
- Cholesterol
  - A steroid
  - 4 interconnected rings forming the background

Cholesterol

- Present in cell membranes
- A precursor of bile acids and steroid hormones
- Travels in the blood in distinct particles containing both lipid and proteins (lipoproteins)
Lipid transport

- Lipids are insoluble in water
  - Transported in plasma as complexes of lipid and proteins known as lipoproteins
- Lipoproteins
  - Spherical shape with lipid core
    - Center: hydrophobic lipid (triglycerides, cholesterol esters)
  - Surface: hydrophilic coat of cholesterol and phospholipid
  - Apolipoproteins embedded on the surface
- Apolipoproteins act as recognition sites for interaction of lipoproteins with tissues
  - Several classes of apolipoproteins
    - A, B, C, D, E, H, and J

Lipoproteins classification

- 3 major classes based on density
- Larger particle, more lipid content, lower density
- VLDL (Very Low Density Lipoprotein)
- LDL (Low Density Lipoprotein)
- HDL (High density Lipoprotein)
- IDL (intermediate density) is measured as LDL in clinical practice
**VLDL**
- Triglyceride rich lipoproteins
- Contain some cholesterol, 10-15% of the total serum cholesterol
- Produced by liver and precursors of LDL
- Major apolipoproteins are apo B 100, apo Cs and apo E
- Appear to promote atherosclerosis
- Major form of transport for endogenously synthesized triglycerides
- Triglycerides degraded by lipoprotein lipase to free fatty acids for storage and oxidation

**LDL**
- AS more triglycerides are removed from VLDL → cholesterol rich LDL
- Major reservoir of cholesterol, typically makes up 60-70% of the total serum cholesterol
- Contains a single apolipoprotein (apo B 100)
- Enhance deposition of cholesterol in arterial walls
- Major atherogenic lipoprotein - “bad” lipoprotein
- Risk of CAD is directly related to ↑ LDL
- Primary target of cholesterol-lowering therapy
Drugs for Dyslipidemia

HDL

- Normally makes up 20-30% of the total serum cholesterol
- Major apolipoproteins are apo AⅠ
- Transport cholesterol from tissues to the liver for secretion into the bile
- Levels are inversely correlated with risk for CHD
- A low HDL level often reflects the presence of other atherogenic factors
- “good” cholesterol

Chylomicrons

- Formed in the intestine from dietary fat
- Appear in the blood after a fat-containing meal
- Triglyceride-rich lipoproteins
LDL receptors

- Located in a wide range of tissues, react with circulating LDL
- Liver contains the greatest number of LDL receptors
- LDL entering cells by receptor mediated endocytosis
- Cholesterol utilized for synthesis of plasma membranes, bile acids, steroid hormones

LDL receptors

- Reduced number of LDL receptors can elevate plasma LDL
- LDL receptors suppress cholesterol synthesis in the liver
- \( \therefore \) LDL receptor controls
  - Uptake of cholesterol
  - Synthesis of cholesterol
- ↑ risk of atherosclerosis associated with a deficit of LDL receptors
Pathophysiology

- The deposition and retention of cholesterol in the arterial walls are the central features of the pathogenesis in atherosclerosis.

Risk factors
- Oxidized LDL
- Glycosylated proteins
- High levels of homocysteine
- Changes in the endothelium (mechanical, immunological, infection-induced)

Pathophysiology

- LDL is modified (mildly oxidized) in the subendothelial layer.
- LDL modification is enhanced in
  - Diabetes
  - Cigarette smoking
  - Hypertriglyceridemic low HDL
Pathophysiology

- Mildly oxidized LDL attracts monocytes into the artery wall
- Monocytes transform into macrophages that accelerate LDL oxidation
- Oxidized LDL provokes an inflammatory response (proinflammatory cytokines, T lymphocytes and growth factors)

Pathophysiology

- Macrophages soak up lipids and become foam cells causing more injury and lumen more restricted
- Repeated injury and repair within an atherosclerotic plaque leads to formation of a fibrous cap
- Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis
Pathophysiology

- **Early stage**
  - coronary remodeling (outgrowth of vessel wall) to preserve coronary lumen
- **Advanced stage**
  - plaque rupture

Detection and Evaluation

- **NCEP ATP III guidelines, 2001, NIH**
  - (National Cholesterol Education Program Adult Treatment Panel)
- Fasting lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) and risk factor assessment at least once q5yr in adults age ≥ 20
**Detection and Evaluation**

- Patients are categorized into different risk groups based on the overall risk of a CHD event over 10 years.
- The intensity of LDL-lowering therapy is adjusted to the individual’s degree of risk for CHD.

**Non-pharmacological Therapy**

**Therapeutic Lifestyle Changes (TLCs)**

- **Dietary therapy**
  - Low consumption of saturated fat and cholesterol
  - Use monounsaturated (olive oil) or polyunsaturated fat (canola oil, fish oils rich in omega-3 fatty acids)
  - Avoid trans-fatty acids (partially hydrogenated fats such as margarine)
  - Increase fiber, complex carbohydrates (whole grains and beans, brown rice, whole wheat bread and cereal, fruit and vegetable)
  - If diet alone is inadequate, dietary supplements of
    - soluble fiber and plant sterols/stanols (↓ LDL-C)
    - fish oil (↓ triglycerides, but not LDL-C)
Non-pharmacological Therapy
Therapeutic Lifestyle Changes (TLCs)

- Physical activity
  - Aerobic exercise 30 min/day for most days of the week
- Weight reduction if overweight
- Stop smoking

Drug therapy

- HMG-CoA reductase inhibitors (Statins)
- Fibrates
- Bile acid binding resins
- Nicotinic acid
- Ezetimibe
- Omega-3 fatty acids
## HMG-CoA reductase inhibitors

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<tr>
<th>Drug</th>
<th>Usual starting dose</th>
<th>Max dose</th>
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<tr>
<td>Lovastatin</td>
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<td>Atorvastatin</td>
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</tr>
<tr>
<td>Rosuvastatin</td>
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### Mechanism of action
- Competitive inhibitor of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A)
  - rate limiting step in hepatic cholesterol biosynthesis
- ↓ cholesterol content of liver cells
- stimulate expression of LDL receptors
- enhance removal of LDL cholesterol from the circulation
Drugs for Dyslipidemia

HMG-CoA reductase inhibitors

- Very effective for lowering LDL-C levels
- Modest effective in reducing triglyceride and increasing HDL-C levels
- Greater LDL-C lowering effects at their highest doses compared with other statins
  – simvastatin, atorvastatin, rosuvastatin
- Considered as 1st-line choice for reducing LDL-C
- Generally safe therapy

HMG-CoA reductase inhibitors

- Use as monotherapy or combination therapy
- Combination therapy
  – bile acid resin
  – ezetimibe
HMG-CoA reductase inhibitors

Administration
- Once daily
- Take with evening meal or with food at bedtime
  - Cholesterol biosynthesis highest at nighttime
- Atorvastatin can be taken anytime during the day (long half-life), morning administration is equally effective
- Most statins have a short half life

Side/ Adverse effects
- GI disturbance, constipation
- Increase liver transaminases
  - Occurrence ~ 0.5 – 2%
  - True hepatotoxicity ?
  - Dose-dependent
  - Usually return to normal upon DC of drug, dose reduction, or even with continued dose
  - Baseline + evaluate liver function periodically
  - If ↑, monitor with 2nd liver function evaluation
  - Risk of hepatotoxicity increase when co-administered with niacin
HMG-CoA reductase inhibitors

Side/ Adverse effects

- **Myopathy (1-5%)**
  - ↑ creatine kinase
  - Muscle ache, soreness, weakness
  - Failure to recognize myopathy and DC drug can lead to rhabdomyolysis

- **Rhabdomyolysis**
  - Rare but severe
  - Breakdown of skeletal muscle
  - Accumulation of the muscle breakdown products leading to myoglobinuria (urine dark color) and renal failure

Myopathy more likely to occur:

- Older patients
- Patients with complex medical problems on multiple medications
- ↑ risk when concomitantly used with potent inhibitors of CYP3A4
- cyclosporine, macrolide antibiotics, certain anti-fungal drugs (ketoconazole, itraconazole), HIV protease inhibitors, amiodarone, verapamil, fibrates, niacin, grapefruit juice
HMG-CoA reductase inhibitors

- Incidence of myopathy and rhabdomyolysis with statins is low
- Up to 1/3 of prescriptions of statins were in combination with drugs that potentially can interact, side effects occurred in 3% of these patients*

*Safety of statins. Circulation, Jun 15, 2004

HMG-CoA reductase inhibitors

- Myopathy
  - Immediately report muscle pain, weakness, or brown urine
  - Creatine kinase measurement
  - Routine laboratory monitoring of creatine kinase is of little value in the absence of clinical signs or symptoms
HMG-CoA reductase inhibitors

- Fluvastatin and Pravastatin not metabolized by P450 3A4 system
  - Less likely to have drug-drug interactions at the level of the liver

Absolute contraindications
- Active or chronic liver disease

Relative contraindications
- Concomitant use of
  - Cyclosporine
  - Macrolide antibiotics
  - Various anti-fungal drugs
  - Cytochrome P450 inhibitors
  - Fibrates and niacin (use with caution)
Drugs for Dyslipidemia

Fibrates

- **Gemfibrozil**
  - 600mg bid
  - Max 1500 mg
  - 900mg ER as a single evening dose

- **Fenofibrate**
  - 100mg tds
  - Max 400mg daily
  - Micronized: 200mg once daily
  - ER: 250-300 mg once daily
  - Supra form: 160mg once daily

- **Clofibrate**
  - 2 g daily in divided doses

Most effective in lowering triglyceride levels
Effective for increase HDL-C
Moderate for reducing LDL-C
Fibrates

**Mechanism**
- Complex
- Agonist for the nuclear receptors -peroxisome proliferator-activated receptors-alpha (PPAR-α)
  - Stimulate lipoprotein lipase activity
  - \( \uparrow \) hydrolysis of triacylglycerols in VLDL
  - Hasten removal of VLDL from plasma
  - Reduce TG-rich lipoproteins from plasma

**Adverse effects**
- GI disturbances (most common)
- Increase risk for hepatotoxicity and skeletal muscle toxicity of statins
- Fenofibrate appears to have a lower risk of interfering with statin metabolism (preferred fibrate for combination therapy)
- Increase risk of gallstones (clofibrate)
Bile acid binding resins

- **Colestyramine**
  - 4-24g pwd/day (tds-qds)

- **Colestipol**
  - 5-30g pwd/day (once or in divided doses)
  - 2-16 g tab/day (once or in divided doses)

- **Colesevelam**
  - 3.75 g/day (once or in 2 divided doses)
  - 2.5-3.75 g/day when used with a statin
  - minimal GI effects

↓↓ LDL-C (a modest reduction)
Mild increase of HDL
Increase hepatic VLDL production, ∴ can raise serum triglyceride level in some persons
Bile acid binding resins

Mechanism
- Anion exchange resin that bind bile acids in the intestinal lumen in exchange for chloride ion
- Resin is not absorbed
- Promotes fecal excretion of bile acids
- ↓ enterohepatic recirculation of bile acids
- Liver increase bile acid synthesis from cholesterol
- Enhance LDL receptor expression
- ↓ LDL-C

Pharmacokinetics
- Insoluble in water, large molecular weight
- Neither absorbed nor metabolized in intestine
- Excreted in feces
Bile acid binding resins

Administration
- Once or twice daily with meals
- If once daily, take with largest meal of the day
- Mix with water or juice, hydrate for a few min to minimize the gritty texture

Useful in combination therapy
- Doubling the dose of a statin produces a 6% further reduction in LDL-C, adding a moderate dose of a bile acid binding resin further lower LDL-C by 12-16%
- Contraindicated as monotherapy in persons with high triglycerides (>400 mg/dL)
- Monotherapy only in patients with triglyceride <200mg/dL
Bile acid binding resins

- Adverse effects
  - Bothersome GI side effects
  - Constipation, abdominal pain, bloating, fullness, nausea and flatulence
  - Interfere with absorption of fat soluble vitamins and some drugs
  - Take drugs 1 hour before or 4 hours after administration of resin

Nicotinic acid (Niacin)

- Extended release nicotinic acid
  - 1-2 g once daily
- Effective on all major lipid fractions
  - ↑ HDL-C
  - ↓↓ triglycerides
  - ↓ LDL-C
Nicotinic acid (Niacin)

Mechanism
- Inhibit lipolysis in adipose tissue (primary producer of circulating FFA)
- Liver uses the circulating FFA to synthesize triglycerides
  - ↓ liver triglyceride synthesis
  - ↓ VLDL production
  - ↓ LDL

Side/Adverse effects
- Intense cutaneous flushing
  - Take ASA or ibuprofen 30 minutes prior to niacin, or take on full stomach can reduce severity of flushing
  - Tolerance after prolonged use
  - Less with prolonged release dosage form
- GI disturbances
- liver dysfunction
- decreased glucose tolerance
- hyperuricemia
Nicotinic acid (Niacin)

**Administration**
- ER dosage form – single dose at hs
- ER form – reduced incidence of flushing and hepatotoxicity
- Can be used as combination therapy

**Contraindications**
- Chronic liver disease
- Severe gout

**Relative contraindications**
- Hyperuricemia
- High doses in Type 2 diabetes
**Ezetimibe**

- Selective inhibitor of intestinal cholesterol absorption
  - Block the transfer of dietary and biliary cholesterol from intestinal micelles to brush border membrane enterocytes
- ↓↓ LDL-C
- ↓ total cholesterol, ↑ HDL-C and ↓ TG levels

**Ezetimibe**

- 10 mg daily
- Major role in combination with a statin
- Vytorin = ezetimibe + simvastatin
  - 10/10mg; 10/20mg; 10/40mg; 10/80mg
  - Inhibits absorption of cholesterol in small intestine
  - Reduce cholesterol synthesis in liver
Fish Oil Supplementation

- NCEP ATP III guidelines
  - Omega-3 fatty acids should be considered as an adjunct to therapy in patients with very high TG levels
- Complications of fish oil supplementation include
  - Thrombocytopenia
  - Bleeding disorders
- Diets high in omega-3 PUFAs (EPA) reduce cholesterol, triglycerides, LDL and VLDL, may elevate HDL-C

The Omega-3 series

- \( \alpha \)-Linolenic Acid 18:3n-3 (green leafy veg, flaxseed oil, canola oil, nuts)
- Desaturase
  - EPA 20:5n-3 (fish oils)
- Elongase
  - DHA 22:6n-3 (fish oils)
- Omega-3-derived eicosanoids
  - 3-series prostanoids: TXA3, PGE3, PGI3
  - 5-series leukotrienes: LTB5, C5, E5
- Anti-inflammatory
- Antithrombotic
Combination Therapy

- Consider combination therapy after adequate trials of monotherapy
- Statins may combine with bile acid resin, niacin, fibrate and omega-3 fatty acid
- Include gemfibrozil or niacin to ↑ HDL-C
- Addition of ezetimibe to a statin provides an additional 14% to 17% reduction in LDL-C
- Monitor carefully for evidence of side effects especially muscle related symptoms and hepatotoxicity