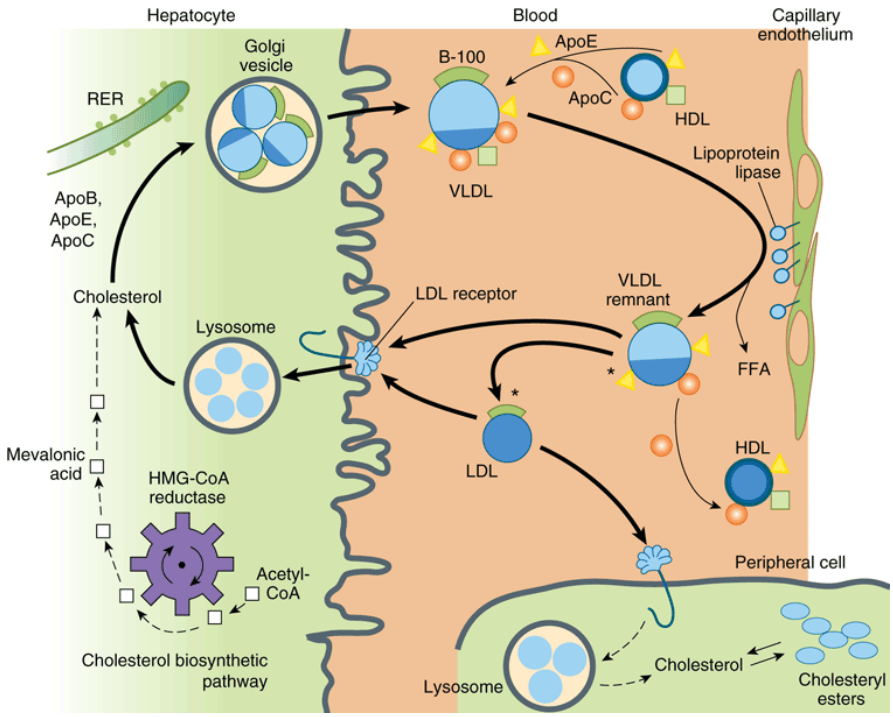
Unit IV – Problem 3 – Pharmacology: Drugs Used in Dyslipidemia

- **Below is a figue showing the metabolism of lipoproteins:**



- **What are the target for drug therapy?**
  - **Decrease in input:**
    - ✓ Inhibition of cholesterol synthesis.
    - ✓ Prevention of cholesterol absorption from the gut.
    - ✓ Inhibition of hepatic VLDL synthesis.
  - **Increase in output:**
    - ✓ Enhanced conversion of cholesterol to bile acids/salts (resulting in increased LDL uptake by the liver).
    - ✓ PPAR-α activation mediated LPL activation (resulting in chylomicrons and VLDL catabolism).
- **Classes of drugs:**

Statins	Atorvastatin, Risuvastatin and Simvastatin
Fibrates	Fenofibrate, Benzafibrate and Gemfibrozil
Resins	Cholestyramine, Colestipol and coleseyelam
Nicotinic acid	Niacin-IR, Niacin-ER
Cholesterol absorption inhibitors	Ezetimibe (Stanols, Sterols and dietary fiber)
Omega-3 fatty acids (fish oil)	Eicosapentaenoic acid and Docosahexaenoic acid

- **Statins:**
  - **There are two important agents which you must memorize**: Atorvastatin and Rosuvastatin (which is considered as the most effective statin).
  - **Mechanism of action**: preventing cholesterol synthesis by inhibiting the rate-limiting enzyme (HMG-CoA reductase). Therefore, there will be increased expression of LDL-receptor on the surface of the liver resulting in removal of LDL (bad cholesterol) from the blood.
  - **Used in**: high cholesterol (drug of choice), mixed dyslipidemia, mild-moderate hypertriglyceridemia (200-500 mg/dL) and atherosclerotic artery disease (such as coronary artery disease).
  - **Adverse reactions include**: hepatotoxicity and myotoxicity.
  - **Contraindications**: hepatic disease, pregnancy and lactation.

- **Bile acid binding resins:**
  - **How to memorize them? → these drugs always start with (cole) = (bile).**
  - **Mechanism of action**: inhibiting bile acid reabsorption from the ileum thus the liver has to take more cholesterol from the blood to synthesize new bile salts (increased cholesterol receptors).
  - **Used in**: high cholesterol (2^{nd} line drugs added to statins). Notice that these drugs are very safe for children, pregnancy and lactation.
  - **Adverse reactions include**: GIT distress and vitamin-K malabsorption (results in bleeding tendency).
  - **Contraindication**: these drugs are not used in mixed dyslipidemia since they increase the levels of triglycerides!
- **Cholesterol absorption inhibitor:**
  - **Agent**: Ezetimibe
  - **Mechanism of action**: blocking NPC1L1 in intestinal brush border thus inhibiting cholesterol absorption in small intestine.
  - **Used in**: high cholesterol (2^{nd} line drug added to statins and it is better than resins).
  - **Adverse reactions are rare and include:** hepatotoxicity and myotoxicity.
- **Fibric acid derivatives:**
  - **Agent**: Gemfibrozil
  - **Mechanism of action**: agonist of PPAR which is up-regulating lipoprotein lipase that is degrading triglycerides.
  - **Used in:** severe hypertriglyceridemia > 500 mg/dL (drug of choice).
  - **Adverse reactions include**: hepatotoxicity (rare), myotoxicity (especially if combined with statins) and gallstones.
  - **Note**: these drugs are potentiating the action of anticoagulants.
- **Niacin (vitamin B3 which is also known as nicotinic acid):**
  - **Mechanism of action:** decreasing the efflux of free fatty acids to the liver thus reducing triglycerides and VLDL synthesis in the liver. It also decreases the conversion of HDL to LDL.
  - **Used in:** low HDL (drug of choice), high triglycerides (2^{nd} line) and high LDL (2^{nd} line).
  - **Adverse reactions include:** hepatotoxicity (rare), hyperglycemia, hyperuricemia (resulting in gout), GI distress and severe flushing.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓