Lesson 4: Drugs for Dyslipidemia

**Bile Sequestrants**

- **cholestyramine (Questran®)**
- **colestipol (Cholestid®)**
- **colesevelam (WelChol®)**

- Bile sequestrants sequester bile acids and prevent their absorption.
- Since bile acids are made from cholesterol, this ends up removing cholesterol from the body.
- These are insoluble resins **made up of polymeric cations**.
- They basically work as **ion exchange resins** where a negative ion like chloride is exchanged for bile acid.
  - For example, cholestyramine is a chloride salt. When the drug comes in contact with bile acids, the chloride is replaced by a molecule of bile acid, which is also negative.
- Bile acids are synthesized within the liver and released in the duodenum when one eats a meal. If a sequestrant is present at the same time, it will basically bind to and soak up all the bile acid. The sequestrant is **insoluble** and too big to get absorbed in blood, so it is **eliminated in feces** and it takes the bile acids with it.
- Normally, 95% of the bile acid is reabsorbed due to **enterohepatic circulation**. However, in the presence of sequestrants, this fraction decreases and the amount excreted increases. The liver responds by converting more cholesterol to bile acid. This creates cholesterol deficiency in hepatocytes.
- Hepatocytes respond to low cholesterol levels by:
  - Increasing LDL-R expression to import more cholesterol from plasma.
  - Increase synthesis of cholesterol.
  - **Result: Decrease in plasma LDL-C and reduction in mortality.**

- **Advantages of sequestrants:**
  - No systemic absorption—thus, no systemic side effects.
  - Safe in children & pregnant women
  - Cause slight increase in HDL-C

- **Disadvantages of sequestrants:**
  - Not as effective as statins
- **Increase TG** levels slightly
  - Why? Because liver increases bile production. This also triggers VLDL production.
- **Timing** of dose: sequestrant dose has to be timed so that it is present in the duodenum when bile acids are released by the gall bladder (i.e. after a meal).
- The most common complaints include general **dyspepsia, bloating**, constipation, and diarrhea.
- unlike a pill or liquid, sequestrants are resins that have to be taken in **large amounts**. For example, a typical dose of cholestyramine is anywhere from 4 to 8 grams, so it is **not very palatable** or easy to take. Consequently then this also raises a **compliance issue**, particularly among young patients.

  - **Drug-Drug Interactions involving sequestrants:**
    - Sequestrants interfere with absorption of fat-soluble vitamins, thiazide diuretics, digoxin, warfarin and many other drugs. So it is generally recommended that patients take such drugs at least one hour before or 4-6 hours after taking a sequestrant to minimize these interactions.

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**EZETIMIBE (Inhibitor of Cholesterol Absorption)**

- ezetimibe (Zetia®)
- ezetimibe + simvastatin (Vytorin®)
- ezetimibe (Ezetrol®) Europe
- ezetimibe + simvastatin (Inegy®) Europe

- Ezetimibe acts on **enterocytes** and **inhibits absorption of sterols**, including cholesterol. It does that by blocking the sterol transporter **NPC1L1**, which is responsible for importing sterols into the enterocytes.
- Cholesterol **absorption** and **reabsorption** are both affected.
- In order to maintain homeostasis, hepatocytes will respond by increasing expression of LDL-R at the cell surface. This will lower plasma LDL-C, but cholesterol biosynthesis will also be stimulated, so the impact of ezetimibe alone is relatively modes. The normal dose of 10 mg once daily results in up to 20% reduction in LDL-C and it also decreases TG by 5 to 8%. However, when combined with simvastatin, the effects are more dramatic.
In addition to using it for dyslipidemia, ezetimibe is also used in cases of phytosterolemia. This is a very rare disorder where the patients do not have the ability to eliminate plant sterols from the body. NPC1L1 is a sterol importer, so it will import cholesterol as well as plant sterols. Patients with phytosterolemia have defects in a transporter complex known as ABCG5 and ABCG8, which is responsible for effluxing sterols from enterocytes. Defects in this complex cause accumulation of plant sterols within the body, resulting in numerous symptoms that are similar to dyslipidemia. Therefore, ezetimibe is used to block absorption of plant sterols in these patients. Why does this defect not affect cholesterol efflux? Because the major route of cholesterol removal is bile excretion, not efflux from enterocytes.

**EZETIMIBE: ADME Properties:**
- Well absorbed
- Conjugated to glucuronic acid
- Undergoes enterohepatic recirculation. Hence, long half-life.

**EZETIMIBE: Adverse effects:**
- Steatorrhea, mild abdominal pain (b/c of unabsorbed cholesterol)
- Headache
- Increase in liver transaminases
- Absorption inhibited by sequestrants
**STATINS**

**Currently in the market:**
- atorvastatin (Lipitor)
- fluvastatin (Lescol)
- lovastatin (Mevacor)
- pitavastatin (Livalo)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastain (Zocor)

- Statins were first isolated from molds, and Lovastatin, which is still in the market was isolated from the species known as *Aspergillus terreus*. Simvastatin and Pravastatin semi-synthetic and were derived from modification of Lovastatin. The rest of the statins in the market are complete synthetics.
- Statins are most commonly used for patients with hypercholesterolemia but they are also used for patients who have other risk factors that increase the likelihood of getting a stroke or coronary heart disease independent of their lipid levels.
- The cholesterol biosynthetic pathway known as the Mevalonic acid pathway. Almost all cell types in the body have this pathway and are able to make cholesterol from AcetylCoA. In this pathway, acetyl coA is HMG CoA through several steps. HMG CoA is then converted to Mevalonic acid. Through several other steps, Mevalonic acid is eventually converted to cholesterol. The conversion of HMG CoA to Mevalonate is the rate limiting step in cholesterol synthesis and it is catalyzed by HMG CoA Reductase. Statins inhibit this enzyme.

- When cholesterol levels in hepatocytes are depleted due to this inhibition of biosynthesis, the cells respond by increasing the expression of LDL receptor, thus importing LDL-C from plasma.
- Depending on the dose and a particular statin used, there is usually a **25% to 50% reduction in plasma LDL-C levels.**
Rosuvastatin is more potent than atorvastatin, which is more potent than simvastatin, which in turn is more potent than lovastatin and pravastatin. Fluvastatin is the least potent statin.

Statins also cause a slight reduction in plasma TG levels.

- **Mechanism:** Low cholesterol levels in hepatocytes slows down the rate of VLDL assembly.

Statins also increase HDL-C levels:

- **Mechanism:** Liver suffers from low cholesterol levels so it imports it from body tissues using HDL-mediated reverse cholesterol transport.
- This effect is dose dependent (except for atorvastatin where increase in dose decreases the impact on HDL-C levels).
- Pitavastatin > Rosuvastatin, Simvastatin > Atorvastatin

Statins are more effective than other drugs at reducing CHD-related deaths. **Pleiotropic effects** are likely a big reason behind this.

- Statins are known to **improve endothelial function**, so that arteries are more sensitive to stimuli that cause vasodilation.
- In animal models, statins have been shown to have **anti-inflammatory** effects. In humans, statins reduce serum CRP levels (CRP is a marker for inflammation).
- Statins have **anti-oxidant type activity** that interferes with oxidation of LDL particles.
- Statins are known to have **anti-thrombotic effects** by which they reduce clots within arteries.
- Thus, statins attenuate the process of atherosclerosis, stabilize existing atherosclerotic plaques, and inhibit clot formation.

**Statin half-lives:**

- Rosuvastatin: 1-3 hrs
- Atorvastatin: 2-5 hrs
- Pitavastatin: 11-12 hrs
- Simvastatin: 14 hrs
- Fluvastatin: 20 hrs
- Lovastatin: 20 hrs
- Pravastatin: 20 hrs
STATIN ADME PROPERTIES:
- Complete oral absorption is in the range of 1-3 hours.
- Once in circulation, statins are imported into the liver through a transporter known as OATP1B1.
- Most statins undergo metabolism in the liver, and with an exception of Fluvastatin and Pravastatin.
- Most metabolites retain pharmacological activity.
- Atorvastatin, simvastatin, and lovastatin are mostly metabolized by CYP3A4.
- Fluvastatin is metabolized mostly by CYP2C9.

STATIN ADVERSE EFFECTS:
- There are two major concerns with statins. These are hepatotoxicity and myopathy.
- In terms of hepatotoxicity, the major common finding is elevation of liver transaminases. Complete liver failures are exceedingly rare.
- Myopathy ranges from very mild form where patients complain of general muscle aches to rhabdomyolysis, which is fatal.
- Myopathy is not only dose dependent but also dependent on many other factors:
  - Advanced age, preexisting liver or kidney disease, or lean body mass are some of the risk factors.
  - Most common complicating factor is pharmacokinetic drug-drug interaction. The fibric acid derivative Gemfibrozil is the most common culprit responsible for 38% of the cases of severe myopathy.
  - The other common interactions include digoxin, warfarin, cyclosporine, macrolides particularly erythromycin and clarithromycin, and azole antifungals.
- PK Interaction due to drugs that inhibit CYP3A4:
  - Macrolides
  - Azole antifungals
  - HIV protease inhibitors
  - Cyclosporine
  - Amiodarone
PK interactions due to inhibition of **OATP1B1**:  
- OATP1B1 actively imports statins into the liver and thus removes them from circulation.
- If another drug competes for this transporter or inhibits it, then the plasma levels of statins will increase, resulting in a greater risk of myopathy.
- The two most common inhibitors that cause increased statin levels are **Gemfibrozil and Cyclosporine**.

- Cholesterol synthesis peaks between 12am-2am. Therefore, traditionally patients are advised to take statins at bedtime. This is particularly important when it comes to statins with short half-lives. However, statins with long-half lives (rosuvastatin, pitavastatin, and atorvastatin) can be taken during the day.

- Statins are not safe during pregnancy.

- Children with familial hypercholesterolemia can take statins, but usually they are given after the age of 10.
Fibrates (Fibric Acid Derivatives)

- Use: To lower plasma TG and increase HDL-C
- Mechanism: Fibrates mediate their effects mainly through activation of a nuclear receptor known as PPAR-alpha. PPAR-alpha along with another transcription factor known as Retinoid-X-receptor act together to regulated transcription of many genes. Fibrates bind to PPAR-alpha and activate numerous genes that are involved in lipid metabolism. Thus, fibrates are also known as PPAR-α activators.
  - Resulting ApoA1 transcriptional activation causes increase in HDL-C.
  - Fibrates also increase the expression of SR-B1, which increases cholesterol delivery to liver by HDL-C.
  - Increase in transcription of Lipoprotein Lipase (LPL) results in increased hydrolysis of TG and decreased plasma levels of TG.
- Fibrates are not used to lower LDL-C. Their effects are modest and unpredictable. For example, in patients with TG levels greater than 500 mg/dL, Gemfibrozil actually increases LDL-C.
- Fibrates very effective at reducing serum TG levels. However, their ability to reduce mortality remains uncertain.
ADME PROPERTIES OF FIBRATES

**Absorption:**
- Rapid & efficient (>90%)
- Fenofibrate best with food

**Distribution:**
- Large $V_d$; 95% albumin bound
- Conc. in liver, kidney, intestine

**Metabolism:**
- Glucuronidation

**Elimination:**
- Renal (60-90%), NR in renal failure
- Half-life:
  - Gemfibrozil (1 h)
  - Fenofibrate (20 h)

- Fibrates highly albumin bound
- Concentration in liver, kidneys, and intestines exceed those in plasma, so fibrates have a **large volume of distribution**
- Fibrates are conjugated to glucuronic acid and **eliminated by the kidneys** (fibrates are not recommended in renal failure).
- Gemfibrozil has a half-life of only one hour but fenofibrate has a 20 hour half-life. Thus, Gemfibrozil is given twice daily but fenofibrate is usually once a day.

**Fibrates: Adverse effects:**
- Fibrates are generally very well tolerated but there are two major adverse effects:
  - The most common effect is **abdominal discomfort** (bloating & mild pain).
  - The other adverse effect that is of a concern is **myopathy**. However, this is seen in patients who are simultaneously taking statins and **have renal dysfunction**. The major culprit is Gemfibrozil and fenofibrate appears to be well tolerated in this regard.

**Fibrates: Interactions:**
- **Gemfibrozil inhibits OATP1B1** which is responsible for import of statins in the hepatocytes, so it raises the serum levels of statins.
- Gemfibrozil also competes for glucuronic acid conjugation of some of the statins, and this could also contribute to the interaction.
- Fibrates as well as Warfarin are bound to plasma proteins, particularly albumin. Therefore, they compete with each other for binding to albumin. This causes an increase in free warfarin levels in plasma and increased bleeding.

### NIACIN

- Niacin, which is also known as nicotinic acid, is commonly available in a crystalline form as over the counter supplement, but there is also a prescription strength extended release form that is marketed as Niaspan.

- Niacin is more commonly used as vitamin B3 supplement. Niacin is converted to its amide form, which is nicotinamide. It is nicotinamide that is required in small amounts for its vitamin function. Niacin itself is used for the treatment of dyslipidemia, but this requires much larger doses and the mechanism is independent of the vitamin function.

#### Mechanism: Decrease in TG levels:
- Niacin serves as a ligand for an inhibitory GPCR on adipocytes.
- Niacin inhibits Hormone Sensitive Lipases by activating this receptor.
- Normally, when active, these lipases breakdown TG in adipocytes into free fatty acids. These free fatty acids reach the liver where they are converted to TG and packed into VLDL particles. Inhibition by Niacin prevents this and decreases VLDL packaging, resulting in a decrease in serum TG levels.
Since there are fewer VLDL particles, LDL-C will also decrease (because VLDL is converted to LDL).

- **Mechanism: Increase in HDL-C levels:**
  - Niacin reduces clearance of Apo-A1
  - Increased Apo-A1 half-life results in increased HDL assembly rate

- Niacin corrects every aspect of dyslipidemia better than any other drug. However, some clinicians question the utility of Niacin in reducing CHD-related deaths because:
  - Statins are more effective at reducing mortality, so niacin has no advantage over statins
  - Adverse effects of Niacin are a major limiting factor.

### Niacin: ADME

- **Absorption:** rapid & complete
- **Metabolism:** not significant
- **Elimination:**
  - Urinary
  - $t_{1/2} = 60$ min (dose bid/tid)
  - Niaspan® ER, (5 hrs)

### Niacin Side Effects:

- **Flushing, dryness, itchiness**
  - Niacin triggers the release of prostaglandins in skin.
  - Flushing is often triggered when a patient drinks something hot, like tea or coffee, and also with alcohol.
  - The side effect usually settles down by two to three weeks, but if a patient misses a dose or restarts the drug after stopping it, then it starts all over again.
  - Taking niacin with a meal helps as does taking aspirin or other NSAIDs, because NSAIDs inhibit prostaglandin production.
**Dyspepsia:**
- Niacin is an organic acid and it is taken in large doses that are very irritating on the GI lining and dyspepsia is very common.
- Niacin is not recommended in patients with a history of GERD or PUD as it may exacerbate their condition.
- Niacin is best tolerated when taken with meals

**Liver:**
- Niacin also has a dose-dependent effect in the liver.
- In over 20% of the patients, niacin is known to cause an increase in liver transaminases.
- While severe problems are rare, niacin is **not recommended in patients with preexisting liver disease**.
- Niaspan, which is an extended release formulation, is less likely to cause this effect.

**Hyperuricemia:**
- Niacin, being an organic acid, inhibits tubular secretion of uric acid, resulting in decreased renal elimination and high blood levels of uric acid.
- Increased uric acid levels exacerbate gout attacks in susceptible patients

**Hyperglycemia:**
- Niacin increases blood glucose levels
- Diabetic patients would need to adjust dosage of their anti-diabetic medications

**Myopathy:**
- Patients already on statins have an increased risk of myopathy when niacin is added, so statin dose must be adjusted accordingly, particularly if the patient has an underlying liver or kidney disease.

_Niacin has many side effects that limit its desirability for the treatment of dyslipidemia_
Omega-3 Fatty Acids

- Omega-3 along with Omega-6 is an essential unsaturated fatty acid that is required for normal body functions.
- There has to be a balanced between Omega-3 and Omega-6. An average diet tends to have excess omega-6 but insufficient omega-3 fatty acids. Thus, this imbalance tends to have inflammatory effects.
- **Omega-3 supplements** are thought to decrease inflammation
- The major source of omega-3 is fish oil, which contains two major omega-3 fatty acids. These are EPA and DHA.
- A prescription strength drug marketed as Lovaza, contains a much greater amount of EPA and DHA then over the counter supplements.
- Omega-3 fatty acids are particularly effective in reducing triglycerides, but their general impact on cardiovascular health still remains unclear.
- Mechanism underlying the reduction of TG likely involves regulation of transcription factors, including PPAR-alpha. This transcription regulation results in decreased TG synthesis as well as increased fatty oxidation, resulting in reduction of plasma TG levels.

PLANT STEROLS

- Plant sterols and stanols are increasingly used to reduce LDL-C.
- These sterols are naturally produced by plants and are present in cereals, fruits, vegetables and nuts. They are also present in significant amounts in things like fortified orange juice and margarine.
- **Mechanism:**
  - Cholesterol and fatty acids, can be absorbed by the enterocytes in the GI tract only if they are part of micelles.
  - Plant sterols can compete with cholesterol for binding to micelles.
  - If they are present in significant amount, plant sterols will replace cholesterol from these micelles so that cholesterol will not be absorbed and is excreted in feces instead. Plant sterols are absorbed into the enterocytes.
  - **Caution:** Patients with phytosterolemia should not consume plant sterols without proper evaluation of their condition.