DRUGS TO LOWER BLOOD CHOLESTEROL AND TRIGLYCERIDES

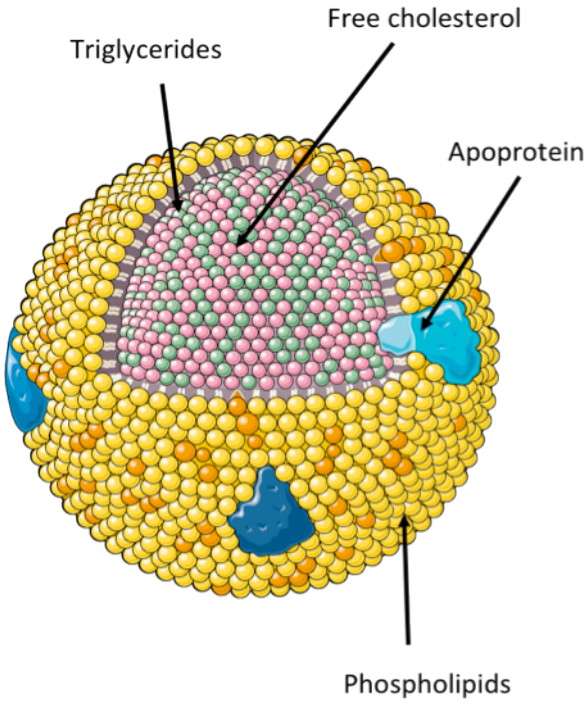
12.1 INTRODUCTION

CORONARY HEART DISEASE

- Coronary heart disease occurs when coronary blood circulation fails to adequately supply the heart with blood.
- Coronary heart disease is primarily caused by atherosclerosis. Atherosclerosis occurs when plaque builds up on the walls of the arteries. This causes the artery to narrow and results in decreased blood flow to the heart.
- The risk of developing coronary heart disease is directly related to the levels of cholesterol in the blood. Therefore people with high blood cholesterol are at risk of developing coronary heart disease. For this reason, large efforts have gone into designing drugs to lower blood levels of cholesterol.
- In Canada, cardiovascular disease causes one third of all deaths. This is more than any other illness.

12.2 CHOLESTEROL

Cholesterol is an important molecule that supports many physiological roles. It is an essential component of cell membranes, a precursor of steroid hormones (i.e. testosterone and estrogen) and a precursor of bile salts. We obtain cholesterol through dietary sources (exogenous cholesterol) or through synthesis (endogenous cholesterol) which occurs primarily in the liver. Approximately 80% of the cholesterol in the body is synthesized by the liver, whereas 20% is obtained from dietary sources. Although cholesterol is an essential molecule for the reasons described above, high blood levels are linked to atherosclerosis and heart disease.



PLASMA LIPOPROTEINS

Structure and Function

- The basic structure of lipoproteins is shown in the figure. Notice the outer hydrophilic shell is made up of phospholipids. This allows lipoproteins to be soluble in plasma. In contrast, the core is composed of lipophilic cholesterol and triglycerides.
- The primary function of lipoproteins is to transport cholesterol and triglycerides in the blood. Since cholesterol and triglycerides are lipophilic, they require lipoproteins in order to be soluble in the blood.
- All lipoproteins also have apolipoproteins embedded in the phospholipid shell.

Apolipoproteins have three functions:

1. Allow recognition by cells which may bind and ingest lipoproteins.
2. Activate enzymes that metabolize lipoproteins.
3. Increase the structural stability of lipoproteins.

- Lipoproteins that contain apolipoprotein A-I transport cholesterol from non-hepatic tissue back to the liver whereas lipoproteins that contain apolipoprotein B-100 transport cholesterol to non-hepatic tissue.

Classes of Lipoproteins

- Lipoproteins are named based on their density. Protein has a higher density than lipid so lipoproteins with a high percentage of protein will have a high density. Conversely, lipoproteins with a low percentage of protein will have a relatively low density.
- In terms of coronary heart disease and atherosclerosis, three classes of lipoproteins are particularly important. They are Very-Low Density Lipoproteins (VLDL), Low Density Lipoproteins (LDL) and High Density Lipoproteins (HDL).

Very Low Density Lipoproteins (VLDL)

- VLDL's deliver triglycerides from the liver to adipose tissue and muscle.
- They have a triglyceride rich core and account for almost all of the triglyceride content in blood.
- The link between VLDL and atherosclerosis is controversial with some, but not all studies, suggesting that high VLDL contribute to atherosclerosis.
- VLDL particles contain one apolipoprotein B-100 molecule, which allows them to bind to cells and transfer their lipid (mostly triglyceride) to cells.

Low Density Lipoproteins (LDL)

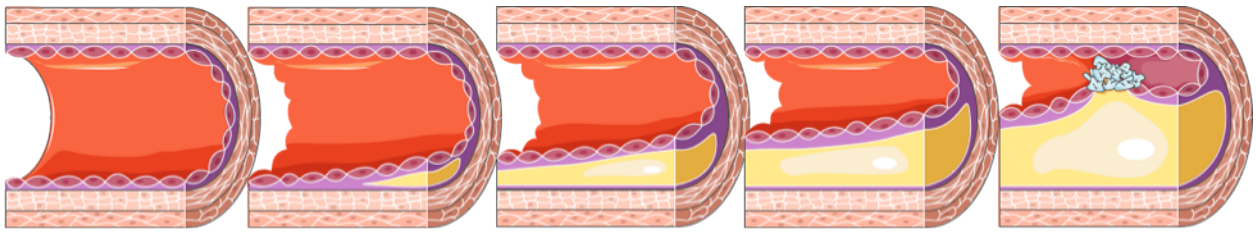
- LDL's deliver cholesterol to non-hepatic tissue.
- Have a cholesterol rich core and account for 60 – 70% of the cholesterol in blood.
- LDL particles contain one apolipoprotein B-100 molecule, which allows them to bind to cells and transfer their lipid (mostly cholesterol) to cells.
- There is a clear link between LDL cholesterol and development of atherosclerosis. The higher the blood LDL level, the greater the risk of developing coronary heart disease.
- Reducing blood LDL levels halts or even reverses atherosclerosis and has been proven to decrease death from coronary heart disease.
- Because of the role it plays in coronary heart disease, LDL cholesterol is often referred to as "bad cholesterol"

High Density Lipoproteins (HDL)

- HDL's deliver cholesterol from non-hepatic tissue back to the liver. Therefore, HDL's promote cholesterol removal from the blood.
- Similar to LDL, HDL's have cholesterol as their main core lipid and account for 20 – 30% of total blood cholesterol.
- The effect of HDL on coronary heart disease is opposite to that of LDL. Therefore, elevated HDL decreases the risk of coronary heart disease.
- HDL particles may contain multiple apolipoproteins including A-I, A-II and A-IV. The A-I apolipoprotein is believed to mediate the beneficial effects of HDL cholesterol.
- Since HDL cholesterol protects against atherosclerosis, it is often referred to as "good cholesterol".

The Role of LDL Cholesterol in Atherosclerosis

- LDL's promote the initiation of atherosclerosis.
- Atherosclerosis is initiated when LDL's move from the blood into the sub-endothelial space of the arterial epithelium. In the sub-endothelial space LDL's may become oxidized, a crucial step in the initiation of atherosclerosis.
- Oxidation of LDL cholesterol causes recruitment of monocytes (a type of immune cell) to the sub-endothelial space.
- Monocytes are then converted to macrophages. Macrophages are another type of immune cell that are capable of "ingesting" foreign material.
- Macrophages then take up oxidized LDL. During this process they become larger and vacuolated. In this form they are referred to as foam cells.
- As more foam cells accumulate beneath the epithelium, a fatty streak appears. This is followed by platelet adhesion, smooth muscle migration and collagen synthesis.
- The end result is an atherosclerotic lesion characterized by a lipid core and a tough fibrous plaque.



Although LDL cholesterol plays a critical role in the development of atherosclerosis, it is important to note that atherosclerosis is PRIMARILY an inflammatory process. LDL penetration of the arterial wall can be thought of as causing a mild injury to the arterial endothelium. It is the subsequent inflammatory response (i.e. monocyte/macrophage infiltration) that that mediates the development of atherosclerosis. The development and progression of atherosclerosis is summarized in the figure.

12.3 CHOLESTEROL SCREENING AND RISK ASSESSMENT

Cholesterol Screening

The cholesterol screening guidelines provided in your textbook are developed by American sources. Notice how cholesterol values in table 49-3 are presented in mg/dL (American) whereas in Canada we report cholesterol in mmol/L. For quiz and examination purposes, follow the screening guidelines, target levels and risk assessment from these lecture notes as they have been generated from the Heart and Stroke Foundation of Canada and/or the Canadian Cardiovascular Society.

- In Canada cholesterol screening is recommended for all males over the age 40 and all females over the age of 50 or females that are post-menopausal.
- Testing is also recommended in all patients regardless of age who:
    - have diabetes
    - have heart disease or a family history of heart disease
    - have hypertension
    - have central obesity: a waist circumference greater than 102 cm (40 inches) for men and 88 cm (35 inches) for women
    - Smoke or have recently stopped smoking
    - have inflammatory (i.e. arthritis, lupus) or renal disease

Cardiovascular Risk Assessment

- Cardiovascular risk assessment is used by health care practitioners to estimate the risk a patient has of developing cardiovascular disease.
- Although cardiovascular risk assessment is imperfect, it provides health care professionals with guidelines and treatment targets.
- The most commonly used form of cardiovascular risk assessment is called the Framingham Risk Score (abbreviated FRS).
- The Framingham Risk Score uses gender, age, total blood cholesterol, smoking status, HDL cholesterol and systolic blood pressure in a formula to calculate a risk score.
- The risk score represents the patient's 10 year risk of developing coronary heart disease.
- Patients with a Framingham 10 year risk score greater than 20% are considered high risk, between 10-19% are considered moderate risk and a score below 10% is considered low risk.
- It is important to note the Framingham score has been shown to underestimate risk in youth, women and patients with metabolic syndrome (*see pg 6*).
- A summary of the tables used to calculate the Framingham Risk Score are shown below.
- Physicians use the Framingham risk score along with guidelines from the Canadian Cardiovascular Society to guide treatment of cholesterol using the following table.

Framingham Risk Assessment - Women

AGE

Age	Points
20 -34	-7
35 - 39	-3
40 - 44	0
45 - 49	3
50 - 54	6
55 - 59	8
60 - 64	10
65 - 69	12
70 - 74	14
75 - 79	16

Systolic BP

Systolic BP	If Untreated	If Treated
< 120	0	0
120 - 129	1	3
130 - 139	2	4
140 - 159	3	5
160+	4	6

HDL Cholesterol (mg/dL)

HDL	Points
60+	-1
50 - 59	0
40 - 49	1
< 40	2

Smoking Status

	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
Non-smoker	0	0	0	0	0
Smoker	9	7	4	2	1

Total Cholesterol (mg/dL)

	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
< 160	0	0	0	0	0
160 - 199	4	3	2	1	1
200 - 239	8	6	4	2	1
240 - 279	11	8	5	3	2
280+	13	10	7	4	2

10 - Year Framingham Risk

Point Total	10 - Year Risk
< 9	< 1%
9	1%
10	1%
11	1%
12	1%
13	2%
14	2%
15	3%
16	4%
17	5%
18	6%
19	8%
20	11%
21	14%
22	17%
23	22%
24	27%
25 or more	30%

Framingham Risk Assessment - Men

AGE

Age	Points
20 -34	-9
35 - 39	-4
40 - 44	0
45 - 49	3
50 - 54	6
55 - 59	8
60 - 64	10
65 - 69	11
70 - 74	12
75 - 79	13

Systolic BP

Systolic BP	If Untreated	If Treated
< 120	0	0
120 - 129	0	1
130 - 139	1	2
140 - 159	1	2
160+	2	3

HDL Cholesterol (mg/dL)

HDL	Points
60+	-1
50 - 59	0
40 - 49	1
< 40	2

Smoking Status

	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
Non-smoker	0	0	0	0	0
Smoker	8	5	3	1	1

Total Cholesterol (mg/dL)

	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
< 160	0	0	0	0	0
160 - 199	4	3	2	1	0
200 - 239	7	5	3	1	0
240 - 279	9	6	4	2	1
280+	11	8	5	3	1

10 - Year Framingham Risk

Point Total	10 - Year Risk
< 0	< 1%
0	1%
1	1%
2	1%
3	1%
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
17 or more	30%

Target LDL Cholesterol Levels Depending on Framingham Risk Score

Risk Level	Initiate Cholesterol Lowering Treatment When:	LDL-cholesterol target
HIGH • Framingham Risk Score > 20% • Patients with Diabetes • Patients with Heart Disease	All patients should be treated	• <2mmol/L or, • ≥50% decrease in LDL-cholesterol
MODERATE • Framingham Risk Score 10%-19%	• LDL-cholesterol > 3.5 mmol/L • Ratio of triglycerides/HDL-cholesterol is > 5.0 • Significant inflammation present	• <2mmol/L or, • ≥50% decrease in LDL-cholesterol
LOW • Framingham Risk Score < 10%	• LDL-cholesterol is ≥ 5.0 mmol/L	• ≥ 50% decrease in LDL-cholesterol

Metabolic Syndrome

- Is a combination of medical disorders that cause increased risk of coronary heart disease and type II diabetes.
- Metabolic syndrome is diagnosed when patients have three or more of:
    1. Central obesity – Waist circumference > 102 cm (40 inches) for men or 88 cm (35 inches) for women
    2. Elevated triglycerides – Blood triglycerides > 1.7 mmol/L
    3. Low HDL cholesterol - HDL cholesterol < 1.03 mmol/L in men or 1.29 mmol/L in women.
    4. Hyperglycemia – Fasting blood glucose > 5.6 mmol/L.
    5. Hypertension – Blood pressure > 135/85 mmHg
- Treatment of metabolic syndrome is targeted at decreasing the risk for coronary heart disease and type II diabetes.
- Estimates suggest that one in four Canadians have metabolic syndrome.

12.4 NON-DRUG TREATMENT OF LDL CHOLESTEROL

- Drug therapy is NOT the first line treatment for elevated LDL cholesterol. The primary treatment for high LDL cholesterol is lifestyle changes including modification to diet, weight, exercise plan and smoking status.

  Diet – Modification of diet is targeted towards decreasing LDL cholesterol and establishing a healthy body weight. Dietary recommendations suggest intake of less than 200 mg/day of total cholesterol and intake of saturated fats of 7% or less of total calories. Further recommendations suggest the intake of soluble fiber of 10 – 25 grams/day and plant stanols and sterols of 2 grams/day.

  Weight Control – Obesity is one of the leading causes of heart disease in Canada and the USA. In most people this is a modifiable risk factor. Weight loss by dietary modification and exercise lowers LDL cholesterol and decreases the risk of coronary heart disease.

  Exercise – More and more Canadians are living sedentary lifestyles making the need for regular exercise greater than ever. Cardiovascular exercise has many benefits which include decreasing LDL cholesterol, elevating HDL cholesterol along with decreasing insulin resistance and blood pressure. Recommendations suggest that all people should exercise for between 30-60 minutes per day.

  Cigarette Smoking – Smoking cigarettes decreases HDL cholesterol and increases LDL cholesterol therefore increasing risk of coronary heart disease. Smoking has been called the "leading preventable cause of death and disease" and is an especially important risk factor in younger (under 50) men and women. All patients should be counselled to quit smoking.

12.5 DRUG TREATMENT OF ELEVATED BLOOD LIPIDS

- Although the first line of treatment for elevated blood lipids are lifestyle changes, many patients are unable to reach target cholesterol levels with lifestyle changes alone. When target cholesterol levels are not achieved by lifestyle changes, drug treatment is initiated. This section will cover the various classes of drugs used to treat elevated LDL cholesterol.
- Classes of drugs used to treat elevated blood lipids include:

  1. Statins
  2. Bile Acid Sequestrants
  3. Nicotinic Acid
  4. Cholesterol Absorption Inhibitors
  5. Fibric Acid Derivatives

HMG-CoA Reductase Inhibitors (Statins)

Cholesterol Synthesis

- Approximately 80% of total body cholesterol is synthesized in the liver.
- Hepatic cholesterol synthesis occurs in what is known as the mevalonic acid pathway. In this pathway, acetyl CoA (from the citric acid cycle) is converted to 3-hydroxy-3-methylglutaryl CoA (HMG CoA). HMG CoA is then enzymatically converted to mevalonic acid by the enzyme HMG CoA Reductase. After several other enzymatic steps, cholesterol is formed. Conversion of HMG CoA into mevalonic acid is the rate-limiting step in cholesterol synthesis.
- Cholesterol synthesis is greatest during the night.

Figure: The mevalonic acid pathway. The enzyme that converts HMG CoA to mevalonic acid is called HMG CoA Reductase. It is the site of action for statin drugs.

Mechanism of Action

- Statins decrease the hepatic synthesis of cholesterol by inhibiting the enzyme HMG CoA reductase, the rate-limiting step of cholesterol synthesis.
- Through complicated mechanisms (beyond the scope of this course), inhibition of HMG CoA reductase causes an upregulation of hepatic LDL receptors. This allows the liver to remove more cholesterol from blood. The net effect is a decrease in LDL cholesterol blood levels.

Statins inhibit the enzyme HMG CoA Reductase therefore blocking the conversion of HMG CoA to Mevalonic Acid.

Benefits of Statins

1. ↓LDL cholesterol
2. ↑HDL cholesterol
3. ↓ Triglycerides

- Primary Prevention Studies - Primary prevention is targeted at preventing the development of cardiovascular disease. Statins are effective in the primary prevention of coronary heart disease. Multiple recent studies have shown that statins decrease the incidence of coronary events (i.e. heart attack and stroke) even in low risk patients with no history of coronary heart disease.

- Secondary Prevention Studies - Secondary prevention aims to prevent the recurrence of cardiovascular events. For example, preventing a patient who has had a heart attack from having another heart attack. Statins are effective drugs for preventing recurrent cardiovascular events in higher risk patients.
- Due to their remarkable ability to prevent the onset and progression of cardiovascular disease, statins are among the highest prescribed drugs in the world. In fact, atorvastatin (Lipitor) is the highest prescribed drug in Canada and the USA, while rosuvastatin (Crestor) is the 4th highest prescribed drug in Canada.

Pharmacokinetics of Statins

Atorvastatin

- Low oral bioavailability (~14%)
- Large fraction of absorbed dose is extracted by the liver (the site of drug action).
- Distribution is primarily to the liver but also to the spleen, adrenal glands and skeletal muscle.
- Metabolized by CYP3A4
- Predominantly eliminated in the feces, minimal renal excretion.

Rosuvastatin

- Low oral bioavailability (~20%)
- Large fraction of absorbed dose is extracted by the liver (the site of drug action).
- Distribution is primarily to the liver but also to skeletal muscle.
- Not extensively metabolized.
- Predominantly eliminated in the feces, minimal renal excretion.
- Plasma rosuvastatin concentrations are approximately two times higher in Asian patients when compared to Caucasian patients. The initial dose in Asian patients should be 5 mg and caution should be used before deciding to increase the dose.

Adverse Effects of Statins

- In general statins are well tolerated.
- The most common adverse event is myopathy (muscle injury). Mild myopathy characterized by muscle aches and weakness occurs in 1-5% of patients.
- Rhabodomyolysis is a rare but serious adverse effect associated with statin use. Rhabdomyolysis is defined as muscle lysis with severe muscle pain. Rhabdomyolysis is diagnosed by measuring blood levels of the muscle enzyme creatine kinase. During significant muscle injury as in rhabdomyolysis, the muscle cell releases large amounts of creatine kinase into the bloodstream. Rhabdomyolysis is diagnosed when blood creatine kinase is 10 times higher than normal. Rhabdomyolysis is accompanied by large increases in blood potassium (hyperkalemia) and may cause acute kidney failure. Treatment is targeted at preserving kidney function by IV administration of fluids.
- There is a low incidence of hepatotoxicity associated with statin use. Liver function tests should be performed before initiating therapy and periodically thereafter.
- Cholesterol is required for the synthesis of cell membranes and many hormones. Therefore, statins should not be used in females who are pregnant or trying to become pregnant.

Nicotinic Acid (Niacin)

- Inhibits the hepatic secretion of VLDL. Since LDL is a by-product of VLDL degradation, nicotinic acid effectively reduces both VLDL and LDL.
- Also increases blood levels of HDL cholesterol.
- Side effects limit its use in many patients. Side effects include intense facial flushing, hepatotoxicity, hyperglycemia, skin rash and increase uric acid levels.

Bile-Acid Sequestrants

Background on Bile-Acids

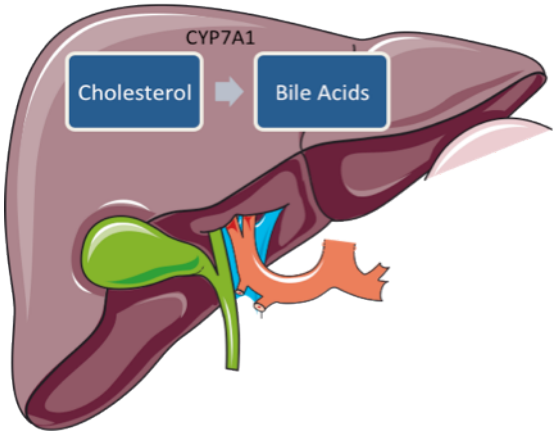
- Bile acids are negatively charged molecules produced in the liver from CYP7A1 mediated cholesterol metabolism.
- Bile acids are secreted into the intestine and function to aid in the absorption of dietary fats and fat soluble vitamins.
- Bile acids undergo enterohepatic recycling and are therefore reabsorbed from the intestine. Over 95% of bile acids are normally reabsorbed from the intestine.

Mechanism of Action – Bile Acid Sequestrants

- Bile acid sequestrants are large positively charged molecules.
- They function by attracting and binding bile acids (negatively charged) in the intestine and prevent their absorption.
- Since over 95% of bile acids are normally reabsorbed, this causes an increased demand for bile acid synthesis in the liver.
- In order to synthesize more bile acids in the liver, LDL cholesterol is required. Therefore liver cells increase the number of LDL receptors. This results in increased uptake of cholesterol from the blood to the liver causing a decrease in plasma LDL cholesterol levels.

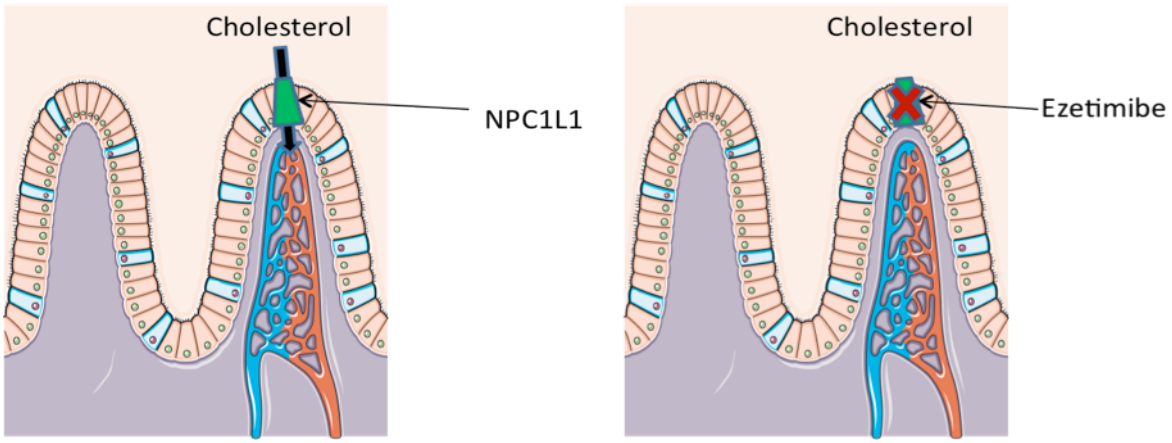
Adverse Effects of Bile Acid Sequestrants

- Bile-acid sequestrants are not absorbed at all and therefore do not have any systemic side effects.
- Predominant side effects are limited to the GI tract and include constipation and bloating.
- As bile acid sequestrants are designed to bind to negatively charged molecules, they may decrease the absorption of some drugs such as thiazide diuretics, digoxin, warfarin and certain antibiotics.



Cholesterol Absorption Inhibitors

- A specific transport protein called NPC1L1 is responsible for the intestinal uptake of the majority of dietary cholesterol. A recent strategy to lower blood cholesterol is to inhibit this transporter.



- The only cholesterol inhibitor on the market is ezetimibe (Zetia) which has been shown to decrease intestinal cholesterol absorption by 54% and lower blood LDL cholesterol by 15 - 20%.
- Decreased intestinal absorption of cholesterol by ezetimibe can produce a compensatory increase in hepatic cholesterol synthesis. Therefore ezetimibe is often prescribed as an adjunct therapy along with a statin.
- A recently approved combination pill called vytorin contains a statin (simvastatin) with ezetimibe. This can reduce LDL cholesterol by up to 60%.

Fibric Acid Derivatives (Fibrates)

- Are the most effective class of drugs for lowering plasma triglyceride levels.
- They also increase HDL cholesterol but have almost no effect on LDL cholesterol levels.
- Fibrates act by binding to and activating a receptor in the liver called PPARα (peroxisome-proliferator activated receptor-alpha).
- Activation of PPARα has multiple effects:
    1. Increased synthesis of the enzyme lipoprotein lipase. Lipoprotein lipase is an enzyme that enhances the clearance of triglyceride rich lipoproteins.
    2. Decreased apolipoprotein C-III production. Apolipoprotein C-III is an inhibitor of lipoprotein lipase. Decreased apolipoprotein C-III allows for increased lipoprotein lipase activity.
    3. Increased apolipoprotein A-I and apolipoprotein A-II levels. This is responsible for the increased HDL levels associated with fibrates.

Adverse Effects of Fibrates

- Increased risk of gallstones
- Myopathy – Fibrates alone may cause myopathy in a small fraction of patients. If fibrates are combined with a statin, a low dose of statin should be used and the patient should be carefully monitored for signs of myopathy.
- Hepatotoxicity