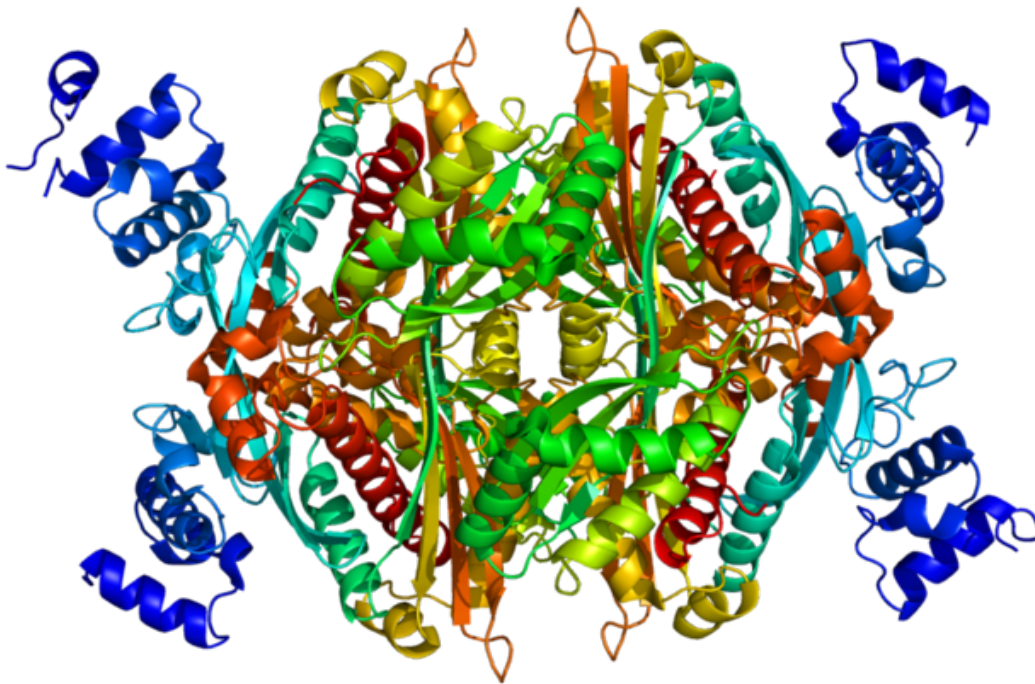


## Lipid Control: HMG-CoA Reductase Inhibitors

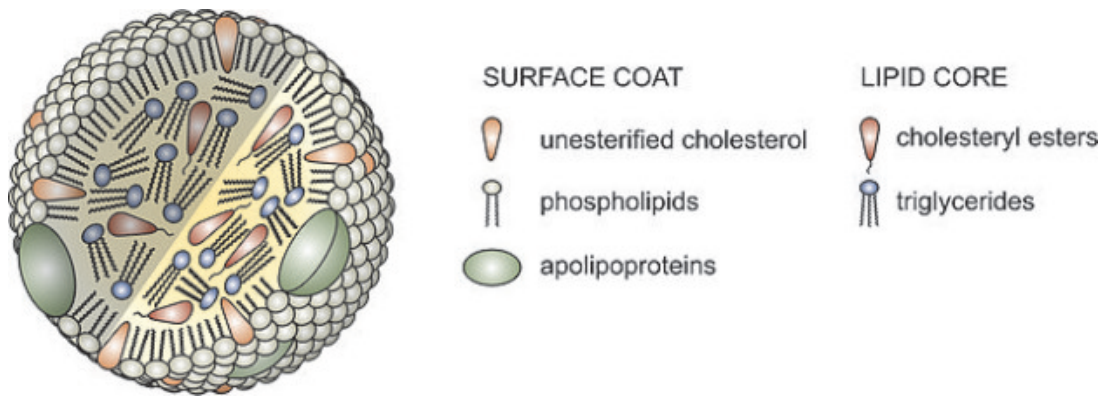
[See online here](#)

Despite its negative connotation, cholesterol actually plays an important role in our body's homeostasis. It basically makes up the most important parts which keep us alive and functioning. For example, the membranes that keep our cells together are made up of cholesterol. However, major problems do arise when there is an alteration along its metabolic pathway in the body. For one, an excessive amount of cholesterol in the body has been linked to a lot of disorders, such as atherosclerosis and fatty liver disease. In this article, we will tackle how cholesterol is metabolized in the body and see where, in the pathway, HMG-CoA reductase inhibitors alter the whole process.



### Overview: Cholesterol and Lipoproteins

**Cholesterol** is part of the lipids family, which serves many functions in the body. Aside from the cellular structure, it plays a significant role in hormone production and lipid transport. Cholesterol also plays a major part in the structure of **lipoproteins**, the primary lipid transport mechanism in the plasma.



**Image:** "Lipoprotein particles are composed of a lipid core containing cholesteryl esters and triglycerides, and a surface coat of phospholipids, unesterified cholesterol, and apolipoproteins." by AntiSense. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

A lipoprotein has two essential parts: its **hydrophobic core** and a **hydrophilic shell**. This structure helps it to transport non-polar triglycerides and other lipids along a polar pathway created by the plasma, lymph, and interstitial fluid. Its core is made up of cholesteryl esters and triglycerides, while the shell is composed of unesterified cholesterol, phospholipids, and apolipoproteins.

Lipoproteins are classified according to their densities, which are dictated mostly by the number of lipids contained in their core. Since lipids are less dense than water (or protein), lipoproteins, which contain the most lipids in their core, are said to be low-density.

## Chylomicrons

Chylomicrons are said to be the largest among the cholesterol groups because they contain the most lipids. It stands out among the rest of the groups as the **only one which carries exogenous or dietary fat from the gut**.

## Very-Low-Density Lipoproteins (VLDL)

The VLDLs are next to the chylomicrons in terms of size and density. These lipoproteins **carry triglycerides from the liver to the peripheries**, where they are hydrolyzed into fatty acids and other forms of cholesterol. The former of these products are used for adipose storage or as fuel for muscles that use ketones for energy. such as the [heart](#) and skeletal muscles.

## Low-Density Lipoproteins (LDL)

LDL is one of the lipoproteins produced when VLDLs are deprived of their triglyceride content. They carry most of the cholesterol in the body. Their degradation and excretion ultimately allow for bile acid formation to occur. They are known as 'bad cholesterol'.

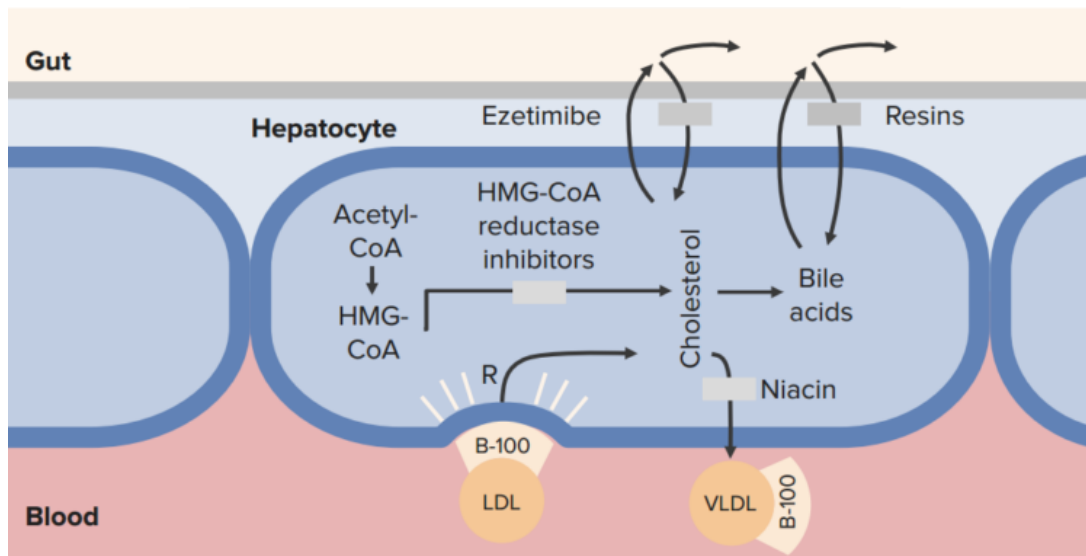
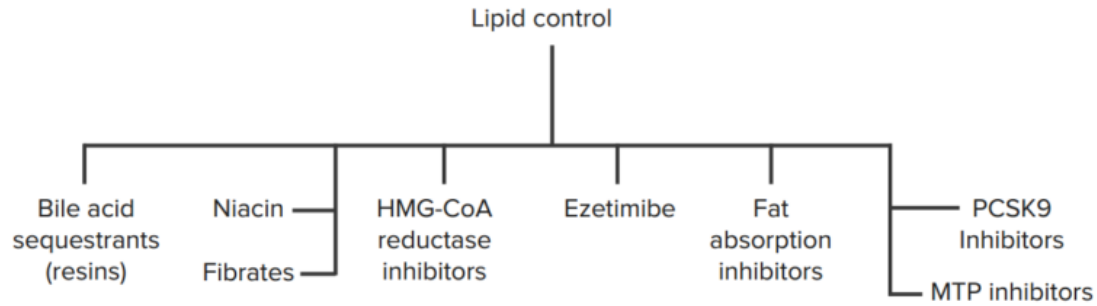
## Lp(a) Lipoprotein

This lipoprotein is somewhat similar to a potential thrombolytic compound called plasminogen (active form: plasmin) in structure and has been found in most atherosclerotic plaques. It is formed by when an (a) protein covalently bonds with an LDL.

## High-Density Lipoprotein (HDL)

Like the rest of the lipoproteins, the liver secretes the shell of these so-called 'good cholesterol.' However, the thing that sets this group apart is that it derives its hydrophobic contents from the triglycerides and cholesterol found lying around in the peripheries. It helps with the eventual metabolism and excretion of these lipids.

## Lipid Control



## Metabolism of Cholesterol

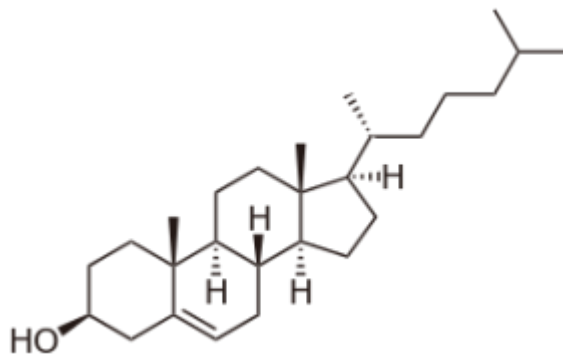


Image: "Structure of Cholesterol" by Boris™. License: Public Domain

Almost half of our **cholesterol** comes from our diet; the rest of it is produced by the body. As long as we have nucleated cells, we will be able to synthesize our own cholesterol by metabolizing other macronutrients. The **liver and intestines** perform about 10% of this metabolic action.

It all starts with acetyl coenzyme a or **acetyl-CoA**, a product of the catabolism of glucose, amino acids, and fatty acids. It undergoes a series of reactions before its ultimate conversion into cholesterol.

First off, acetyl-CoA is converted into **mevalonate**. This involves the creation of 3-hydroxy-3-methylglutaryl-CoA or **HMG-CoA**, an intermediate that must be produced inside the mitochondria. Before this occurs, two molecules of acetyl CoA must be condensed to form acetoacetyl-CoA. Another acetyl-CoA molecule comes into the picture to condense with this product, forming HMG-CoA, which is then reduced to mevalonate with the help of the rate-limiting enzyme **HMG-CoA reductase**.

Once mevalonate is produced, it is phosphorylated and decarboxylated to form an **isoprenoid unit**. Each unit is made up of **isopentyl diphosphate**. This reaction is repeated until six isoprenoid units are produced. These are then isomerized into **dimethylallyl diphosphate** and condensed with another isoprenoid unit to form **geranyl diphosphate**. Yet again, another isoprenoid unit condenses with this to form **farnesyl diphosphate**. It takes two of these compounds to form **squalene** by condensation.

Since cholesterol needs a steroid nucleus for its chemical structure, the cell has to convert squalene into something that would resemble one, such as **lanosterol**. This happens as squalene undergoes a series of reactions with **squalene epoxidase** and **oxidosqualene-lanosterol cyclase** enzymes.

Cholesterol is finally created in the endoplasmic reticulum membranes once the side chains and the nucleus of lanosterol are changed by a series of reactions.

## Cholesterol Transport Inhibitors: Ezetimibe

- The prodrug undergoes glucuronidation in the liver
- Inhibits cholesterol transporter: prevents absorption of dietary cholesterol and phytosterol, reactive increase in LDL receptors

### Uses:

- Treatment of hypercholesterolemia (20 % reduction as monotherapy, 25-30% add-on reduction with a statin)
- Treatment of phytosterolemia

### Toxicity

- Well tolerated
- May increase hepatotoxicity

### Sold as:

- Ezetrol®
- Vytorin®

# Disorders Affecting Cholesterol Metabolism

## Screening

Screening for patients who might be at risk for developing lipoprotein disorders is usually part of routine examinations. Therefore, encountering these problems, along with its associated complications, are somewhat common in practice. This is done by extracting blood samples from patients after doing a 12-hour overnight fast.

## Dyslipidemias

In general, problems in lipid metabolism are categorized into two. If they are not associated with other conditions such as any concurrent disease, poor diet, or long-term drug therapy, they are thought to be **primary** dyslipidemia. Single-gene mutations are usually implicated in this classification. Examples are outlined in the table:

Genetic disorder	Gene defect	Elevated lipoproteins	Transmission
<b>Hypertriglyceridemia</b>			
Lipoprotein lipase deficiency	LPL	Chylomicrons, VLDL	Autosomal recessive
Familial apoC-II deficiency	APOC2	Chylomicrons, VLDL	Autosomal recessive
ApoA-V deficiency	APOA5	Chylomicrons, VLDL	Autosomal recessive
GPIHBP1 deficiency	GPIHBP1	Chylomicrons	Autosomal recessive
<b>Combined Hyperlipidemia</b>			
Familial hepatic lipase deficiency	LIPC	VLDL remnants, HDL	Autosomal recessive
Familial dysbetalipoproteinemia	APOE	Chylomicron remnants, VLDL remnants	Autosomal recessive
<b>Hypercholesterolemia</b>			
Familial hypercholesterolemia	LDLR	LDL	Autosomal dominant
Familial defective apoB-100	APOB	LDL	Autosomal dominant
Autosomal dominant hypercholesterolemia, type 3	PCSK9	LDL	Autosomal dominant
Autosomal recessive hypercholesterolemia	LDLRAP	LDL	Autosomal recessive
Sitosterolemia	ABCG5 or ABCG8	LDL	Autosomal recessive

(Table adapted from Harrison's Principles of Internal Medicine, 19th ed. by Fauci AS, et al.)

Problems in lipid metabolism can also exist as a manifestation of other disorders or conditions in the body. In this case, they are classified as **secondary** dyslipidemias and may be caused by the following conditions:

- High-carbohydrate diet
- Excessive alcohol intake
- Obesity and insulin resistance
- Excessive glucocorticoid levels

## Treatment

The approach to patients with cholesterol metabolism problems is ideally **individualized per patient**. It usually is geared towards preventing complications, such as the development of cardiovascular diseases. One of the first steps in addressing this goal is the assessment of the patient's cardiovascular risks.

**Lifestyle modification** is usually a part of the management of patients with hypercholesterolemia. Obese patients should be counseled to achieve ideal body weight. Nutrition counseling is also advocated for patients to maintain proper nutrition, without significantly increasing lipid levels in the body.

Along with lifestyle changes, the addition of **pharmacologic therapy** to reduce plasma levels of cholesterol may also be instigated. Medications typically given to patients with hypercholesterolemia may be classified into any of the following groups:

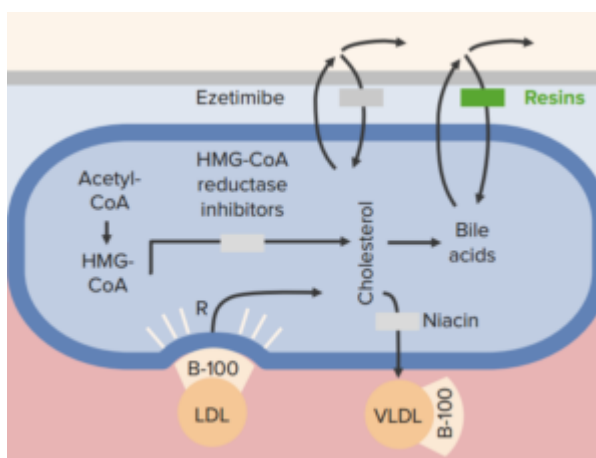
- HMG-CoA reductase inhibitors
- Cholesterol absorption inhibitors
- Bile acid sequestrants

Among these medications, **HMG-CoA reductase inhibitors**, otherwise known as statins, are frequently the first medications to be prescribed.

## Bile acid sequestrants (resins)

### Cholestyramine, colestipol, colesevelam

92% of bile acids are reabsorbed normally



- Resins prevent reabsorption
- The liver needs to make more bile acids
- The liver uses up cholesterol to do so
- Sucks up more LDL from the blood to use as fuel

### Effects:

- Mild LDL reduction
- May increase TG and VLDL in FH and FTG

## HMG-CoA Reductase Inhibitors

- Lovastatin
- Atorvastatin

- Fluvastatin
- Pravastatin
- Simvastatin
- Rosuvastatin
- Pitavastatin

## Mechanism of action

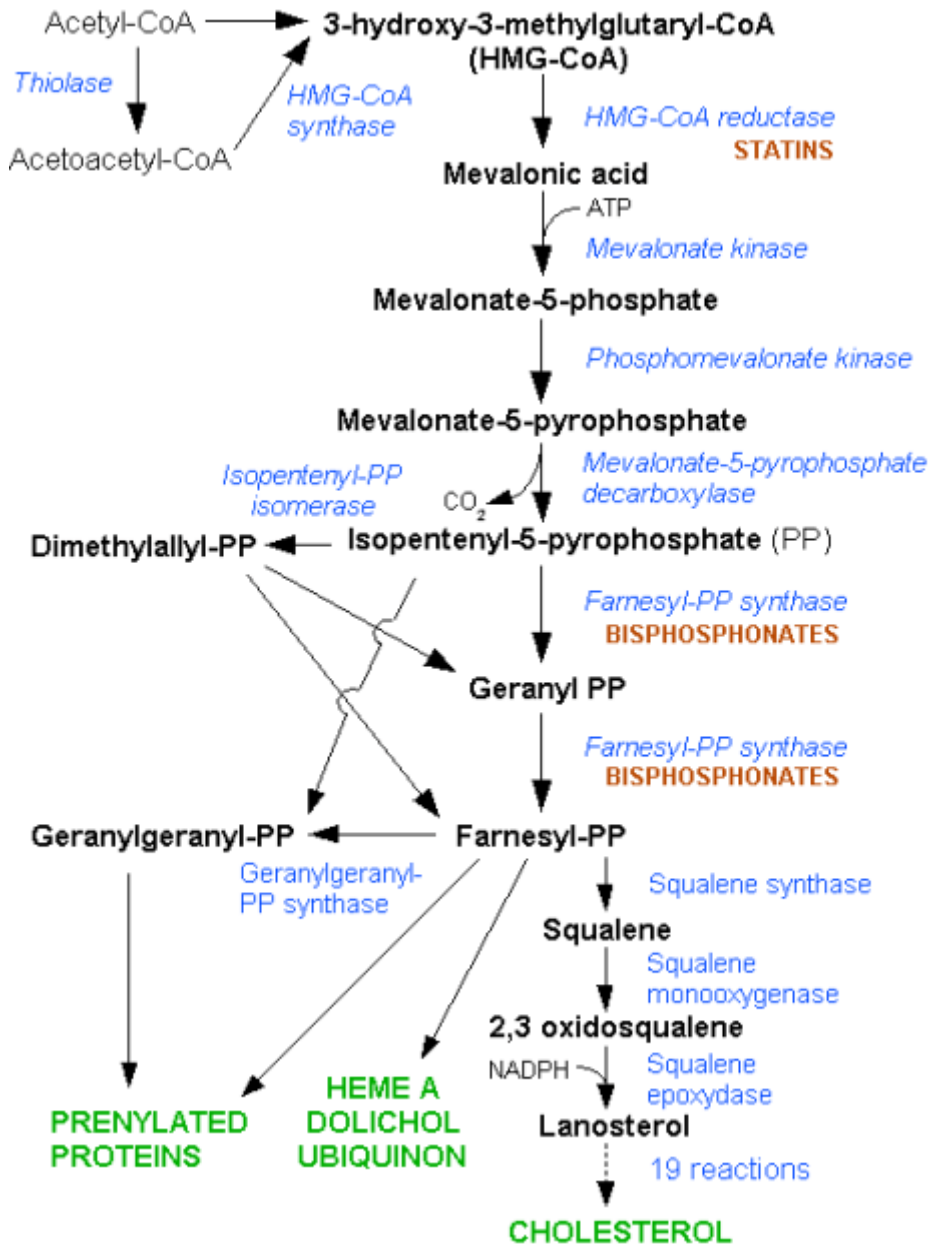


Image: "HMG-CoA Reductase Pathway (Cholesterol)" by BorisTM. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

These medications work by acting as analogs to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) and are very effective in reducing LDL. From the name itself, HMG-CoA reductase inhibitors, or **statins**, interfere with the rate-limiting first step of cholesterol synthesis - the conversion of acetyl acetate into mevalonate. This drug also increases the ability of LDL receptors in the hepatocytes to bind with LDL, thereby increasing their degradation and excretion from the circulation. It acts primarily on the liver and is linked to significant decreases in LDL, moderate decreases in triglycerides, and slight increases in HDL.

Most treatment plans to reduce cholesterol levels include HMG-CoA reductase inhibitors for patients who have had [acute coronary syndromes](#). This is because HMG-CoA reductase inhibitors are also proven to reduce vascular damages brought about by oxidation. They also stabilize atherosclerotic lesions, preventing further development of complications from atherosclerotic plaques.

- Block a step in the conversion of HMG-CoA to cholesterol
- Competitive inhibitor of the HMG-CoA reductase enzyme
- Most of the effects due to LDL expression

#### **Secondary effects:**

- May prevent bone loss
- Anti-inflammatory effects
- Anti-atherosclerotic effects (anti-inflammatory)
- May be protective against contrast nephropathy

## Indications

Statins can be prescribed as monotherapy, or in combination with other lipid-reducing medications such as bile acid sequestrants, niacin or ezetimibe. They are usually prescribed for patients suffering from hyperlipidemia (hypercholesterolemia). They are also given to patients with coronary heart disease and atherosclerosis as prophylaxis for [myocardial infarction](#) and stroke.

## Precautions and Side Effects

Since these medications interfere with the synthesis of cholesterol needed for fetal development, they are not recommended for use during pregnancy.

Since statins primarily exert their effects on hepatocytes, most of their side effects are associated with altered liver functioning, such as the elevation of serum aminotransferase activity. However, this does not usually warrant discontinuation as long as no other debilitating signs and symptoms of liver toxicity appear. The use of statins among patients with concurrent liver diseases or a history of [alcohol abuse](#) may be accompanied by [anorexia](#), malaise, and an undesirable rapid drop of LDL levels in the circulation. For this reason, reduced statin doses are given to these patients. Other side effects that may be seen include:

- Increased fasting plasma glucose
- Slight increases in creatinine kinase (skeletal muscle weakness)
- Myoglobinuria
- Myopathy

#### **Toxicity**

- Mild CK elevation
- Mild transaminitis
- A potentially fatal reaction in patients on statins plus fibrates (such as cerivastatin and gemfibrozil)
- May also react similarly with niacin
- Metabolized by CYP450 3A4 (grapefruit juice — furanocoumarins; bitter oranges — citrus aurantium; or marmalade)



# Drug and Food Interactions

Lovastatin, simvastatin, and atorvastatin are specifically catabolized in the liver through the CYP3A4 enzyme system. Food and medications that are catabolized through this system somewhat displace these particular statins, thereby increasing their levels in the blood. Some medications that cause this include:

- Macrolides
- Cyclosporine
- Ketoconazole
- Some HIV protease inhibitors
- Tacrolimus
- Nefazodone
- Fibrates
- Paroxetine
- Venlafaxine
- Grapefruit juice (> 1L/day)

In contrast, CYP3A4 statins are inhibited by medications that increase the expression of CYP3A4 enzymes:

- Phenytoin
- Griseofulvin
- Barbiturates
- Rifampin
- Thiazolidinediones

Fluvastatin, rosuvastatin, and pitavastatin are metabolized using the CYP2C9 enzyme system. Their levels are increased in the plasma by medications that inhibit the expression of CYP2C9 enzymes, including:

- Ketoconazole
- Metronidazole
- Sulfinpyrazone
- Amiodarone
- Cimetidine

Red yeast rice, a fermented product used as a natural food coloring and fermentation agent in Asian cuisine, is known to have statin activity. Therefore, this food should be avoided when taking statins.

## Fibrates

Peroxisome-activated receptor  $\alpha$  (PPAR- $\alpha$ )

- Increased gene expression of ApoA-I, -II, and ApoC-III which **increases** HDL levels
- Increased gene expression for lipoprotein lipase to help clear TG at endothelium, and increase FFA oxidation in the liver

### Uses:

- Treat hypertriglyceridemia
- Toxicity
- May increase LDL

- Rash, increased WBC, potentiate anticoagulants
- Risk of myopathy

## Important Points

1. The statin effect is mostly due to increased LDL receptor expression and not the reduction of internal cholesterol biosynthesis
2. Normal LDL receptors are required for statins to work
3. Homozygous familial hypercholesterolemia is a disease of dysfunctional LDL receptors. Statins are less effective in these patients.

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