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STATEMENT OF STATIN: AN ANCHOR OF MEVALONATE PATHWAY

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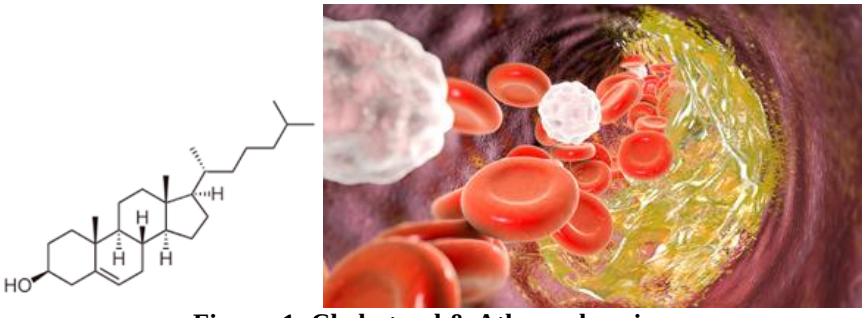
ABSTRACT

Hydroxymethylglutaryl–CoA (HMG–CoA) reductase inhibitors, also known as "statins," are used adjunctively to diet and exercise to treat hypercholesterolemia by lowering total cholesterol (TC), low–density lipoprotein cholesterol (LDL–C), and triglycerides (TG) concentrations while increasing high–density lipoprotein cholesterol (HDL–C) concentrations. The approved FDA indications vary slightly between each statin but generally are indicated for the treatment and/or prevention of primary and secondary prevention clinical atherosclerotic cardiovascular disease (ASCVD) (e.g., myocardial infarction or stroke). The choice of agent should have its basis on patient–specific characteristics, the pharmacokinetic profiles of each medication.

KEYWORDS: Chylomicrons, VLDL, IDL, LDL, HDL, Cholesterol, HMG HMG–CoA reductase inhibitors, Statins, PCSK9 inhibitor.

INTRODUCTION

Lipid profile or lipid panel is a panel of blood tests that serves as an initial screening tool for abnormalities in lipids, such as cholesterol and triglycerides. The results of this test can identify certain genetic diseases and can determine approximate risks for cardiovascular disease, certain forms of pancreatitis, and other diseases. The lipid profile typically includes: Low–density lipoprotein (LDL), High–density lipoprotein (HDL), Triglycerides, Total cholesterol. Using these values, a laboratory may also calculate: Very low–density lipoprotein (VLDL), Cholesterol: HDL ratio.[1]



Figure–1: Cholesterol & Atherosclerosis.

The lipid profile tests are of 7 types: Total lipids, Serum total cholesterol, Serum HDL cholesterol, Total cholesterol/HDL cholesterol ratio, Serum triglycerides, Serum Phospholipids, Electrophoretic fractionation to determination percentage of: (a) Chylomicrons (b) LDL (c) VLDL (d) HDL

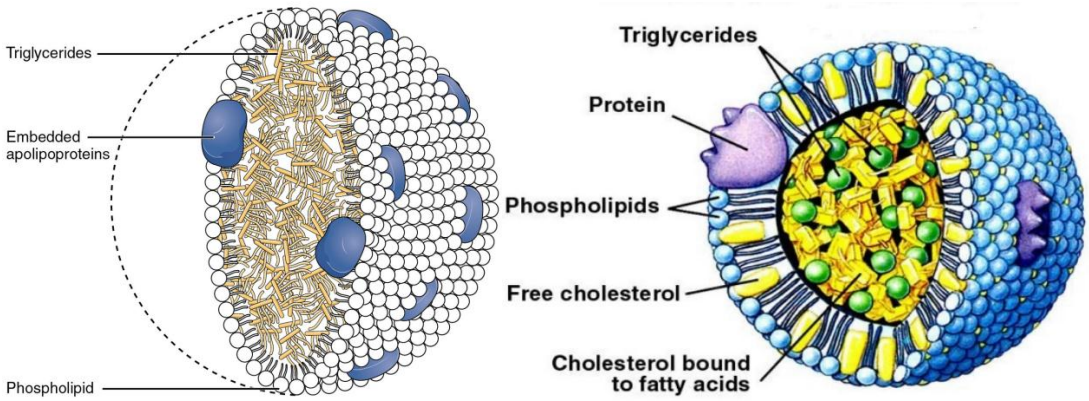
For healthy adults with no cardiovascular risk factors, the ATP III guidelines recommend screening once every five years. A lipid profile may also be ordered at regular intervals to evaluate the success of lipid–lowering drugs such as statins. In the paediatric and adolescent population, lipid testing is not routinely performed. However, the American Academy of Paediatrics and the National Heart, Lung, and Blood Institute (NHLBI) recommend that children aged 9–11 be screened once for severe cholesterol abnormalities. This screening can be valuable to detect genetic diseases such as familial hypercholesterolemia that can be lethal if not treated early. Traditionally, most laboratories have required

patients to fast for 9–12 hours before screening. However, studies have questioned the utility of fasting before lipid panels, and some diagnostic labs routinely accept non–fasting samples.[2]

Typically, the laboratory measures only three quantities: Total cholesterol, HDL, Triglycerides. From these three data LDL may be calculated. According to Friedewald's equation: **LDL=Total cholesterol–HDL–Triglycerides/5**

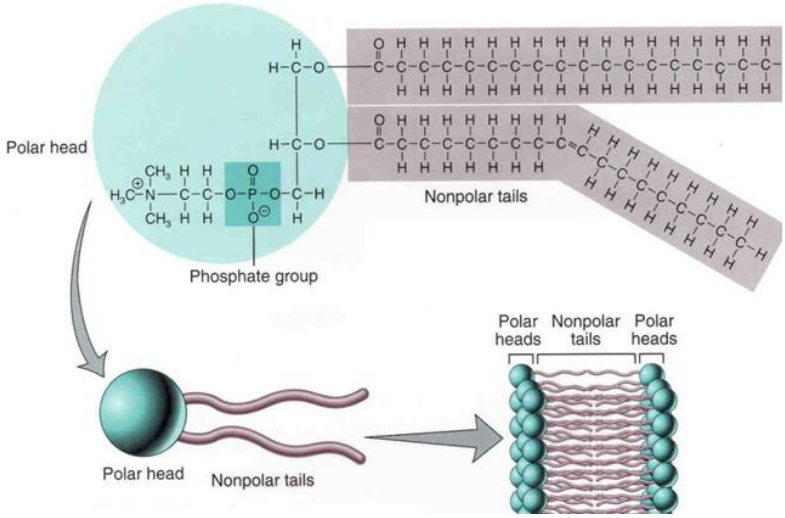
Other calculations of LDL from those same three data have been proposed which yield some significantly different results. VLDL may be defined as the total cholesterol that is neither HDL nor LDL. Then Friedewald's equation mentioned above yields: **VLDL=Triglycerides/5**

The alternative calculations mentioned above may yield significantly different values for VLDL. Hypercholesterolemia, also called high cholesterol, is the presence of high levels of cholesterol in the blood. It is a form of hyperlipidaemia, high blood lipids, and hyperlipoproteinemia (elevated levels of lipoproteins in the blood). Elevated levels of non–HDL cholesterol and LDL in the blood may be a consequence of diet, obesity, inherited (genetic) diseases (such as LDL receptor mutations in familial hypercholesterolemia), or the presence of other diseases such as type 2 diabetes and an underactive thyroid. Cholesterol is one of three major classes of lipids which all animal cells use to construct their membranes and is thus manufactured by all animal cells.



Figure–2: Chylomicron &Lipoprotein.

Plant cells do manufacture cholesterol in small quantities although other related sterols in larger quantities.[3-5] It is also the precursor of the steroid hormones and bile acids. Since cholesterol is insoluble in water, it is transported in the blood plasma within protein particles (lipoproteins). Lipoproteins are classified by their density: very low–density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL) and high–density lipoprotein (HDL). All the lipoproteins carry cholesterol, but elevated levels of the lipoproteins other than HDL (termed non–HDL cholesterol), particularly LDL–cholesterol, are associated with an increased risk of atherosclerosis and coronary heart disease. In contrast, higher levels of HDL cholesterol are protective.[6]



Figure–3: Phospholipid.

Avoiding trans fats and replacing saturated fats in adult diets with polyunsaturated fats are recommended dietary measures to reduce total blood cholesterol and LDL in adults. In people with very high cholesterol (e.g., familial hypercholesterolemia), diet is often not sufficient to achieve the desired lowering of LDL, and lipid–lowering medications are usually required. If necessary, other [pre–treatments such as LDL apheresis or even surgery (for particularly severe subtypes of familial hypercholesterolemia) are performed. About 34 million adults in the United States have high blood cholesterol.

Biochemical parameters

***Triglyceride level*:**

Normal Triglyceride: Less than 150 milligrams per deciliter (mg/dL), or less than 1.7 millimoles per liter (mmol/L)
Borderline Triglyceride: 150 to 199 mg/dL (1.8 to 2.2 mmol/L)
HighTriglyceride: 200 to 499 mg/dL (2.3 to 5.6 mmol)
IDL: [broad β–lipoprotein]
VLDL level: [pre–β lipoprotein]. Composition:Triglycerides: 70%+Cholesterol: 10%+Proteins: 10%
Normal VLDL: 2 to 30 mg/dL (0.1 to 1.7 mmol/l).
Elevated VLDL: cholesterol level is more than 30 milligrams per deciliter (0.77 millimole/liter).
LDL [β–lipoprotein]. Composition: 50% cholesterol+10% triglyceride

LDL (Bad)	Cholesterol Level	LDL Cholesterol Category
	Less than 100mg/dL	Optimal
	100–129mg/dL	Near optimal/above optimal
	130–159 mg/dL	Borderline high
	160–189 mg/dL	High

HDL[α–lipoprotein]. Composition: 25% Cholesterol+50% protein

	At risk	Desirable
Men	Less than 40 mg/dL (1.0 mmol/L)	60 mg/dL (1.6 mmol/L) or above
Women	Less than 50 mg/dL (1.3 mmol/L)	60 mg/dL (1.6 mmol/L) or above

Blood Cholesterol: Cholesterol levels should be less than 100 mg/dL. Levels of 100 to 129 mg/dL are acceptable for people with no health issues but may be of more concern for perfect health.

Chylomicrons (from the Greek, *chylos*, meaning juice (of plants or animals), and micron, meaning small particle), also known as ultra–low–density lipoproteins (ULDL), are lipoprotein particles that consist of triglycerides (85–92%), phospholipids (6–12%), cholesterol (1–3%), and proteins (1–2%).Chylomicrons are large triglyceride–rich lipoproteins produced in enterocytes from dietary lipids–namely, fatty acids, and cholesterol. Chylomicrons are composed of a main central lipid core that consists primarily of triglycerides, however like other lipoproteins, they carry esterified cholesterol and phospholipids.[7]

Lipoprotein particle	Size (Å)	Density
Chylomicrons	800–5000	0.95
Very–low–density lipoprotein (VLDL)	300–800	0.95–1.006
Intermediate–density lipoprotein (IDL)	250–350	1.006–1.019
Low–density lipoprotein (LDL)	180–280	1.019–1.063

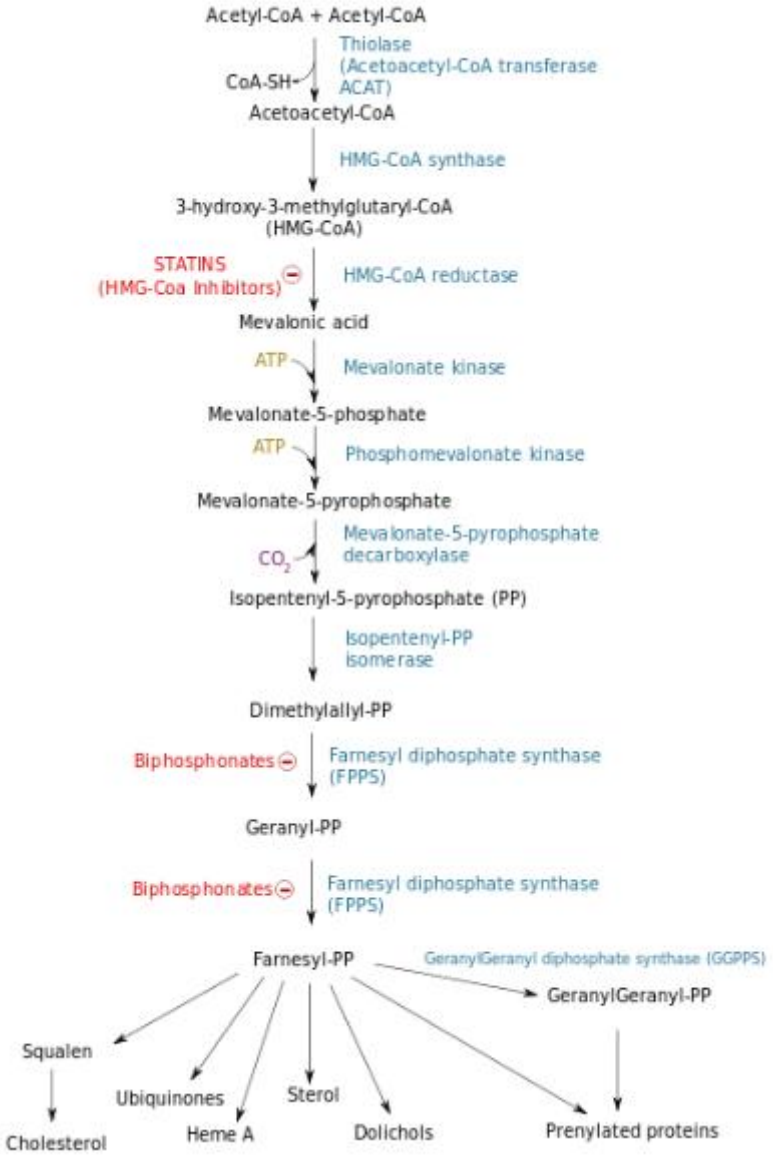
Familial hypercholesterolemia (type II a hyperlipoproteinemia), characterized by LDL receptor deficiency
Familial combined hyperlipidemia (type II b hyperlipoproteinemia), characterized by decreased LDL receptor and increased apo β–lipoprotein.
Familial dysbetalipoproteinemia (type III hyperlipoproteinemia), characterized by abnormal function of apo E receptor that is necessary for the clearance of chylomicron remnants.
Familial hypertriglyceridemia (type IV hyperlipoproteinemia), characterized by increased VLDL production.

Mechanism of Action: Statins act by competitively inhibiting HMG–CoA reductase, the rate–limiting enzyme of the mevalonate pathway. Because statins are similar in structure to HMG–CoA on a molecular level, they will fit into the enzyme's active site and compete with the native substrate (HMG–CoA). This competition reduces the rate by which HMG–CoA reductase is able to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol. A variety of natural statins are produced by Penicillium and Aspergillus fungi as secondary metabolites. These natural statins probably function to inhibit HMG–CoA reductase enzymes in bacteria and fungi that compete with the producer. HMG [3–hydroxy–3–methyl–glutaric acid] and Mevalonic acid both are five membered carbon compounds. Mevalonic acid undergoes lactonization to form lactone [cyclic ester] and same lactone ring is present in **Lovastatin, Mevastatin, Pravastatin and Simvastatin** and the other statins **Atorvastatin, Cerivastatin Fluvastatin, Pitavastatin, Rosuvastatin** don't have lactone ring but the ester bondage is open. The five–carbon side chain of lactone gets action on inhibiting the mevalonic acid

pathway by competitive inhibition on HMGCoA reductase to stop cholesterol biosynthesis.[8]

Inhibiting cholesterol synthesis: By inhibiting HMG–CoA reductase, statins block the pathway for synthesizing cholesterol in the liver. This is significant because most circulating cholesterol comes from internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall. Cholesterol synthesis appears to occur mostly at night, so statins with short half–lives are usually taken at night to maximize their effect. Studies have shown greater LDL and total cholesterol reductions in the short–acting simvastatin taken at night rather than the morning, but have shown no difference in the long–acting atorvastatin.

Increasing LDL uptake: In rabbits, liver cells sense the reduced levels of liver cholesterol and seek to compensate by synthesizing LDL receptors to draw cholesterol out of the circulation. This is accomplished via proteases that cleave membrane–bound sterol regulatory element binding proteins, which then migrate to the nucleus and bind to the sterol response elements. The sterol response elements then facilitate increased transcription of various other proteins, most notably, LDL receptor. The LDL receptor is transported to the liver cell membrane and binds to passing LDL and VLDL particles, mediating their uptake into the liver, where the cholesterol is reprocessed into bile salts and other by–products. This results in a net effect of less LDL circulating in blood.[9]



Figure–4: Mevalonate pathway.

Decreasing of specific protein prenylation: Statins, by inhibiting the HMG CoA reductase pathway, inhibit downstream synthesis of isoprenoids, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. Inhibition of protein prenylation for proteins such as RhoA (and subsequent inhibition of Rho–associated

protein kinase) may be involved, at least partially, in the improvement of endothelial function, modulation of immune function, and other pleiotropic cardiovascular benefits of statins, as well as in the fact that a number of other drugs that lower LDL have not shown the same cardiovascular risk benefits in studies as statins, and may also account for some of the benefits seen in cancer reduction with statins. In addition, the inhibitory effect on protein prenylation may also be involved in a number of unwanted side effects associated with statins, including muscle pain (myopathy) and elevated blood sugar (diabetes).

The statins are divided into two groups: fermentation–derived and synthetics. Some specific types are listed in the table below. Note that the associated brand names may vary between countries.

Conversion of 3–hydroxy–3–methyl glutaryl–CoA (HMG–CoA) to mevalonate by HMG–CoA reductase in the hepatocytes is the first and rate–limiting step in cholesterol biosynthesis. Statins competitively inhibit HMG–CoA reductase enzyme. Statins bind to the active site of the enzyme and induce a conformational change in its structure, thus reducing its activity. Also, the binding affinity of statins for HMG–CoA reductase is 10000 times higher than the substrate (HMG–CoA), thus preventing the action of the enzyme and reducing the intracellular synthesis of cholesterol. Statins have a significant impact on lowering cholesterol since most of the circulating plasma cholesterol comes from the internal synthesis in hepatocytes rather than the diet.[10]

The reduced level of cholesterol in hepatocytes secondary to statin use activates the proteases that cleave membrane–bound sterol regulatory element–binding proteins (SREBP), which further migrate to the nucleus and binds sterol response elements. This binding results in increased transcription of the LDL receptor, which translocate to the liver cell membrane. The LDL and VLDL particles in plasma bind to the LDL receptors and endocytose in hepatocytes, where their cholesterol component gets processed into bile salts, which are then excreted or recycled. This process increases the catabolism of LDL and VLDL cholesterol and results in further reduction of plasma cholesterol levels. Statins reduce the level of total cholesterol, LDL–Cholesterol, VLDL–Cholesterol, triglycerides, apo–B, and increase the level of HDL–Cholesterol. Apart from lowering lipid concentrations, statins also have cardiovascular protective effects (pleiotropic effects), which are primarily because of the inhibition of production of prenylated proteins (mainly farnesyl pyrophosphate and geranylgeranyl pyrophosphate) in the cholesterol biosynthetic pathway. Statins prevent cardiovascular disease progression via the following mechanisms:
Plaque stabilization: Coronary artery plaque rupture predisposes to acute coronary syndrome. Statins maintain the integrity of the fibrous cap of atherosclerotic plaque, inhibit the proliferation of macrophages and decreases the expression of matrix metalloproteinases (MMP).[11]

Reduces inflammation: Inflammation plays an essential role in atherosclerotic plaque rupture.[12] Statins reduce the level of pro–inflammatory cytokines (TNF–a, IL–6, IL–8) and decrease the level of CRP.

Improve endothelial function: Statins increase eNOS activity within the endothelial cells resulting in vasodilation and thus improving myocardial blood flow.

Decreased thrombogenicity: Statins decrease the activity of platelets and reduce thromboxane A2 synthesis.

Administration: Since a majority of the cholesterol synthesis occurs at night in a fasting state, the recommendation is that statins with a shorter half–life (i.e., simvastatin, pravastatin, or fluvastatin) should be taken orally before bedtime to maximize its action. Dosing with statins with a longer half–life such as atorvastatin, rosuvastatin, or pitavastatin can be in the morning or evening, but individuals should take the medication around the same time every day. Lovastatin should be taken with morning or evening meals since its absorption increases with food.

Statins are classified based on their intensity as follows:
Low–intensity statins: These include 20 to 40 mg fluvastatin, 20 mg lovastatin, 1 mg pitavastatin, 10 to 20 mg pravastatin, or 10 mg simvastatin. Low–intensity statins reduce LDL–C by less than 30%.

Moderate–intensity statins: These include 10 to 20 mg atorvastatin, 80 mg fluvastatin, 40 mg lovastatin, 2 to 4 mg pitavastatin, 40 to 80 mg pravastatin, 5 to 10 mg rosuvastatin, or 20 to 40 mg simvastatin. Moderate–intensity statins reduce LDL–Cholesterol by 30 to 50%.

High–intensity statins: These include 40 to 80 mg atorvastatin or 20 to 40 mg rosuvastatin. High–intensity statins reduce LDL–Cholesterol by greater than 50%.

Rosuvastatin is the most potent statin followed by atorvastatin. Statins also classify as lipophilic or hydrophilic. Lipophilic statins include simvastatin, lovastatin, and atorvastatin. Hydrophilic statins include pravastatin, fluvastatin, and rosuvastatin. Simvastatin 80 mg should not be a therapeutic choice in most patients. Statins administration in specific patient population groups:
Elderly patients: In individuals older than 75 years of age, who have a clinically significant Atheros Sclerotic Cardio Vascular (ASCV), the recommendation is to start them on moderate–intensity statins rather than high–intensity statins; this is because of increased side effects associated high–intensity statins, and reduction in the efficacy of metabolic pathways in elderly individuals.[13]

Renal impairment: atorvastatin, fluvastatin, pravastatin, or simvastatin are indicated in patients with chronic kidney disease since they do not undergo renal elimination, and hence, no dose adjustment is required.

Liver impairment: pravastatin and rosuvastatin can be used in patients with compensated liver disease since they are metabolized to a lesser extent by the liver in comparison to other statins. When initiating statins in patients with liver disease, patients must abstain from alcohol. The statins mentioned above should initiate at a low dose and liver enzymes, and LDL–Cholesterol should get monitored within 1 to 3 months. If no significant change occurs in the level of aminotransferase, therapy does not achieve the LDL–Cholesterol target, increase the dose of statins. Statins are contraindicated in patients with acute liver failure or decompensated cirrhosis.[14]

Drug interactions:
Increase in plasma concentration of statins result from the following:
CYP 3A4 inhibition: Statins that are metabolized by CYP450 3A4 include lovastatin, simvastatin, and atorvastatin.If patients use these statins in combination with CYP 3A4 inhibitors, it causes an increase in the plasma level of statins and increases the risk of dose–related adverse effects (including myopathy). Pravastatin, fluvastatin, rosuvastatin, and pitavastatin are the drugs of choice when patients are concurrently using drugs that interfere with CYP 3A4. Medications which increase the plasma levels of statins are:
Macrolide antibiotics: clarithromycin and azithromycin

Immunosuppressants: immunosuppressive agents, including cyclosporine, or tacrolimus, are CYP 3A4 inhibitors, and they also inhibit OATP1B1. All the statins are substrates of OATP1B1 transporter, and thus, using them along with immunosuppressive agents increases the plasma concentration of statins. Among the statins, pravastatin or fluvastatin are the recommended agents for use in combination with immunosuppressive agents.[15]

Protease inhibitors: protease inhibitors interact with statins metabolized by CYP 3A4 and increase the risk of muscle toxicity. Fluvastatin or pravastatin is the statin of choice in patients taking protease inhibitors.

Grapefruit juice, Azole antifungals: itraconazole, ketoconazole
Using statins in combination with gemfibrozil increases the risk of muscle toxicity, including rhabdomyolysis. Fenofibrate is preferred if there is a need to start statin–fibrate combination therapy. However, if gemfibrozil is the only available fibrate or fenofibrate is not tolerated, then gemfibrozil should be used in combination with low–dose atorvastatin, pitavastatin or rosuvastatin.

Calcium channel blockers: Using amlodipine, diltiazem or verapamil in combination with simvastatin and lovastatin, increases the risk of toxicity due to statins.

A decrease in plasma concentration of statins result from the following:
CYP 3A4 induction: When the statins that are metabolized by CYP 3A4 are co–administered with CYP 3A4 inducers (efavirenz, rifampin, phenytoin), it results in a decrease in plasma level of statins and decreases their effectiveness.

Bile acid sequestrants: The plasma concentration of statins decreases when used in combination with bile acid sequestrants such as colestipol.

Antacids: The plasma concentration of statins decrease when combined with antacids.

Adverse Effects: Side effects of statins include muscle pain, increased risk of diabetes mellitus, and abnormal blood levels of liver enzymes. Additionally, they have rare but severe adverse effects, particularly muscle damage. They inhibit the enzyme HMG–CoA reductase which plays a central role in the production of cholesterol. High cholesterol levels have been associated with cardiovascular disease.

Musculoskeletal: Myalgia is the most common side effect of statins, and 1 to 10% of individuals using statins have myalgias. Myositis is less common and characteristically presents by an increase in creatine kinase (CK). Rhabdomyolysis rarely occurs (0.1% individuals) but is the most serious side effect of statins and is associated with marked elevation in CK (10 times the upper limit of normal), acute renal failure secondary to myoglobinuria, electrolyte disturbances and hemodynamic instability. Statins cause musculoskeletal toxicity because they decrease the concentration of coenzyme Q_{10} (ubiquinone) and end products of the mevalonate pathway (farnesyl pyrophosphate, geranylgeranyl pyrophosphate), which are essential for skeletal muscle energy production. The symptoms usually occur within weeks to months of therapy initiation. Individuals experience relief, and serum CK normalizes within days to weeks of medication discontinuation. Amongst the statins, pravastatin and fluvastatin have the least muscle–related adverse effects. In patients who develop myopathy on statins other than pravastatin or fluvastatin, the recommendation is to switch to one of these two statins once symptoms have resolved. In patients who develop muscle side effects on pravastatin or fluvastatin, decrease the dose of statins.

Hepatic dysfunction: Statins can cause an increase in the level of serum transaminases. If an individual develops serum transaminases three times the upper limit of normal, then reduce the dose of statin or change to a different statin (preferably pravastatin) or switch to a different class of lipid–lowering drugs.[16]

Renal dysfunction: High–intensity statins can cause proteinuria and hematuria. Also, rhabdomyolysis secondary to statin use can lead to renal failure. Rosuvastatin and simvastatin are the statins which cause kidney injury. Atorvastatin, fluvastatin, or pravastatin are the indicated choices in patients with renal impairment.

Diabetes mellitus: Individuals taking high–intensity statins have a slightly increased risk of developing diabetes. The proposed mechanism is that statins inhibit the biosynthesis of cholesterol, which is essential for the production of GLUT–1, which mediates glucose uptake into the cell. This mechanism results in increased plasma levels of glucose.

Other side effects reported with statins in various case reports/case series include:

Respiratory: shortness of breath, interstitial lung disease

Gastrointestinal: statin–induced pancreatitis

Neurological: peripheral neuropathy, insomnia, dizziness, reversible cognitive impairment

Reproductive: sexual dysfunction, gynecomastia, oligospermia

Psychiatric: irritability, aggression or behavioral changes

Autoimmune: lupus–like syndrome, myasthenia gravis

Ophthalmic: cataract

Urinary tract: urinary tract infection, hematuria, albuminuria

The contraindications of statins include the following:

Hypersensitivity to medication

Pregnancy: Statins are contraindicated in pregnancy (category X under the prior FDA pregnancy classification system). Cholesterol and its substrates are imperative for fatal development. Since statins inhibit cholesterol synthesis, it causes damage to the foetus. Reports exist of congenital anomalies including anal atresia, tracheoesophageal fistula in women taking statins. If a patient becomes pregnant while taking statins, they should discontinue the medication immediately, and the patient should have counselling regarding the potential hazards.

Lactation: Statin contraindications also include breastfeeding mothers.

Acute liver failure or decompensated cirrhosis.[17]

Monitoring

Monitor lipid profile, liver function tests, creatine kinase (CK) and thyroid function tests in individuals who start statin treatment:

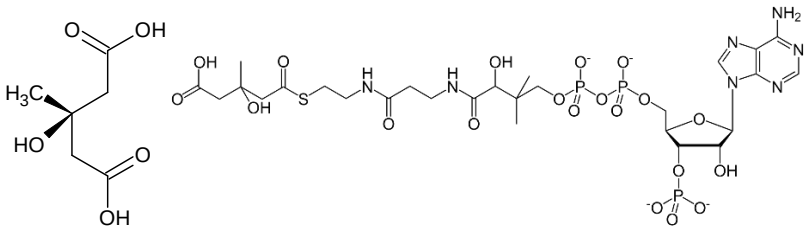
Lipid profile: Perform lipid profile at baseline before initiating statins. The lipid panel should be repeated two months after starting the therapy. If the level of LDL–Cholesterol reduction is less than expected in an individual adherent to medication, then increase the dose of statin or change to another potent statin medication and repeat lipid profile after two months. If the level of LDL–Cholesterol is within the expected range, repeat the lipid profile every 6 to 12 months.

Liver function tests: Perform liver function tests at baseline before initiating statins. Routine monitoring of LFTs is not a recommendation. LFTs require rechecking when the patient develops symptoms of liver disease.

Creatine kinase (CK): CK levels are optionally obtainable at baseline before initiating statins. Routine monitoring of CK is not a recommendation.

Thyroid function tests: Hypothyroidism can cause abnormal lipid profile and myopathy. Recommendations are to obtain thyroid hormone levels before starting statin therapy.[18]

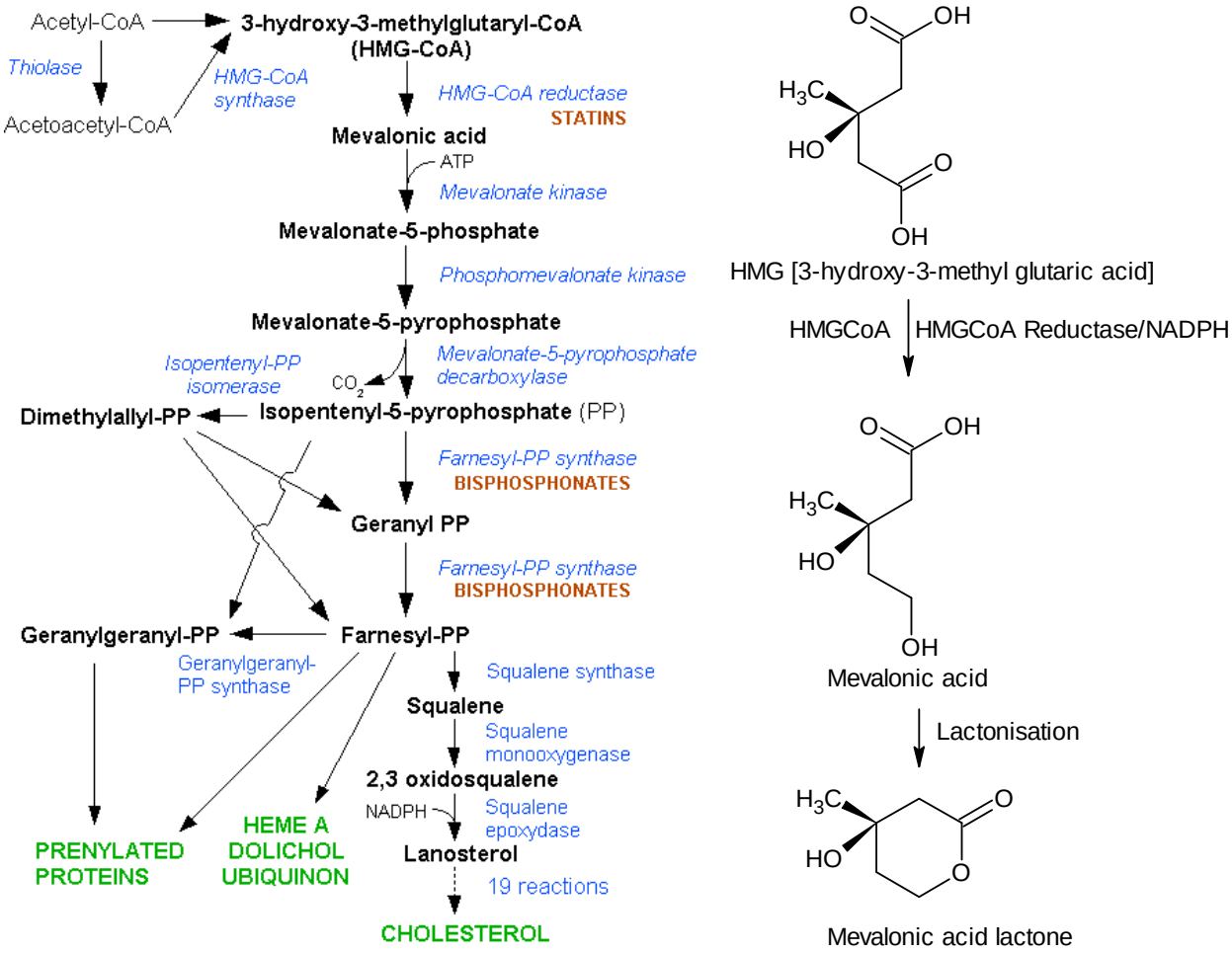
Toxicity: The most common presentation of statin overdose is muscle toxicity. In case of severe muscle symptoms or rhabdomyolysis, statins therapy should stop immediately, and patients require symptomatic care. This care includes adequate fluid resuscitation, monitoring urine output, and correcting electrolyte imbalances, especially hyperkalemia. There is no antidote available for statin overdose. After the recovery from an overdose, patients should restart on low–dose statins.



Figure–5: HMG & HMG–CoA.

HMG: β–Hydroxy β–methylglutaryl–CoA (HMG–CoA), also known as 3–hydroxy–3–methylglutaryl–CoA, is an intermediate in the mevalonate and ketogenesis pathways. It is formed from acetyl CoA and acetoacetyl CoA by HMG–CoA synthase. The research of Minor J. Coon and Bimal Kumar Bachhawat in the 1950s at University of Illinois led to its discovery. HMG–CoA is a metabolic intermediate in the metabolism of the branched–chain amino acids, which include leucine, isoleucine, and valine. Its immediate precursors are β–methylglutaconyl–CoA (MG–CoA) and β–hydroxy β–methylbutyryl–CoA (HMB–CoA). HMG–CoA reductase (3–hydroxy–3–methyl–glutaryl–coenzyme A reductase, officially abbreviated HMGCR) is the rate–controlling enzyme (NADH–dependent) of the mevalonate pathway, the metabolic pathway that produces cholesterol and

other isoprenoids. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low–density lipoprotein (LDL) via the LDL receptor as well as oxidized species of cholesterol. Competitive inhibitors of the reductase induce the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, which is considered, by those who accept the standard lipid hypothesis, an important determinant of atherosclerosis. This enzyme is thus the target of the widely available cholesterol–lowering drugs known collectively as the statins.[19]



Figure–6: Cholesterol biosynthesis.

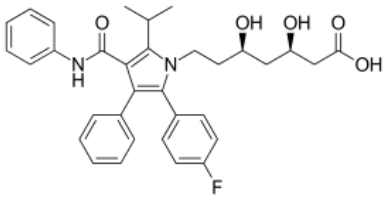
HMG–CoA reductase is anchored in the membrane of the endoplasmic reticulum, and was long regarded as having seven transmembrane domains, with the active site located in a long carboxyl terminal domain in the cytosol. More recent evidence shows it to contain eight transmembrane domains. In humans, the gene for HMG–CoA reductase (NADPH) is located on the long arm of the fifth chromosome. Related enzymes having the same function are also present in other animals, plants and bacteria.

Structure: The main isoform (isoform 1) of HMG–CoA reductase in humans is 888 amino acids long. It is a polytopic transmembrane protein (meaning it possesses many α–helical transmembrane segments). It contains two main domains: (1) A conserved N–terminal sterol–sensing domain (SSD, amino acid interval: 88–218). The related SSD of SCAP has been shown to bind cholesterol. (2) A C–terminal catalytic domain (amino acid interval: 489–871), namely the 3–hydroxy–3–methyl–glutaryl–CoA reductase domain. This domain is required for the proper enzymatic activity of the protein. Isoform 2 is 835 amino acids long. This variant is shorter because it lacks an exon in the middle region (amino acids 522–574). This does not affect any of the aforementioned domains. Statins, also known as HMG–CoA reductase inhibitors, are a class of lipid–lowering medications that reduce illness and mortality in those who are at high risk of cardiovascular disease. They are the most common cholesterol–lowering drugs.Low–density lipoprotein (LDL) carriers of cholesterol play a key role in the development of atherosclerosis and coronary heart disease via the mechanisms described by the lipid hypothesis. Statins are effective in lowering LDL cholesterol and so are widely used for primary prevention in people at high risk of cardiovascular disease, as well as in secondary prevention for those who have developed cardiovascular disease.[20,21]

There are various forms of statins, some of which include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Several combination preparations of a statin and another agent, such as ezetimibe/simvastatin, are also available.[22–26]

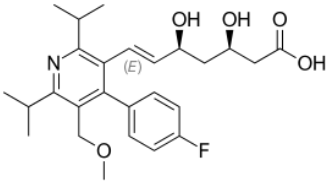
Statins in the market

Atorvastatin



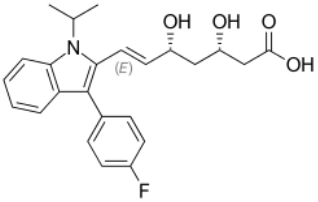
[Synthetic] IUPAC: (3R,5R)–7–[2–(4–Fluorophenyl)–3–phenyl–4–(phenylcarbamoyl)–5–propan–2–ylpyrrol–1–yl]–3,5–dihydroxyheptanoic acid. Market preparation: Arkas, Ator, Atoris, Lipitor, Torvast, Totalip. Metabolism by CYP3A4, Half–life: 14–19 hours

Cerivastatin



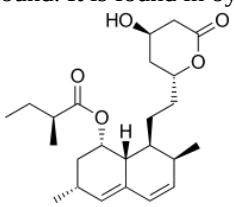
[Synthetic] IUPAC: (3R,5S,6E)–7–[4–(4–Fluorophenyl)–5–(methoxymethyl)–2,6–bis(propan–2–yl)pyridin–3–yl]–3,5–dihydroxyhept–6–enoic acid. Market preparation:Baycol, Lipobay (withdrawn from the market in August, 2001 due to risk of serious rhabdomyolysis)
Metabolism by various CYP3A isoforms, Half–life: 12–16 hours

Fluvastatin



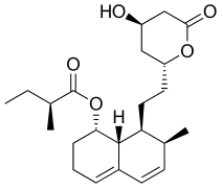
[Synthetic] IUPAC: 3R,5S,6E)–7–[3–(4–Fluorophenyl)–1–(propan–2–yl)–1H–indol–2–yl]–3,5–dihydroxyhept–6–enoic acid. Market preparation: Lescol, Lescol XL, Lipaxan, Primesin
Metabolism by CYP2C9, Half–life: 1–3 hours

Lovastatin [Naturally occurring, fermentation–derived compound. It is found in oyster mushrooms and red yeast

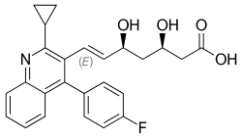


rice] IUPAC: (1S,3R,7S,8S,8aR)–8–{2–[(2R,4R)–4–Hydroxy–6–oxooxan–2–yl]ethyl}–3,7–dimethyl–1,2,3,7,8,8a–hexahydronaphthalen–1–yl (2S)–2–methylbutanoate. Market preparation: Altocor, Altoprev, Mevacor Metabolism by CYP3A4, Half–life: 1–3 hours

Mevastatin [Naturally occurring compound found in red

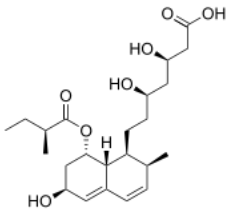


yeast rice] IUPAC: (1S,7S,8S,8aR)–8–{2–[(2R,4R)–4–Hydroxy–6–oxotetrahydro–2H–pyran–2–yl]ethyl}–7–methyl–1,2,3,7,8,8a–hexahydronaphthalen–1–yl (2S)–2–methylbutanoate. Market preparation: Compactin
Metabolism by CYP3A4, Half–life: 3–4 hours



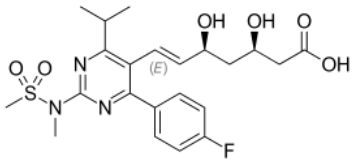
Pitavastatin [Synthetic] IUPAC: (3R,5S,6E)–7–[2–Cyclopropyl–4–(4–fluorophenyl)quinolin–3–yl]–3,5–dihydroxyhept–6–enoic acid. Market preparation: Alipza, Livalo, Livazo, Pitava, Zypitamag
Metabolism by CYP2C9 and CYP2C8, Half–life: 8–12 hours

Pravastatin [Fermentation–derived (a fermentation product of bacterium Nocardia autotrophica)]



IUPAC: (3R,5R)–3,5–dihydroxy–7–((1R,2S,6S,8R,8aR)–6–hydroxy–2–methyl–8–{[(2S)–2–methylbutanoyl]oxy}–1,2,6,7,8,8a–hexahydronaphthalen–1–yl)–heptanoic acid. Market preparation: Aplactin, Lipostat, Prasterol, Pravachol, Pravaselect, Sanaprav, Selectin, Selektine, Vasticor
Metabolism by Non–CYP, Half–life: 1–3 hours

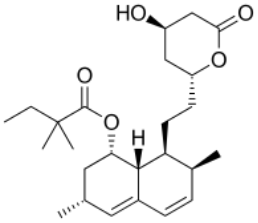
Rosuvastatin



[Synthetic] IUPAC: (3R,5S,6E)–7–[4–(4–Fluorophenyl)–2–(N–methylmethanesulfonamido)–6–(propan–2–yl)pyrimidin–5–yl]–3,5–dihydroxyhept–6–enoic acid. Market preparation: Colcardiol, Colfri, Crativ, Crestor,

Dilivas, Exorta, Koleros, Lipidover, Miastina, Provisacor, Rosastin, Simestat, Staros.
Metabolism by CYP2C9 and CYP2C19, Half–life: 14–19 hours

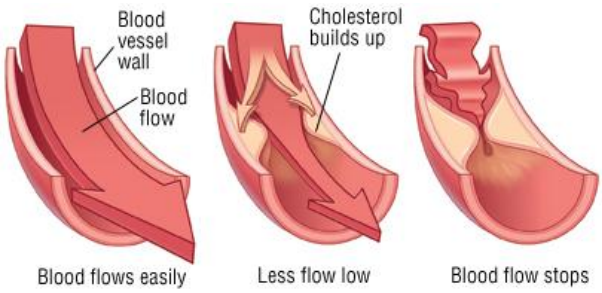
Simvastatin [Fermentation–derived (simvastatin is a synthetic derivate of a fermentation product of



Aspergillus terreus)] IUPAC: (1S,3R,7S,8S,8aR)–8–{2–[(2R,4R)–4–hydroxy–6–oxotetrahydro–2H–pyran–2–yl]ethyl}–3,7–dimethyl–1,2,3,7,8,8a–hexahydronaphthalen–1–yl 2,2–dimethylbutanoate. Market preparation: Alpheus, Krustat, Lipenil, Lipex, Liponorm, Medipo, Omistat, Rosim, Setorilin, Simbatrix, Sincol, Sinvacor, Sinvalip, Sivastin, Sinvat, Vastgen, Vastin, Xipocol, Zocor
Metabolism by CYP3A4, Half–life: 1–3 hours

CONCLUSION

Cholesterol is a fatty substance that occurs naturally in the body. It performs several vital functions. It is needed to make the walls surrounding the body's cells and is the basic material that is converted to certain hormones. Your body makes all the cholesterol you need. You need only a small amount of fat in your diet to make enough cholesterol to stay healthy. The fat and cholesterol you eat are absorbed in the intestine and transported to the liver. The liver converts fat into cholesterol, and releases cholesterol into the bloodstream. There are two main types of cholesterol: low–density lipoprotein (LDL) cholesterol (the "bad" cholesterol) and high–density lipoprotein (HDL) cholesterol (the "good" cholesterol). High levels of LDL cholesterol are linked to atherosclerosis, which is the accumulation of cholesterol–rich fatty deposits in arteries. This can cause arteries to narrow or become blocked, slowing or stopping the flow of blood to vital organs, especially the heart and brain. Atherosclerosis affecting the heart is called coronary artery disease, and it can cause a heart attack. When atherosclerosis blocks arteries that supply blood to the brain, it can cause a stroke.



People with high levels of HDL cholesterol are less likely to develop cardiovascular disease. However, if a person has both a high HDL and high LDL cholesterol level, he or she might still need treatment to lower the LDL level.

According to guidelines established by the government–sponsored National Cholesterol Education Program, the desirable level for LDL cholesterol depends on whether or not a person already has a disease caused by atherosclerosis or diabetes or other risk factors for coronary artery disease. In addition to a high LDL cholesterol level and diabetes, risk factors for coronary artery disease include: (1) Being a male older than 45 years (2) Being a female older than 55 years (3) Being a female with premature menopause (4) Having a family history of premature coronary artery disease (a father or brother younger than 55 years with coronary artery disease or a mother or sister younger than 65 years with coronary artery disease) (5) Smoking cigarettes (6) Having high blood pressure (6) Not having enough good cholesterol (high density lipoprotein or HDL).

The ideal cholesterol LDL level is less than 70 milligrams per decilitre. If you have coronary artery disease, peripheral arterial disease or have had a stroke from atherosclerosis, this should be your goal. However, if you do not have cardiovascular disease and no risk factors for it, an LDL cholesterol level of 100 – 130 milligrams may be acceptable.

People with HDL levels below 40 milligrams per deciliter are more likely to develop atherosclerosis, heart disease and stroke.

Symptoms: Most people with high cholesterol don't have any symptoms until cholesterol–related atherosclerosis causes significant narrowing of the arteries leading to their hearts or brains. The result can be heart–related chest pain (angina) or other symptoms of coronary artery disease, as well as symptoms of decreased blood supply to the brain (transient ischemic attacks or stroke). About 1 out of every 500 people has an inherited disorder called familial hypercholesterolemia, which can cause extremely high cholesterol levels (above 300 milligrams per decilitre). People with this disorder can develop nodules filled with cholesterol (xanthomas) over various tendons, especially the Achilles tendons of the lower leg. Cholesterol deposits also can occur on the eyelids, where they are called xanthelasmas.

Diagnosis: Your doctor will ask if anyone in your family has had coronary artery disease, high cholesterol or diabetes. The doctor will ask about your diet and if you have ever smoked. He or she will check your blood pressure and look for xanthomas and xanthelasmas. Your doctor can confirm a diagnosis of high cholesterol with a simple blood test.

Expected Duration: Your doctor will ask if anyone in your family has had coronary artery disease, high cholesterol or diabetes. The doctor will ask about your diet and if you have ever smoked. He or she will check your blood pressure and look for xanthomas and xanthelasmas. Your doctor can confirm a diagnosis of high cholesterol with a simple blood test.

Prevention: You may help to prevent high cholesterol by staying on a healthy diet and exercising daily. Avoid processed foods, especially those that contain saturated fats. Instead eat more fresh fruits and vegetables, whole–grain breads and cereals, and low–fat dairy products.

Treatment: The initial treatment of high cholesterol should always be lifestyle changes. This means altering your diet and getting more exercise. Some people respond dramatically to dietary changes.

Diet: There is no consensus on the best diet. The most effective diet to lower total and LDL cholesterol is a vegetarian diet. However, this is not an easy diet to follow.

Many people prefer a "Mediterranean style" diet. There is no strict definition for what should be included in this type of diet. In general, this means getting the majority of daily food calories from plant sources, especially fruits and vegetables, grains, beans, nuts, and seeds. Using olive oil as the principal fat, replacing other fats and oils. Having some low–fat cheese and/or yogurt daily. Eating fish at least a couple times per week. Limiting processed foods. Drinking alcohol in moderation unless medically not indicated. No more than two drinks per day for men and one per day for women. To maintain a desirable weight, you should take in only as many calories as you burn each day. If you need to lose weight, you need to take in fewer calories than you burn. People who aren't sure how to follow such a diet may find it useful to work with a health care professional such as a dietitian, nutritionist, doctor or nurse. In addition to dietary changes, you should get at least 30 minutes of moderate–intensity exercise, such as brisk walking, daily.

Medications: Whether you need medication to lower your cholesterol level depends on how you respond to diet and your personal risk of heart attack and stroke. There are five types of cholesterol–lowering medications. However, a statin drug should almost always be the first choice to lower LDL cholesterol. Statins are also called HMG–CoA reductase inhibitors. They include lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol), atorvastatin (Lipitor), and rosuvastatin (Crestor). Statins block an enzyme called HMG–CoA reductase, which is necessary for the production of cholesterol. Statins do much more than lower your LDL cholesterol number. They lower your risk of developing hardening of the arteries (atherosclerosis) and reduce the chance that you will have a heart attack or stroke. When a person taking a statin does not reach goal, doctors sometimes add ezetimibe. Ezetimibe inhibits absorption of cholesterol from the intestine. By itself the brand name drug is called Zetia. When combined with simvastatin, it's known as Vytorin. The newest cholesterol lowering therapies, called PCSK9 inhibitors, are more potent than statins. PCSK9 inhibitors are most useful for people with familial hypercholesterolemia. These people have extremely high cholesterol levels. People with coronary artery disease who either don't reach goal with a high dose statin drug or cannot tolerate statins because of side effects may also be candidates for this new therapy. PCSK9 inhibitors are much more expensive than most statins. Also, they are not available as pills. They must be injected. Other drugs that can lower cholesterol include: Bile acid–binding resins, including cholestyramine (Questran) and colestipol (Colestid). They are used less often today because they lower HDL (good) cholesterol as well as LDL (bad) cholesterol. Niacin (several brand names). Niacin is also being used less often. In doses needed to reduce LDL cholesterol, side effects are common. Fibrates, including gemfibrozil (Lopid), fenofibrate (Tricor) and clofibrate (Abitrate). Fibrates are especially helpful for people with high triglyceride levels. In addition to dietary changes or medication, people with high cholesterol should try to control their other risk factors for coronary artery disease. This means keeping blood pressure at normal levels, not smoking, controlling your blood sugar, maintaining or losing weight and following a regular exercise schedule.

When to Call a Professional: Because it is possible to have high cholesterol for many years without symptoms, it is important to have your blood cholesterol level checked periodically. Current guidelines recommend that adults older than 20 undergo a full lipid profile once every five years. This test measures LDL and HDL cholesterol and triglyceride levels. If the numbers are outside the desirable range, your doctor may suggest that you change your diet and monitor your cholesterol more frequently.

Prognosis: The effectiveness of following a healthy diet and using medications to lower cholesterol varies from person to person. On average, diet and exercise can lower LDL cholesterol by about 10%. Medications can lower LDL cholesterol by another 20% to more than 50%.

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