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Review article

The role of statin drugs in combating cardiovascular diseases

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ABSTRACT

Statins clearly confer substantial benefit in people with established cardiovascular (CV) disease. Increased cholesterol levels have been associated with cardiovascular diseases (CVD), and statins are therefore used in the prevention of these diseases. Studies have found that the ability of a particular statin to lower or reduce LDL is proportional to the amount it can increase HDL levels. This review article will focus on the effective role of statin in cardiovascular disease and comparison was made between various classes of statin drugs.

1. Introduction

Statins (or HMG-CoA reductase inhibitors) are a class of drug used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (CVD), and statins are therefore used in the prevention of these diseases. Randomized controlled trials have shown that they are most effective in those already suffering from cardiovascular disease (secondary prevention), but they are also advocated and used extensively in those without previous CVD but with elevated cholesterol levels and other risk factors (such as diabetes and high blood pressure) that increase a person's risk.A number of statins are on the market: atorvastatin (Lipitor and Torvast), fluvastatin (Lescol), lovastatin (Mevacor, Altocor, Altoprev), pitavastatin (Livalo, Pitava), pravastatin (Pravachol, Selektine, Lipostat), rosuvastatin (Crestor) and simvastatin (Zocor, Lipex)(Table.1)[1].

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1.2.Naturally-occurring statins

Some types of statins are naturally occurring, and can be found in such foods as oyster mushrooms and red yeast rice.

1.3.Indications and uses

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On average, statins can lower LDL cholesterol (so-called "bad cholesterol") by 1.8 mmol/l (70 mg/dl), which translates into a 60% decrease in the number of cardiac events (heart attack, sudden cardiac death) and a 17% reduced risk of stroke after long-term treatment. They have less effect than the fibrates or niacin in reducing triglycerides and raising HDL-cholesterol ("good cholesterol"). Clinical practice guidelines generally recommend that the patient has tried "lifestyle modification", including a cholesterol-lowering diet and physical exercise, before statin use is considered; statins or other pharmacologic agents may then be recommended for patients who do not meet their lipid-lowering goals through diet and lifestyle approaches.

Table.1.Brand Name, Derivation and Metabolism of Statin Drugs[1].

Statin	Brand Name	Derivation	Metabolism
Atorvastatin	Lipitor, Torvast	Synthetic	CYP3A4
Fluvastatin	Lescol, Lescol XL	Synthetic	CYP2C9
Lovastatin	Mevacor, Altocor, Altoprev	Fermentation-derived. Naturally occurring compound. Found in oyster mushrooms and red yeast rice.	CYP3A4
Pitavastatin	Livalo, Pitava	Synthetic	-
Pravastatin	Pravachol, Selektine, Lipostat	Fermentation-derived.(A fermentation product of bacterium Nocardia autotrophica).	Non CYP
Rosuvastatin	Crestor	Synthetic	CYP2C9 and CYP2C19
Simvastatin	Zocor, Lipex	Fermentation-derived. (Simvastatin is a synthetic derivate of a fermentation product of Aspergillus terreus.)	CYP3A4

The indications for the prescription of statins have broadened over the years. Initial studies, such as the Scandinavian Simvastatin Survival Study (4S), supported the use of statins in secondary prevention for cardiovascular disease, or as primary prevention only when the risk for cardiovascular disease was significantly raised, as indicated by the Framingham risk score. Indications were broadened considerably by studies such as the Heart Protection Study (HPS), which showed preventative effects of statin use in specific risk groups, such as diabetics. The ASTEROID trial, published in 2006, using only a statin at high dose, achieved lower than usual target calculated LDL values and showed disease regression within the coronary arteries using intravascular ultrasonography[2].

Statins are generally accepted as effective in decreasing mortality in people with preexisting cardiovascular disease. They are also currently advocated for use in patients at high risk of developing heart disease, but the evidence for this is questioned. A 2010 meta-analysis of studies found no benefit in terms of all-cause mortality when statins were used as a high-risk primary prevention intervention.

1.4.Comparative effectiveness

An independent analysis has been done to compare atorvastatin, pravastatin and simvastatin, based on their effectiveness against placebos. It found that, at commonly prescribed doses, there are no statistically significant differences amongst statins in reducing cardiovascular morbidity and mortality. The CURVES study, which compared the efficacy of different doses of atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin for reducing LDL and total cholesterol in patients with hypercholesterolemia, found that atorvastatin was more effective without increasing adverse events[Table.2].

Statins differ in their ability to reduce cholesterol levels. Doses should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or dose changes, lipid levels should be analyzed within 1–3 months and dosage adjusted accordingly, then every 6–12 months afterwards. A link between cholesterol and cardiovascular disease, known as the lipid hypothesis, had already been suggested [3,4].

1.5.Effects of Statin

Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. The ASTEROID trial showed direct ultrasound evidence of atheroma regression during statin therapy.Researchers hypothesize that statins prevent cardiovascular disease via four proposed mechanisms (all subjects of a large body of biomedical research):

1. Improve endothelial function
2. Modulate inflammatory responses
3. Maintain plaque stability
4. Prevent thrombus formation

Cholesterol is the main constituent of atheroma, the fatty lumps in the wall of arteries that occur in atherosclerosis and, when ruptured, cause the vast majority of heart attacks, Treatment consisted mainly of dietary measures such as a low-fat diet, and poorly tolerated medicines such as clofibrate, cholestyramine and nicotinic acid.Cholesterol researcher Daniel Steinberg writes that while the Coronary Primary Prevention Trial of 1984 demonstrated that cholesterol lowering could significantly reduce the risk of heart attacks and angina, physicians, including cardiologists, remained largely unconvinced[5].

Table.2. Comparative effectiveness of the Statin Drugs [3,4].

Statin Equivalent Dosages						
%LDLReduction (approx.)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
10-20%	-	20 mg	10	10	-	5
20-30%	-	40 mg	20	20	-	10
30-40%	10 mg	80 mg	40	40	5	20
40-45%	20 mg	-	80	80	5-10	40
46-50%	40 mg	-	-	-	10-20	80
50-55%	80 mg	-	-	-	20	-
56-60%	-	-	-	-	40	-
Starting dose						
Starting dose	10–20 mg	20 mg	10-20 mg	40 mg	10 mg;5 mg if hypothyroid,>65 yo, Asian	20 mg
If higher LDL reduction goal	40 mg if >45%	40 mg if >25%	20 mg if >20%	-	20 mg if LDL >190 mg/dL (4.87 mmol/L)	40 mg if >45%
Optimal timing	Anytime	Evening	With evening meals	Anytime	Anytime	Evening

2.Mechanism of action

Statins act by competitively inhibiting HMG-CoA reductase,the first committed enzyme of the HMG-CoA reductase pathway (Fig.1). HMG-CoA reductase inhibitors are a group of prescription drugs used to lower cholesterol, a white waxy substance that can stick to the inside of blood vessels, resulting in clogged arteries, heart disease, and strokes. These medicines work by slowing down the body's ability to make cholesterol. Because statins are similar to HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonate,the next molecule in the cascade that eventually produces cholesterol, as well as a number of other compounds. This ultimately reduces cholesterol via several mechanisms[6].

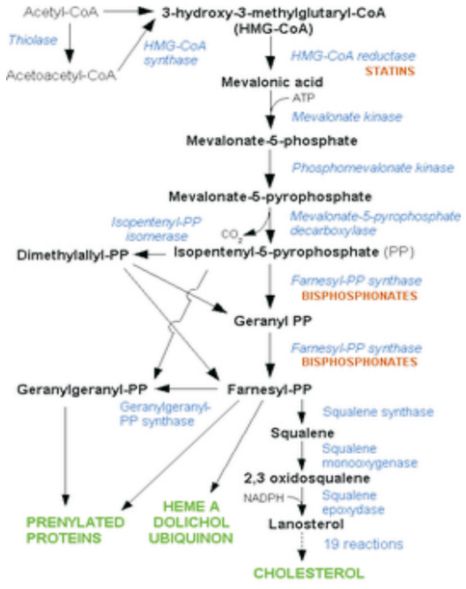
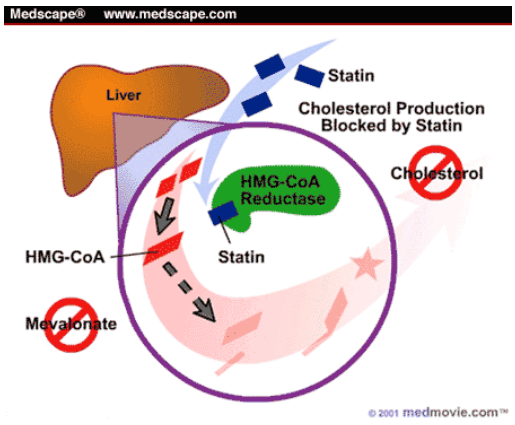


Fig.1.The HMG-CoA reductase pathway, which is blocked by statins via inhibiting the rate-limiting enzyme HMG-CoA reductase[6].

Inhibiting cholesterol synthesis

By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in the liver(Fig.2). 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[6].

Fig.2. Statins block the pathway for synthesizing cholesterol in the liver [6].



Increasing LDL uptake

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 protease enzymes that cleave a protein called "membrane-bound sterol regulatory element binding protein ", which migrates to the nucleus and causes increased production of various other proteins and enzymes, including the LDL receptor. The LDL receptor then relocates to the liver cell membrane and binds to passing LDL and VLDL particles (the "bad cholesterol" linked to disease). LDL and VLDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts. These are excreted, and subsequently recycled mostly by an internal bile salt circulation.

3.Atorvastatin

Atorvastatin is a cholesterol-lowering medication that blocks the production of cholesterol (a type of fat) in the body.Atorvastatin reduces low-density lipoprotein (LDL) cholesterol and total cholesterol in the blood. Lowering your cholesterol can help prevent heart disease and hardening of the arteries, conditions that can lead to heart attack, stroke,and vascular disease.Atorvastatin is used to treat high cholesterol.Atorvastatin is also used to lower the risk of stroke, heart attack, or other heart complications in people with coronary heart disease or type 2 diabetes.

In rare cases, atorvastatin can cause a condition that results in the breakdown of skeletal muscle tissue. This condition can lead to kidney failure. Call your doctor at once if you have unexplained muscle pain or tenderness, muscle weakness, fever or flu symptoms, and dark colored urine.This medication can cause birth defects in an unborn baby. Do not use if you are pregnant. Use an effective form of birth control, and tell your doctor if you become pregnant during treatment.Do not take atorvastatin if you are pregnant or breast-feeding, or if you have liver disease.

Atorvastatin is used to treat dyslipidemias,which are disorders characterized by abnormal levels of lipids in the blood. Specifically, atorvastatin is used along with dietary therapy to decrease elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C; so-called “bad” cholesterol), apolipoprotein B (apo B), and triglyceride concentrations. It is also used to increase concentrations of high-density lipoprotein cholesterol (HDL-C; the so-called “good” cholesterol).

Familial hypercholesterolemia is an inherited condition characterized by high cholesterol levels. Atorvastatin is used to lower cholesterol in individuals as young as ten years who have familial hypercholesterolemia (LDL-C levels >than 190 mg/dl (or >than 160 mg/dl) and who have a family history of coronary heart disease (CHD).

The lipid-lowering effect of atorvastatin reduces the risk of CHD. Therefore, atorvastatin is used as primary prevention of heart attack,stroke, or angina in people who have multiple risk factors for CHD: age, smoking,high blood pressure,low HDL-C, or a family history of early CHD. Primary prevention refers to interventions that prevent the first occurrence of a disease or condition. Primary prevention of CHD is done for people who have no clinical evidence of cardiovascular disease but who at risk. Atorvastatin is also used in primary prevention of cardiovascular events (e.g., heart attack, stroke)in people with type 2 diabetes.

Atorvastatin is also used as secondary prevention. Secondary prevention refers to interventions that protect against recurrence of a disease or condition. Secondary prevention with atorvastatin is done in people who have CHD. In these people, atorvastatin is used to reduce the risk of heart attack, stroke, or hospitalization for congestive hear failure (CHF). Atorvastatin has also been shown to slow the progression of coronary atherosclerosis in patients with CHD [7].

Atorvastatin is taken as tablets by mouth once a day, with or without food. Tablets containing 10 mg, 20 mg, 40 mg, or 80 mg are available. Low doses may be given initially, with gradual escalation depending on changes in blood lipid concentrations and the presence or absence of side effects.

4.Fluvastatin

Fluvastatin (trade names Lescol, Canef, Vastin) is a member of the drug class of statins, used to treat hypercholesterolemia and to prevent cardiovascular disease. Fluvastatin is an enzyme blocker (HMG-CoA reductase inhibitor), also known as a "statin". It is used along with a proper diet to help lower cholesterol and fats (triglycerides) in the blood. In general, this drug is prescribed after non-drug treatment options have not been fully successful at lowering cholesterol (e.g., diet change, increase in exercise, weight loss if overweight). Reducing cholesterol and triglycerides help prevent strokes and heart attacks.

High blood LDL cholesterol is first treated with exercise, weight loss, and a diet low in cholesterol and saturated fats. When these measures fail, cholesterol-lowering medications such as fluvastatin can be added. The National Cholesterol Education Program (NCEP) has published treatment guidelines for use of these medications. These treatment guidelines take into account the level of LDL cholesterol as well as the presence of other risk factors such as diabetes, hypertension, cigarette smoking, low HDL cholesterol level, and family history of early coronary heart disease. Blood cholesterol determinations are performed in regular intervals during treatment so that dosage adjustments can be made.

Fluvastatin is generally well- tolerated by most patients. The medication should be used with caution in patients with alcohol or liver diseases. Persistently abnormal liver blood tests are rare, but may lead the doctor to discontinue the medication. Rare cases of muscle inflammation (myositis) and breakdown have been reported with other medications in the same class. Muscle breakdown causes the release of muscle protein (myoglobin) into the blood and kidney tubules, and may result in kidney failure [8].

Side effects are rare. Minor side effects include constipation, diarrhea, fatigue, gas, heartburn, headache, insomnia, and joint pains. Major side effects include abdominal pain or cramps, blurred vision, dizziness, easy bruising or bleeding, itching, muscle pain or cramps, rash, and yellowing of the skin or eyes.

5.Lovastatin

Lovastatin is lowering cholesterol (hypolipidemic agent) in those with hypercholesterolemia and so preventing cardiovascular disease. Lovastatin is a naturally occurring drug found in food such as oyster mushrooms and red yeast rice. Lovastatin, a compound isolated from Aspergillus terreus, was the first statin to be marketed.Lovastatin natural products with a powerful inhibitory effect on HMG-CoA reductase,were discovered in the 1970s, and taken into clinical development as potential drugs for lowering LDL cholesterol. Lovastatin at its maximal recommended dose of 80 mg daily produced a mean reduction in LDL cholesterol of 40%, a far greater reduction than could be obtained with any of the treatments available at the time. Equally important, the drug produced very few adverse effects, was easy for patients to take, and so was rapidly accepted by prescribers and patients. Lovastatin is used for reducing total cholesterol and LDL cholesterol, and triglycerides, and for increasing HDL cholesterol in patients with elevated blood cholesterol levels (hypercholesterolemia). Lovastatin is used for reducing the risk of heart attacks,angina, coronary revascularization procedures in individuals without symptomatic cardiovascular disease, average to moderately elevated cholesterol levels and below average HDL cholesterol levels. It also is used for slowing the progression of coronary atherosclerosis in individuals with coronary heart disease[9].

In general, lovastatin is prescribed after non-drug treatments have not been fully successful at lowering cholesterol (e.g., diet change, increase in exercise, weight loss if overweight). Lowering "bad" cholesterol and triglycerides and raising "good" cholesterol decreases the risk of heart disease and helps prevent strokes and heart attacks. Lovastatin is usually well tolerated. Lovastatin, and all statin drugs, can rarely cause myopathy or rhabdomyolysis.This can be life-threatening if not recognised and treated in time, so any unexplained muscle pain or weakness.

6.Rosuvastatin

Rosuvastatin (marketed by AstraZeneca as Crestor) is a member of the drug class of statins,used to treat high cholesterol and related conditions, and to prevent cardiovascular disease. Rosuvastatin has structural similarities with most other synthetic statins,e.g., atorvastatin,cerivastatin,pitavastatin,but rosuvastatin unusually also contains sulfur. Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase,having a mechanism of action similar to that of other statins.Its approximate elimination half life is 19 hours and its time to peak plasma concentration is reached in 3–5 hours following oral administration.

Putative beneficial effects of rosuvastatin therapy on chronic heart failure may be negated by increases in collagen turnover markers as well as a reduction in plasma coenzyme Q10(CoQ10) levels in patients with chronic heart failure.Rosuvastatin is approved for the treatment of high LDL cholesterol (dyslipidemia) total cholesterol (hypercholesterolemia) and/or triglycerides (hypertriglyceridemia).In February 2010, rosuvastatin was approved by the FDA for the primary prevention of cardiovascular events.Rosuvastatin may decrease the relative risk of heart attack and stroke in patients without hyperlipidemia but with elevated levels of highly-sensitive C-reactive protein.This could strongly impact medical practice by placing many patients on statin prophylaxis that otherwise would have been untreated.As a result of this clinical trial, the FDA approved rosuvastatin for the primary prevention of cardiovascular events[10].

Low-density lipoprotein (LDL) cholesterol is the “bad” cholesterol that increases a person's risk for cardiovascular disease (heart problems or stroke). C-reactive protein is another substance in the blood that serves as a marker for cardiovascular disease risk. Statins are drugs that lower both LDL cholesterol and C-reactive protein levels. It has been known for a long time that statins reduce cardiovascular disease in persons with high levels of LDL cholesterol. In 2008, a study showed that the statin rosuvastatin reduced cardiovascular problems in persons with no previous cardiovascular disease and normal LDL cholesterol levels but elevated levels of C-reactive protein. The results of the initial report of this study suggested that rosuvastatin benefited persons regardless of their age. However, this study included larger numbers of older persons than did many previous studies of statins and provided an opportunity to look closely at the benefits and risks of this statin in older persons. The most common rosuvastatin side effects are Muscle aches or pain, Joint pain, Headache, Nausea, Constipation, Body weakness, Abdominal pain[11].

7.Pitavastatin

Pitavastatin (usually as a calcium salt) is a member of the medication class of statins,marketed in the United States under the trade name Livalo. Like other statins, it is an inhibitor of HMG-CoA reductase,the enzyme that catalyses the first step of cholesterol synthesis. It has been available in Japan since 2003, and is being marketed under licence in South Korea and in India. It is likely that pitavastatin will be approved for use in hypercholesterolaemia (elevated levels of cholesterol in the blood) and for the prevention of cardiovascular disease outside South and Southeast Asia as well.Like the other statins, pitavastatin is indicated for hypercholesterolaemia (elevated cholesterol) and for the prevention of cardiovascular disease. There have been many studies confirming that pitavastatin can consistently increase HDL cholesterol (10–25%), especially in patients with HDL lower than 40 mg/dl, in addition to strong reducing LDL cholesterol (–40%). As a consequence, pitavastatin is most likely to be appropriate for patients with metabolic syndrome with high LDL, low HDL and diabetes mellitus.Another reason is that pitavastatin, unlike other potent statins, does not affect glycelate control of type 2 diabetes mellitus.[Common statin-related side-effects (headaches, stomach upset, abnormal liver function tests and muscle cramps) were similar to other statins. However, pitavastatin seems to lead to less muscle side effects than other statins. Most statins are metabolised in part by one or more hepatic cytochrome P450 enzymes, leading

to an increased potential for drug interactions and problems with certain foods (such as grapefruit juice). Pitavastatin appears to be a substrate of CYP2C9,and not CYP3A4 (which is a common source of interactions in other statins). As a result, pitavastatin is less likely to interact with drugs that are metabolized via CYP3A4, which might be important for elderly patients who need to take multiple medicines[12].

Pitavastatin is used together with a proper diet to treat high cholesterol levels and high triglyceride (fat) levels in the blood. High levels of cholesterol or triglycerides can clog blood vessels and cause medical problems. Pitavastatin may help prevent some medical problems that are caused by clogged blood vessels. Pitavastatin belongs to the group of medicines called HMG-CoA reductase inhibitors or "statins". It works by blocking an enzyme that is needed by the body to make cholesterol. This reduces the amount of cholesterol in the blood.

8.Pravastatin

Pravastatin (marketed as Pravachol or Selektine) is a member of the drug class of statins, used for lowering cholesterol and preventing cardiovascular disease. Initially known as CS-514, it was originally identified in a bacterium called Nocardia autotrophica. Pravastatin is a cholesterol-lowering medication that blocks the production of cholesterol (a type of fat) in the body. Pravastatin reduces low-density lipoprotein (LDL) cholesterol and total cholesterol in the blood. Lowering your cholesterol can help prevent heart disease and hardening of the arteries, conditions that can lead to heart attack, stroke, and vascular disease. Pravastatin is used to treat high cholesterol. Pravastatin is also used to lower the risk of stroke, heart attack, or other heart complications in people with coronary heart disease. The most common side effects of pravastatin Nausea and vomiting, Headache, Diarrhea, Unexplained rash, Fatigue, Dizziness, Muscle pain. The active beta-hydroxy acid form of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors competitively inhibits the enzyme HMG-CoA reductasem. Inhibition of HMG-CoA reductase prevents conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. The primary site of action of HMG-CoA reductase inhibitors is the liver.Inhibition of cholesterol synthesis in the liver leads to upregulation of LDL receptors and an increase in catabolism of LDL cholesterol. There may also be some reduction in LDL production as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL. HMG-CoA reductase inhibitors reduce LDL cholesterol, VLDL cholesterol, and to a lesser extent, plasma triglyceride concentrations, and slightly increase high-density lipoprotein (HDL) concentrations[13].

9.Simvastatin

Simvastatin is a hypolipidemic drug used to control elevated cholesterol, or hypercholesterolemia.Simvastatin is a member of the statin class of pharmaceuticals, is a synthetic derivate of a fermentation product of Aspergillus terreus.It is marketed under the trade names Zocor, Simlup, Simcard, Simvacor. The development of simvastatin was closely linked with lovastatin.Simvastatin is a powerful lipid-lowering drug that can decrease low density lipoprotein (LDL) levels by up to 50%. It is used in doses of 5 mg up to 80 mg. Higher doses (160 mg) have been found to be too toxic, while giving only minimal benefit in terms of lipid lowering.In secondary prevention,80 mg per day reduced major cardiovascular events.

All statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase,the rate-limiting enzyme of the HMG-CoA reductase pathway,the metabolic pathway responsible for the endogenous production of cholesterol.Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration. In the blood, statins lower total and LDL ("bad") cholesterol as well as triglycerides. LDL cholesterol is believed to be an important cause of coronary artery disease. Lowering LDL cholesterol levels slows and may even reverse coronary artery disease. Statins also increase HDL ("good") cholesterol. Raising HDL cholesterol levels, like lowering LDL cholesterol may slow coronary artery disease.

In patients with coronary heart disease, diabetes peripheral vessel disease or history of stroke or other cerebrovascular disease, simvastatin is prescribed for reducing the risk of mortality by reducing death from coronary heart disease, reducing nonfatal myocardial infarction (heart attack)and stroke, and reducing the need for coronary and noncoronary revascularization procedures[14].

The drug is in the form of an inactive lactone that is hydrolyzed after ingestion to produce the active agent. It is a white, nonhygroscopic,crystalline powder that is practically insoluble in water, and freely soluble in chloroform,methanol and ethanol.

Usually, patients are started at 20 mg, but the dispersion index can go from 5 mg to 80 mg a day. If adjustments are required, the adjustment must be performed at intervals no less than 4 weeks. The highest approved dose of simvastatin is 80 mg.Common side effects (>1% incidence) may include abdominal pain, diarrhea, indigestion, and a general feeling of weakness. Rare side effects include joint pain, memory loss, and muscle cramps.Cholestatic hepatitis, hepatic cirrhosis, rhabdomyolysis and myositis have been reported in patients receiving the drug chronically.

10.C-reactive protein

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (i.e. C-reactive protein is an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system.Arterial damage results from white blood cell invasion and inflammation within the wall. CRP is a general marker for

inflammation and infection, so it can be used as a very rough proxy for heart disease risk. Since many things can cause elevated CRP, this is not a very specific prognostic indicator.Nevertheless, a level above 2.4 mg/l has been associated with a doubled risk of a coronary event compared to levels below 1 mg/l;Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes,hypertension and cardiovascular disease.A study of over 700 nurses showed that those in the highest quartile of trans fat consumption had blood levels of CRP that were 73% higher than those in the lowest quartile.Although one group of researchers indicated that CRP may only be a moderate risk factor for cardiovascular disease[15].

In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes. These highly consistent clinical data are supported by abundant laboratory and experimental evidence that demonstrate that atherothrombosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. In terms of clinical application, CRP seems to be a stronger predictor of cardiovascular events than LDL cholesterol, and it adds prognostic information at all levels of calculated Framingham Risk and at all levels of the metabolic syndrome[16]. Using widely available high-sensitivity assays, CRP levels of <1, 1 to 3, and >3 mg/L correspond to low-, moderate-, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL who have CRP levels >3 mg/L represent a high-risk group often missed in clinical practice. The addition of CRP to standard cholesterol evaluation may thus provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches.

11. CK-MB

CK-MB is relatively specific when skeletal muscle damage is not present. CK-MB resides in the cytosol and facilitates high-energy phosphates into and out of mitochondria. It is distributed in a large number of tissues even in the skeletal muscle. Since it has a short duration, it cannot be used for late diagnosis of acute MI but can be used to suggest infarct extension if levels rise again. This is usually back to normal within 2–3 Days+

Creatine kinase is an enzyme responsible for transferring a phosphate group from ATP to creatine. It is composed of M and/or B subunits that form CK-MM, CKMB, and CK-BB isoenzymes. Total CK (the activity of the MM, MB, and BB isoenzymes) is not myocardial-specific. However, the MB isoenzyme (also called CK-2) comprises about 40% of the CK activity in cardiac muscle and 2% or less of the activity in most muscle groups and other tissues. In the proper clinical setting, MB is both a sensitive and specific marker for myocardial infarction. MB usually becomes abnormal three to four hours after an MI, peaks in 10–24 hours, and returns to normal within 72 hours. However, an elevated serum MB may occur in people with severe skeletal muscle damage (such as in muscular dystrophy or a crush injury) and renal failure. In such cases, the CK index (MB divided by total CK) is very helpful. If the index is under 4%, a nonmyocardial cause of a high MB should be suspected. CK-MB is considered the benchmark for cardiac markers of myocardial injury. Measurement of CK-MB may be performed via electrophoresis or immunoassays; the latter demonstrates better analytical sensitivity and better precision[17] .

12.Conclusion

Cholesterol has been singled out as the primary factor in the development of atherosclerosis. HDL is regarded as one of the most important protective factors against arteriosclerosis. HDL's protective function has been attributed to its active participation in the reverse transport of cholesterol. Numerous cohort studies and clinical trials have confirmed the association between a low HDL and an increased risk of coronary heart disease. The concentration of LDL correlates positively whereas HDL correlates inversely to the development of coronary heart disease. Smokers have significantly higher serum cholesterol, triglyceride, and LDL levels, but HDL is lower in smokers than in non-smokers. Evidence suggests that oxidatively modified LDL contribute to the pathogenesis of atherosclerosis. Increased oxidative stress and the generation of the free oxygen radicals can result in modification of LDL to oxidized LDL that could lead to atherosclerotic lesions. CK and more particularly its isoenzyme CK-MB still have a formal place in defining myocardial infarction. These enzymes normally exist in cellular compartment and leak out into the plasma during myocardial injury due to disintegration of contractile elements and sarcoplasmic reticulum. Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity worldwide. Reducing high blood cholesterol, which is a risk factor for CVD events, is an important goal of medical treatment. Available for almost 2 decades, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have emerged at the forefront of preventive drugs for cardiovascular disease because of a substantial clinical trial database demonstrating that statins reduce the risk for coronary artery disease morbidity and death across a broad range of at-risk patient cohorts.

In the present administration of 10 mg of simvastatin was found to be most effective in reducing the level of triglycerides.The administration of statin did not contribute to a significant increase in HDL levels.Simvastatin also considerably reduced the LDL level in hyperlipidaemic patients.Apolipoprotein B level was considerably reduced by the administration of simvastatin and Apolipoprotein A-1 was reduced by intake of atrovastatin.

Atrovastatin also markedly reduced the level of CK and CK-MB isoenzymes which are regarded as efficient markers of cardiovascular diseases.Atrovastatin had a profound effect on the liver function test markers where it lead to an increase in total protein and albumin level and SGPT and SGOT was markedly reduced.

In short, the administration of rosuvastatin and atrovastatin was found to be more effective in the treatment of hyperlipidaemic patients than that of pravastatin. Although flavostatin also had a profound effect, the dosage was high compared to other statins. Hence its effectiveness compared to rosuvastatin and atrovastatin need to be further investigated.

Rosuvastatin and Atrovastatin can be more effective in reducing hyperlipidemia compared to other classes of statin drugs and thus further reduce the risk of cardiovascular disease in such patients.In addition to that,Rosuvasatin had less side effects in patients as compared to atrovastatin and can be defined as the most effective among the statin class of drugs.

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