

Statin Use Will Cure Disease? A Review of Statin Safety and Efficacy

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Abstract:- Statins [HMG CoA reductase inhibitors] are very much effective in reducing the low density lipoproteins [LDL] cholesterol in patients with risk of coronary artery diseases and cerebrovascular events. Statins competitively inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase which acts as the catalyst in the cholesterol synthesis pathway (mevalonate pathway). Statins reduce the low density lipoproteins [LDL] cholesterol depends on the strength /dose. A high dose of statin will reduce >50% of LDL cholesterol. Also reduces the atherosclerotic events, leading cause of cardiovascular and cerebro vascular diseases. Apart from the benefits, statin use may show some side effects like myopathy, Rhabdomyolysis, increased transaminase level, new onset diabetes. This article discusses the benefits and safety of statins.

Key words: Statins, Cardiovascular diseases, Primary prevention, Intensity, secondary prevention, Myalgia, Rhabdomyolysis.

I. INTRODUCTION

Cardiovascular diseases are the leading cause of death in most of the population. The morbidity and mortality associated with the coronary artery disease and dyslipidaemias can be reduced by treating the condition with statins.¹ The various clinical trials showed that the benefit of statins is achieved only after 1 to 2 years of its use. The rate of cardiovascular disease among the patients with acute coronary syndrome can be reduced by administering atorvastatin.² The heart protection study showed that simvastatin decreased the total death rate and the rate of all vascular events.³

On analysing the cardiovascular life expectancy model to estimate the benefits of risk factors modification in the primary and secondary prevention of cardiovascular disease showed that the benefit is more in high risk individuals than the lower risk individuals, younger individuals had more than elderly and men more than that of the women.^{4,5} A randomized controlled trial which demonstrated statin benefits showed that each 1mmol/l (39mg/dl) reduction in LDL cholesterol effects a consistent ~22% reduction in cardiovascular events according to various cardiovascular risk profiles, clinical and demographic characteristics and baseline LDL cholesterol levels.⁶

The European society of cardiology (ESC)/ European atherosclerotic society (EAS) and Italian guidelines recommended that statins are the first line pharmacological treatment of hypercholesterolemia. The 2011 ESC/EAS cholesterol treatment guideline suggests that patients with very high cardiovascular risk (established cardiovascular

disease, type 1 or 2 diabetic mellitus with end organ damage, chronic kidney disease, or 10 year systemic coronary risk of >10%) achieve an LDL cholesterol treatment goal of <70 mg/dl. For patients with high cardiovascular risk (markedly increased single risk factor or 10 year risk score >5% to <10%), the LDL cholesterol reduction was <100mg/dl.⁷

The first statin, Lovastatin, was developed by *Albert, chen* and others at the Merck research laboratories in a fermentation broth of *Aspergillusterreus* and Lovastatin was marketed in 1987. The other statins marketed were simvastatin (1988), Pravastatin (1991), Fluvastatin (1994), Atorvastatin (1997), Cerivastatin (1998) and Rosuvastatin (2003) respectively.⁸

II. STATIN REGIMEN

Statins are useful in both primary and secondary prophylaxis of hypercholesterolemia. Their main indications are Coronary heart disease, acute coronary syndrome, transient ischemic attack, stroke etc. Statins used in their maximum doses can reduce LDL level by 30-50%. And statin therapy can reduce the 5 year incidence of major coronary events and stroke significantly irrespective of the initial lipid level.⁹

High-dose statins are effective in reducing cardiovascular outcomes in patients with stable CHD and acute coronary syndrome. The clinical utility of statins depends on its tolerability profile and on the capacity to reduce LDL-C values. If a drug is well tolerated, treatment compliance and efficacy will increase.¹⁰

Patients with clinical evidence of ASCVD and those with LDL-cholesterol > 190 mg/dl are treated with high intensity statin therapy, which reduces LDL-cholesterol by >50%. Others are treated with moderate intensity, wherein a decrease by 30 to 50% is expected (Table 1).¹⁰

Table 1: Statin regimen

Statins	High intensity statin therapy (mg/day)	Moderate intensity statin therapy (mg/day)
Atorvastatin	40 to 80	10 to 20
Rosuvastatin	20 to 40	5 to 10
Simvastatin	-	20 to 40
Pravastatin	-	40 to 80
Lovastatin	-	40
Fluvastatin	-	extended-release: 80 40 twice a day
Pitavastatin	-	2 to 4

Table 2: Different statins have different effects and properties.¹⁰

Statins	Precautions	Cardiac benefits	Additional dosing information
Atorvastatin	Antacids may decrease plasma concentrations. Use with oral contraceptives may increase the hormones' duration of action. May elevate serum digoxin levels. Grapefruit juice in large amounts (> 1 quart per day) has been shown to elevate serum concentrations and increase area under the curve, therefore, increasing the possibility of myopathy.	The ASCOT-LLA study showed a 36% reduction in fatal CHD and non-fatal MI in patients with average cholesterol levels given 10 mg of atorvastatin.	No modification of dosage is necessary for patients with mild to moderate renal insufficiency.
Rosuvastatin	Coadministration of Rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). When prescribing Rosuvastatin and warfarin together, determine baseline INR prior to starting Rosuvastatin and monitor frequently to ensure that no significant alterations of INR occur. Consider dosing modification when prescribing Rosuvastatin for patients of Japanese and Chinese descent, due to a 2-fold elevation in median exposure.	Lipid and Apo lipoprotein ratios have been shown to be strongly associated with CAD risk in previous studies. Pooled-data analysis showed that 12 weeks of Rosuvastatin 10 mg resulted in clinically important reductions in lipid ratios that were significantly greater than those resulting from the treatment with the usual starting dose of atorvastatin, simvastatin, or pravastatin	No modification of dosage is necessary for patients with mild to moderate renal insufficiency (CLcr>30ml/min/1.73m2). Dosing of Rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily in patients with severe renal impairment (CLcr<30mL/min/1.73m2) not on hemodialysis. Coadministration of an antacid (aluminum and magnesium hydroxide combination) with Rosuvastatin resulted in a decrease in plasma concentration of Rosuvastatin by 54.
Simvastatin	May elevate serum digoxin levels. Large amounts of grapefruit juice (> 1 quart per day) reported to significantly increase serum concentrations, increasing myopathy risk. Protease inhibitors, nefazodone and amiodarone increase risk for Rhabdomyolysis. Concurrent use with verapamil may increase risk of myopathy	The Heart Protection Study demonstrated a 25% reduction in the first event rate for major coronary events, stroke and revascularizations in patients given simvastatin 40 mg daily. ¹³ A significant reduction in all case mortality for primary prevention was shown with simvastatin in the 4S trial	For patients taking concurrent immunosuppressive agents, it is recommended that simvastatin is initiated at 5 mg daily and does not exceed 10 mg daily. For patients with severe renal insufficiency, begin therapy with 5 mg daily and monitor closely

Various epidemiological data clearly indicates that elevated low-density lipoprotein (LDL) cholesterol (LDL-C) is a major cause of CHD. The recent clinical trials strongly demonstrate that LDL-lowering therapy reduces the risk of CHD. The NCEP-ATP III 2001 guidelines suggested that starting drug therapy for patients with an LDL-C above 100 mg/dL and CHD or CHD equivalents and considering an additional goal of LDL below 70 mg/dL, especially in very high-risk patients (Table 3).¹⁰

Table 3: NCEP-ATP III LDL cholesterol objectives and outpoints drug therapy according to risk categories.

Risk category	LDL-C objective	LDL-C level at which to consider drug therapy
High risk: CHD or CHD risk equivalent (10-year risk >20%)	<100 mg/dL (2.58 mmol/L); optional goal <70 mg/dL (1.82 mmol/L) in very high risk patients	≥100 mg/dL (2.58 mmol/L); <100 mg/dL (2.58 mmol/L) consider drug options
Moderately high risk: 2 or more risk factors (10-year 10 year risk 10 to 20%)	<130 mg/dL (3.36 mmol/L)	≥130 mg/dL (3.36 mmol/L); 100 to 129 mg/dL consider drug options
Moderate risk: 2 or more risk factors (10-year risk <10%)	<130 mg/dL (3.36 mmol/L)	≥160 mg/dL (4.13 mmol/L)

Lower risk: 0 to 1 risk factor	<160 mg/dL (4.13 mmol/L)	≥190 mg/dL (4.91 mmol/L); 160 to 189 mg/dL consider drug options
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III. BENEFITS OF STATINS

Effects on LDL, HDL and pleiotropic effects

Statins competitively inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase which act as the catalyst in the cholesterol synthesis pathway (mevalonate pathway).¹¹

By the inhibition of HMG CoA reductase, decreases the de-novo synthesis of hepatic cholesterol and which leads to hepatic LDL cholesterol receptor up regulation. This will increase the LDL cholesterol uptake and thereby decrease the plasma LDL cholesterol levels.¹¹ Statins also reduce the triglycerides in some patients by decreasing the rate of VLDL synthesis and increase its clearance. They also increase Apo lipoprotein A1 (ApoA1) and HDL cholesterol levels. But its mechanism is unclear.¹¹

Statins improves the inflammatory response, endothelial function and smooth muscle proliferation by its pleiotropic effects. These are the important factors to be considered in the pathogenesis of atherosclerosis.¹²

The endothelial dysfunction associated risk factors are the more conventional treatment for atherosclerosis. Endothelial dysfunction occurred as a result of the damage caused by reactive oxygen species which promotes the release of transcription factors, growth factors, pro inflammatory cytokines and chemokine and adhesions molecules.¹³ Statins reduces the morbidity and mortality in patients with coronary artery disease and hyperlipidaemia along with improving endothelial function, decreasing the plasma concentration of tumour necrosis factors (TNF).¹⁴

C-reactive proteins have a direct role in the pathogenesis of atherosclerosis. Statins also reduce the C-reactive proteins level.^{15,16}

Primary cardiovascular prevention

The major risk factors for the development of cardiovascular diseases such as coronary, cerebrovascular and peripheral vascular disease are age, obesity, dyslipidaemia, hypertension and diabetes mellitus. 80% of the population with age of 75 years or older have clinically manifested cardiovascular disease.¹⁷

It is important to prevent the cardiovascular disease by using the optimum dose of statin. The meta analysis from randomized clinical trials of statin therapy shows a marked reduction in cardiovascular events in primary and secondary prevention population.¹⁸ And also one Cochrane found that statin therapy is safe and effective for primary prevention in all age group patients.¹⁸

Secondary cardiovascular prevention

Coronary heart diseases are the leading cause of death in elderly patients. The third National Cholesterol Education Program Adult Treatment Panel recommends that the continuous use of statins intensively lowers the lipid levels in elderly patients after Myocardial infarction.¹⁹

The use of statins for secondary prevention of cardiovascular events was commonly accepted in young and elderly patients. A Hierarchical Bayesian meta-analysis by the American College Of Cardiology found that statin reduces all-cause mortality in elderly patients.²⁰ Statins reduces all-cause mortality by 22%, coronary heart disease mortality by 30%, non-fatal MI by 26% and stroke by 25% in patients with coronary heart disease documented.²⁰

A population based study of commonly used statins found that statin reduces the incidence of recurrent AMI or death among elderly patients. Also the study shows that the effect of each statin in the secondary prevention of cardiovascular disease was similar when compared with Atorvastatin.²¹

IV. ADVERSE EFFECTS

Statins are important in the treatment of various disease conditions like dyslipidaemias, atherosclerotic events, coronary heart disease etc. They are also responsible for a wide range of adverse events like mild gastro-intestinal

disturbances, life-threatening conditions such as Rhabdomyolysis. The side effects are described in terms of events per person year of treatment when considering the risk-benefit profile of statin therapy as described by the NLA. Based on the data available, excluding Cerivastatin, current statins on the market have a very good safety profile and a proven reduction in mortality due to cardiovascular disease.²²

Musculoskeletal

Musculoskeletal side effects are associated with almost all statins. Myalgia is the most common and associated with a risk in creatinine kinase.²³ The condition in which creatinine kinase greater than the upper limit of normal (10×) along with the features of myoglobinuria, renal impairment and serum electrolyte abnormalities known as Rhabdomyolysis, which is the most severe musculoskeletal form observed.²³ Nevertheless, statins associated severe musculoskeletal side effects are low in newer statins.²⁴

Different clinical trials showed the different musculoskeletal side effects of statins. The Cochrane database systematic review reported the musculoskeletal side effects. A total of 37939 patients underwent randomization. Out of this 3551 participants developed the symptoms of myalgia (9.4%). Rhabdomyolysis occurred very rarely (0.01%).²⁵ The large cholesterol treatment trialists' meta-analysis found that the rate of Rhabdomyolysis was 1 per 10000 regardless of the group of statin and placebo. The Rhabdomyolysis risk is slightly higher in intensive statin groups (4 per 10000) compared with less intensive statin groups (2 per 10000).²⁶

From various clinical trials and meta-analysis, it is concluded that the overall benefits of statins overweigh the small risk, musculoskeletal side effects. The mechanism behind the statin associated myopathy is unclear. Although some patient related factors and drug related factors involves in the mechanism.²⁷

Hepatic dysfunction

Patients on statins have elevated liver enzymes. The patients who have known liver conditions should monitor the patient's liver values over the course of their statin therapy.²⁰ Some literatures related to statin hepatotoxicity suggests that the asymptomatic elevation in the aminotransferase occurs as a result of high dose of statin. But the rate of occurrence is low (3%). Statins are not recommended for the patients with active liver diseases.²⁸

The Cochrane data based systematic review of more than 18 trials examines the role of statin therapy in primary prevention reported the elevation in hepatic enzymes with statins.²⁵

Diabetes mellitus

Statins increases the risk of diabetes mellitus by disrupting the insulin signalling pathways there by affects the pancreatic beta cell function and increase the insulin resistance.²⁹ In a study, 27% patients were diagnosed to have diabetes mellitus in a statin taking population which is higher compared to that

of placebo. Even though the effects of statin in heart attack, stroke and all-cause mortality is more.³⁰

Several trial data, meta-analysis and observational studies show that the new onset diabetes mellitus risk is associated with statin use. So it is important to monitor the new onset diabetes mellitus association with statin duration, intensity and cumulative dose.³¹ A national wide observational cohort study conducted by American Heart Association on statin use and new onset diabetes concluded that there was a time and dose dependent association of statin use with an increasing risk of new onset diabetes mellitus.³¹

V. CONCLUSION

Statins, HMG CoA inhibitors, are effective in the treatment of hypercholesterolemia for primary and secondary prevention of cardiovascular and cerebrovascular diseases. Atherosclerotic events are the major risk factor for these conditions. So the use of statins reduces the atherosclerosis by inhibiting cholesterol synthesis. Statins will reduce the LDL cholesterol concentration in the blood depends on the doses / intensity of statins. A high intensity statin reduces >50% of LDL cholesterol. Apart from the benefits, statin exert some adverse effects like myalgia, Rhabdomyolysis, liver enzyme elevations etc. However, the benefits of statins outweigh the adverse effects.

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