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SM Analytical and Bioanalytical Techniques

Review Article

Statin-updates

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Abstract

Cholesterol common part of cell membrane is transported in blood in form of particles containing lipids and proteins called lipoproteins. Level of Low Density Lipoprotein (LDL-c) associate with Cardio Vascular Disease (CVD) and level of High Density Lipoprotein (HDL-c) are related with a lower risk of such disease. Many medications are available for lipid lowering therapy and statin is first line drug. From the introduction of Lovastatin in 1978 to pitavastatin till now, the research has not been finished in findings of beneficial to adverse events of statin. Many face to face clinical studies was reported to explain statin role in lipid profile modification, pleiotropic effects, pharmacodynamic and kinetics, lipophilicity, adverse event reporting, dose/dosage recommended etc. This review gives the update of such trials.

Background

Hyperlipidemia is the condition which reflects the abnormal elevated level of any or all lipids and or lipoprotein in blood [1]. According to National Commission on Macroeconomics and Health (NCMH), Cardio Vascular Diseases (CVD) is most prevalent cause of death in both developing as well as developed countries (Chronic diseases and their common risk factors WHO Oct 2005). South Asians around the globe have highest rates of Coronary Artery Disease (CAD). It has been estimated that around 62 million patients will have CAD by 2015 in India and out of these; 23 million would be patients younger than 40 years of age [2]. Currently many formulations are commercially available containing active ingredient that function to decrease circulating LDL and Triglyceride or to increase HDL. Drugs aimed at lipid reduction in Indian Health Service (IHS) national pharmacy and Therapeutics committee report include HMG COA reductase inhibitors (Statin), fibrates and niacin [3].

Currently seven statin are available towards the treatment of CVD. cerivastatin (baycol) was withdrawn and Atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), pravastatin (Pravachol), fluvastatin (Lescol) rosuvastatin (Crestor), pitavastatin (livalo) are seven statin available in market. Issue of Statin safety came into force in 2001 after withdrawal of cerivastatin from market [4], which caused many risk patients to discontinue other safer statin. Rosuvastatin and pitavastatin are recently introduced, Pitavastatin was approved by FDA on 2009 [5] and many clinical trials showed significant and continuous elevations of HDL-c, glomerular filtration rate, reduction in LDL-c, long term safety and comparable effects with other statins.

In march 2004 Dr.sidney M.Wolfe, Director Of Health research group of public citizen, filed a petition with FDA to remove rosuvastatin from market because at approved doses it carries to a high risk for severe myopathy with kidney failure and other types of kidney damage. The FDA responses to Dr. Wolfe is 36 page document that (posted FDA website) [6] indicated that rosuvastatin does not pose a risk of muscle toxicity and serious renal injury greater than that of other approved statins. Furthermore the report of Alsheik Ali [7] reexamines and interpreted adverse event reports obtained by the FDA and found that rosuvastatin is accompanied by more adverse event (myopathy, renal failure, proteinuria etc) than other statin. But FDA indicated that adverse drug events reports alone doesn't independently justify in making clinical decision and didn't call for removal of rosuvastatin from market. This all indicates its safe up to approved doses.

All above issue made patients who taking other statin to discontinue and put themselves at greater risk of heart problems. So one should keep in mind that, adverse events report can be useful for identifying signals of drug toxicity and less useful for quantifying relative risk of different drugs of same class. The statins are safe and that they reduce risk for coronary events in higher risk patients. Statins like all drugs can have side effects and care must be taken in their use. The researchers should engage in more clinical studies and in developments of novel technologies for new drug delivery system to address these challenges.

Disease and drug background

The goal of primary prevention in cardiovascular care is to prevent the development of atherosclerosis leading to coronary heart disease before a clinical event such as a myocardial infarction can occur. Primary prevention through improved control of risk factors, life style changes and secondary prevention through drug therapy in different risk categories, proposed medication were issued by Adult Treatment Panel III (ATP III) guidelines (2001 & 2004) for cholesterol testing and clinical management [8]. Preventing coronary events before they occur is a strategy that could significantly benefit the public. A study calculated that full adherence to existing ATP III guidelines could prevent CHD deaths [9] and another suggest that strategies for primary prevention are not being fully implemented during routine screening, treatment for other health conditions and diagnosed only after cardiovascular symptoms have developed [10] and another method, Framingham risk scoring calculator is one of a number of scoring systems used to determine an individual's chances of developing cardiovascular disease within 5 or 10 years and used to determine drugs to lower blood pressure and cholesterol levels. A number of these scoring systems are available online.

Many of clinical trial evidences has demonstrated that statin therapy is effective in reducing LDL-C levels and in lowering the risk of coronary events and mortality among all other lipid lowering drugs. Statins are drugs that can lower our cholesterol. They work by blocking the HMG-COA reductase enzyme that is rate limiting step in cholesterol production. Statins may also help our body reabsorb cholesterol that has built up in plaques on our artery walls, preventing further blockage in our blood vessels and heart attacks. Studies carried out once the introduction of drug candidates like Scandinavian simvastatin survival study (4s), heart protection study for simvastatin, PRVE-IT-TIMI 22-for pravastatin and atorvastatin, treating to New targets study, WOSCOPS, AFCAPS/Tex CAPS), ASCOT-LLA, SPARCL, JUPITER proved both primary and secondary effects of the statin [11-19].

Statin has two types

Type-1 (Figure 1A) statins that have substituted decalin-ring structure that resemble the first statin discovered, mevastatin are classified as type 1 statins due to their structural relationship. Statins that go to this group are Lovastatin, Pravastatin, and Simvastatin.

Type-2 (Figure 1B) statins are fully synthetic and have larger groups linked to the HMG-like moiety is referred to as type 2 statins. viz. Fluvastatin, Cerivastatin, Atorvastatin, Rosuvastatin, pitavastatin.

One of the major differences between the type 1 and type 2 statins is the replacement of the butyryl group of type 1 statins by the fluorophenyl group of type 2 statins. This group is responsible for additional polar interactions that cause tighter binding to the HMGR enzyme [20].

Pravastatin is extremely hydrophilic, fluvastatin has intermediate characteristics, lovastatin, simvastatin, atorvastatin and cerivastatin are hydrophobic. Atorvastatin, cerivastatin, fluvastatin and pravastatin are administered as active compounds (acid form). Lovastatin and simvastatin are administered as inactive forms (lactone), which have to be enzymatically hydrolyzed to generate active forms [21]. This lower Tri-Glycerides (TG) improves endothelial function decrease platelet aggregation and reduces inflammation. Side effects include myopathy (with or without Creatine Kinase levels) increased aminotransferase, poly neuropathy, memory loss; sleep disturbances, impotence, gynecomastia, lupus like syndrome and pancreatitis.

Pharmacokinetics

Statins show several clinically significant pharmacokinetic differences. Lipophilic drugs are transported by passive diffusion and others by active carrier mediated transportation. Percentage of absorption ranges from 30-90 %. Systemic bioavailability ranges from 5% with simvastatin, lovastatin to more than 80% with pitavastatin. The extent of first-pass metabolism and variations in the activity of intestinal and hepatic transport proteins contribute to these

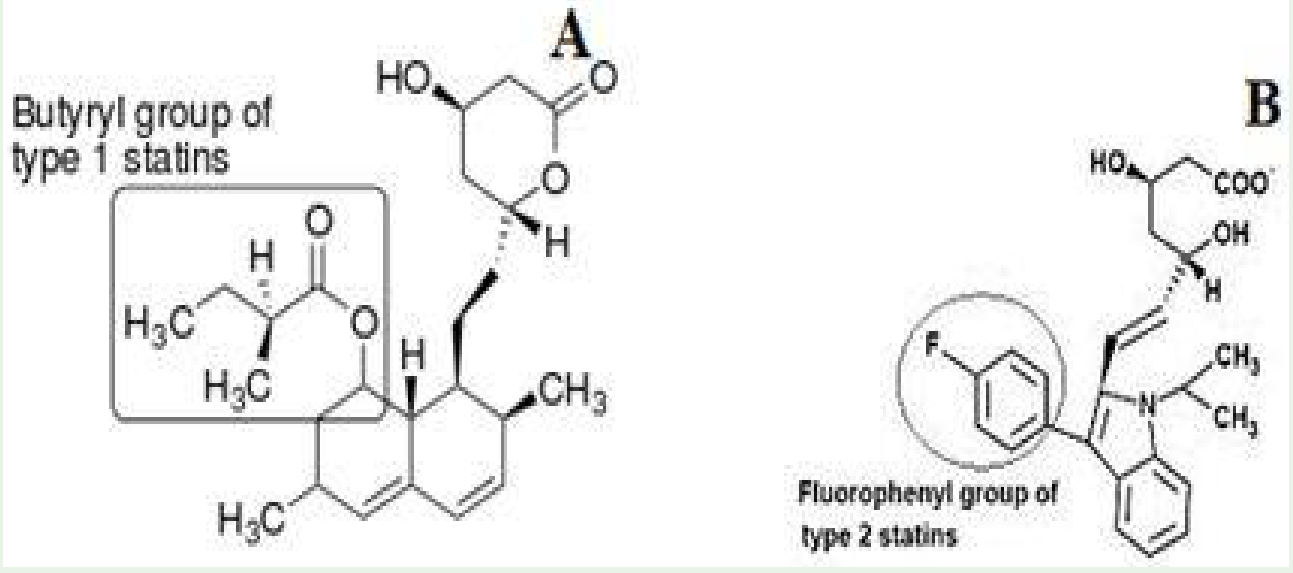

Figure 1: Type of statins -Type 1 (A) & Type 2 (B).

differences in bioavailability. Most statins have a short half-life of about 1-3 hr except for rosuvastatin which has highest half life of about 19 hrs. Furthermore, protein binding varies from more than 95% for pitavastatin, simvastatin, atorvastatin and lovastatin to 50% for pravastatin.

Pharmacokinetic differences arise from variations in the metabolic and excretory pathways. Lovastatin, simvastatin and atorvastatin are substrates for CYP3A4, fluvastatin and rosuvastatin are metabolized by CYP2C9 and pravastatin by sulfation [21]. The cyclopropyl group on the pitavastatin molecule, which accounts for the potency of the molecule, appears to 'protect' pitavastatin from metabolism by CYP3A4. Therefore, pitavastatin appears to have less potential for interactions compared with statins extensively biotransformed by CYP3A4 [21,22]. The pharmacokinetic properties can understand by table 1 [23-29].

Pharmacodynamic

LDL- reduction

According to drug class review 2008 completed by Oregon Evidence based practice center, patients requiring LDL-c reductions of upto 35% will achieve results with any of the statins and who require upto 35% to 50% reduction will meet the goal with atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more and simvastatin 20 mg or more [30].

HDL increases

When statins are provided in doses that reduced LDL-c, similar percent increases in HDL can be attained. Many studies were reported to indicate HDL elevation and few reported that statin have no effect on HDL increase. Two such studies compared simvastatin and atorvastatin and found no difference in one case and other found simvastatin to be superior [30].

Cardiovascular mortality

Controlled trials in patients with coronary disease reveal that atorvastatin, lovastatin, pravastatin and simvastatin can lower cardiac events, stroke and mortality from all causes [31]. Similar effect was seen with rosuvastatin and fluvastatin [32,33].

Comparison of lipid profile of different statin

Though the statins share a common mechanism of action (blockade in cholesterol synthesis), they have some percentage deviation in lipid reduction because of different functional group attached to different statin. According to one study the LDL-C reductions may be estimated to range from 18% to 55%, in this fluvastatin have lower effect of 22% and rosuvastatin have higher reduction percentage of 55%. HDL-C elevations range between 5% to 15%. Triglycerides can be reduced by 7% to 30% in which pitavastatin have 32% and pravastatin have 11% of reduction [29,34]. The results of the Lipid Treatment Assessment Project (L-TAP) 2, a multinational survey of lipid goal attainment in individuals being treated for dyslipidemia indicate that a larger proportion of patients are reaching their lipid targets compared with a decade ago [35].

Primary and Secondary Prevention

As mentioned above since the statins have beneficial effects in changes of lipid level, this is attributed to primary prevention of certain cardiac diseases and also in decreasing mortality in people with pre-existing CVD (secondary prevention). Statins also have pleiotropic (anti-inflammatory, antioxidant) effects that further justify their use in the primary and secondary prevention of cardiovascular disease. Many clinical trials justify the primary and secondary prevention of statin in coronary events.

With the initiation of statin clinical trials mentioned earlier [12-20] a meta-analysis showed that the overall relative risk reduction is 21% [36]. Statins conferred a vital and great reduction in cardiovascular events including stroke among hypertensive patients who are not typically deemed dyslipidemic (primary prevention) [18]. Pretreatment with statins seem to reduce clinical severity in patients with stroke, especially among diabetics [37,38]. High-risk hypertensive patients with CAD, adults having diabetes with additional risk factors, patients with coronary artery disease and low HDL should be treated with lifestyle measures and a statin [39-41].

Heart protection study [42] and SPARCL STUDY in 2006 [43] confirmed that Statins are expected to reduce stroke risk by stabilizing and/or repressing plaque (Secondary prevention). Statins are recommended in patients with coronary heart disease or symptomatic atherosclerotic disease, patients with ischemic stroke atherosclerosis to lower cholesterol levels to LDL<100 [7,8,42,43]. While all statin are

Table 1: Pharmcokinetic parameters of statins.

S.No	Name/Dose/ DosageSolubility/ Nature	Absorption Administered as/% Absorption	Bioavailability	Distribution			Metabolism			Excretion		
				Cmax ng/ml	Tmax hrs	% protein binding	% Hepatic metabolism	Metabolites	Pharmcogenetics	t1/2	Urine	Bile
1	Atorvastatin/10-80mg/ oral/lipophilic/synthetic	Active –OH form/30	~14	27-66	2-3	98	>70	Active	3Aa4	14	<5	70
2	Fluvastatin/20-80mg/ oral/Lipophilic/Synthetic	Active –OH form/98	~24	44.8	0.5-1.5	68	68	Inactive	2C9	1.2	6	90
3	Lovastatin/20-80mg/ oralLipophilic/Microbial	Lactone prodrug/31	~5	10-20	2-4	95	>70	Active	3A4	3	10	83
4	Pravastatin/1080mg/ oralHydrophilic/ Semisynthetic	Active –OH form/37	~17	45-55	0.9-1.6	50	66	Inactive	Sulfation	1.8	20	71
5	Simvastatin/5-80mg/ oralLipophilic/ Semisynthetic	Lactone prodrug 65	~5	10-34	1.3-2.4	95-98	78-87	Active	3A4	2	13	58
6	Rosuvastatin/5-40mg/ oralHydrophilic/ Synthetic	Active –OH form/ 50	~20	37	3	90	90	Active-minor	Limited	19	10	90
7	Pitavastatin/1-4 mgLipophilic/Synthetic	Active –OH form/80	~80	26.7	0.5-0.8	96	NA	Inactive	Limited	11	<2	great

measured to have same mechanism of action, they fluctuate in their pharmacodynamic and pharmacokinetic characteristics. Difference in each drug and every dose of drug from same class, will reflect minor percentage of deviations in the therapeutic effect so it is obvious that confronting each statin is preferable than comparing clinical trials [43]. In one study of HIV-1 infected patients who received either Rosuvastatin 10mg/day or pravastatin 40 mg/day for dyslipidemia, it was concluded that Rosuvastatin was more effective than pravastatin 40 mg/day on LDL-c and triglyceride levels [44].

Similar effect which is called class effect was observed with hypercholesterolemic patients with metabolic syndrome who received different Statin doses (i.e.,) 10 mg/day rosuvastatin, 20 mg/day atorvastatin, 40 mg/day simvastatin, and 40 mg/day pravastatin [45].

Bellia et al., [46] compared rosuvastatin and simvastatin in 29 patients with type 2 diabetes and mild untreated dyslipidemia. Findings on insulin-resistance and endothelial dysfunction revealed that Rosuvastatin was less effective than simvastatin at improving endothelium-dependent vasodilation, without affecting insulin-resistance.

Hall et al., [47] were aimed to assess the reports that rosuvastatin 10 mg was more efficacious than simvastatin in treatment of hyperlipidaemia. They observed no superiority of either treatment in achieving European society of cardiology 2003 lipid targets and rosuvastatin 10 mg lowered mean cholesterol effectively than simvastatin 40 mg.

In Comparison of the efficacy of rosuvastatin 20mg/day Vs atorvastatin 80 mg/day in reducing apolipoprotein B, apolipoprotein A-1 ratio in patients with acute coronary syndrome, it was found that rosuvastatin lowered the ratio more than atorvastatin at one month and no such difference at three month period [48].

A randomized controlled trial was conducted in 857 patients with either primary hypercholesterolaemia or combined dyslipidemia who had administered pitavastatin 2-4 mg Vs simvastatin 20-40 mg to reduce LDL-c and for achievement of National Cholesterol Education Program Adult Treatment Panel (NECP) and European Atherosclerosis Society (EAS). Results showed that reduction in LDL-c observed with pitavastatin 2 mg was 39 % and with simvastatin 20 mg was 35% and moreover pitavastatin 4 mg showed similar effects on all lipid parameters to simvastatin 40 mg. So the final report evidenced that pitavastatin is an efficacious treatment choice than simvastatin which have equivalent effects in lower dose than simvastatin [49].

Sansanayudh et al., [50] compared efficacy and safety of low-dose (1 mg) pitavastatin versus atorvastatin (10 mg) in hundred numbers of patients with hypercholesterolemia and concluded that even if pitavastatin 1 mg in daily dose was not as efficient as atorvastatin 10 mg daily at lowering LDL-C and TC levels, it may be an option with cost-saving benefits but without a considerable decrease in therapeutic benefit or increase in adverse events.

Athyros VG, K. Tziomalos et al., [51] were assessed whether statin therapy was safe and effective for patients with coronary heart disease and abnormal liver tests through post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study population and interpreted positive results. Corresponding to above study, SPARCL TRIAL in 2010 showed that CHD risk can be reduced by atorvastatin 80 mg/ day placebo therapy in patients with recent stroke or transient ischemic attack regardless of stroke subtype [52].

CARDS randomized placebo-controlled trial examined Patients with type 2 diabetes, kidney outcomes and cardiovascular disease with atorvastatin 10 mg/day or placebo. They observed its effectiveness and decrease in CVD in patients those with and without a moderately decreased estimated glomerular filtration rate [53].

JUPITER trial [54] hypothesized that people with elevated high sensitivity C-reactive protein (inflammatory biomarkers) levels but without hyperlipidemia might benefit from statin therapy and reduced CVD events in women with a relative risk reduction similar to that in men had been observed . These findings were supported by a Meta analysis in 2010 with 6801 women and 11 001 men [55].

Everett et al., [56] justified the JUPITER trials with 17,802 subjects and concluded that Rosuvastatin 20mg daily reduces partially the incidence of ischemic stroke among men and women with low levels of low-density lipoprotein cholesterol levels that are at risk because of elevated levels of high-sensitivity C-reactive protein.

Secondary analysis of above trial (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) evaluated primary prevention in older persons with elevated C-reactive protein then, low to average low-density lipoprotein cholesterol levels and reported that rosuvastatin reduces the incidence of major cardiovascular events [57].

Chronic Kidney Disease (CKD) is related with an amplified risk of Cardio Vascular Disease (CVD). The part of Lovastatin 20 mg or placebo for the principal prevention of acute cardiovascular events in patients with CKD and on kidney function failure in persons without CVD had been analyzed by Post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study with 5,608 men and 997 women without CVD. The result showed that it was effective for the primary prevention of CVD in patients with CKD, but was not effective in decreasing kidney function failure in persons with no CVD [58].

The safety and efficacy of statin administration is not clear in the first-line therapy of Acute Coronary Syndrome (ACS) patients and FACS-trial aimed to assess the effect of statin treatment. It failed to prove the effect of fluvastatin given as first-line therapy of ACS on serum markers of inflammation and plaque instability. But reported that fluvastatin was safe and it might reduce cardiovascular event rate that supports immediate use of a statin in patients admitted for ACS [59].

Efficacy and safety of intensive statin therapy in patients with a recent cardiac event with longer-term follow-up (4.8 years) had not been evaluated until the IDEAL trial. This post hoc analysis of 999 patients who had a first acute Myocardial Infarction (MI)<2 months with atorvastatin 80 mg/day (intensive therapy) versus simvastatin 20 to 40 mg/day (Standard therapy) provided support for the approach of placing patients on intensive statin therapy and maintaining the high dose over the long term, beyond 2 years. Also statistical command was smaller than that of the PROVE IT trial (2 year study-short term) (53and decrease in relative risk observed at 5 years was constant with that in the 2-year follow-up of PROVE IT study [60].

The children are having different body mass, pharmacokinetic and pharmacodynamic activities for which many rules were used to calculate the dose required for particular disease. So research should not be limited to young or elderly and be required to extend to children. Recently few studies were carried out for the evaluation of the statin effect choosing children as subjects.

One such study evaluated efficacy and safety of rosuvastatin therapy with dose 5, 10, or 20 mg once daily in 177 pubertal children, ages 10 to 17 years with familial hypercholesterolemia were studied and reported reduction in LDL-C by 50%. However only 40% attained the harmony LDL-C target of <110 mg/dl, reflecting these patient's high baseline LDL-C levels [61]. One clinical trial which is at end of its stage have the primary objective to establish the efficacy of once-daily rosuvastatin in dropping LDL-C from baseline (Day 0) to the end of the 12-week double-blind treatment period in children and adolescents (10-17years) with Heterozygous familial hypercholesterolemia [62].

Another trial designed pilot study to find the dosage and short-term efficacy of simvastatin (5 mg,10 mg) and potential adverse events in children from 4 years to 17 years with chronic kidney diseases and interpreted that the short-term the combination of diet and simvastatin was effective in lowering hyperlipidemia in children with renal disorders [63].

Pleiotropic effects of statin

The effects that may emerge during preclinical or clinical studies in drug development, but more often not discovered long after the therapeutic agent is marketed as in statin, recognized as adverse side effects that may be beneficial is pleiotropic effect. In addition to hypolipidemic action the statin have non lipid modifiable pleiotropic effects like anti inflammatory, antiproliferative and antithrombotic ones, improving endothelial dysfunction, decrease left ventricular mass, blood pressure, left ventricular fibrosis, cardiac valve sclerosis, arterial fibrillation, and mortality in patients with diabetes and renal disease, ischemic heart disease [64-68]. Many clinical trials carried out for this beneficial effect that brought both positive and negative effect.

Kruger et al., [69] studied cohort of bacteracemia patients and found a significantly lower incidence of mortality with statin therapy. Matching this result the systemic review included total of 20 studies examined the effect of statins on mortality in patients with sepsis demonstrated protective effect of statin therapy for various infection comparing placebo patients [70]. Dodesh et al evaluated patients over age of 40 with severe sepsis exposed to statin therapy and showed lower mortality compared with patients with no statin [71]. Two more studies [72,73] were observed with a mortality reduction after simvastatin but not with atorvastatin that might be related to higher lipophilicity of simvastatin.

In contrary to above beneficial effect Fernandez et al., [74] analyzed data from 438 patients receiving ventilation for more than 96 hrs and found that hospital mortality was significantly higher with statin therapy. Yung et al., [75] conducted a retrospective study and found no difference in mortality between statin and non statin groups and lack of benefit might be due to difference in patients' disease mix, severity of illness or statin type or dose. Some studies reveal that statin is having no effect on infection. Fell strom et al., in their randomized double blind study of 2773 patients with cardiovascular event undergoing haemodialysis received Rosuvastatin 10 mg Vs placebo and monitored for safety and efficacy [76]. Another two studies [77,78] by Kjekshus and Tavazzi L et al., [79] of 5011 and 4574 patients with heart disease received Rosuvastatin 10 mg Vs placebo assessed for adverse events and reported the composite of cardiac event as outcome. The study by Newman with 2838 diabetes patients who received atorvastatin 10 mg assessed for adverse event and reported positive events. 5245 Patients with renal disease were studied by study of heart and renal protection with 20 mg of simvastatin and major atherosclerosis events were reported [80] and above all study showed that statin have no effect on risk of infection.

Statin also has favorable effect on patients with variable disease. James shepherd et al investigated with 10,001 patients with CAD, 1501 with diabetes, the effect of intensive lipid lowering with high dose atorvastatin and concluded marked reduction in Cardio vascular events [81]. Accepting above study Berne and siewert-Delle compared rosuvastatin with atorvastatin in type 2 diabetes for reduction of LDL-c and found rosuvastatin patients reached 65% goal comparing atorvastatin [82]. Since 2006 population based observational studies had reported association between statins and reduced risk of pneumonia in diabetes patients [83,84] and sepsis in chronic kidney disease [85].

Other issues still require resolution including the dose effect relationship whether the mechanism of action is related to pleiotropic or lipid lowering effect of statin and whether the observed effect is class effect or an individual Statin effect [86]. Ongoing clinical trials address these findings [87-90].

Adverse events

Though statin have primary and secondary prevention in lipid lowering it exhibit some adverse events which has been proved by clinical trials. Statin inhibit the enzyme HMG-CoA reductase at a stage early in the mevalonate pathway. This pathway generates an array of other products in addition to cholesterol, such as heme-A, co enzyme Q10 and isoprenylated proteins those have fundamental roles in cell biology. Cholesterol itself is not a final product but also midway to set of additional fundamental products to health and welfare such as sex steroids, corticosteroids, bile acid and vitamin D, several of which been shown to be affected with statin administration leading to adverse events [91-93]. Reduction in co enzyme Q10 key for mitochondrial anti oxidant and electron transport carrier lead to additional adverse events [94].

Adverse events in muscle

Statin cause in some cases muscle breakdown-(Rhabdomyolysis) release protein myoglobin into blood stream which damage kidney. Statin-induced myopathy may be multifactorial, the consequence of impaired oxidative phosphorylation signals transduction, gene transcription, structural protein formation [95-97]. Abnormal fat oxidation or mitochondrial dysfunction reduced sarcolemmal cholesterol and isoprenoids is core mechanism in statin myopathy for muscle fiber apoptosis [98-101].

A European study prospectively identified patients with muscle complaints with statin use and concluded statin cause clinically important muscle symptoms without inducing a marked creatinine kinase elevation [102].

In one case Rhabdomyolysis occurred 2-4 days after statin initiation or addition of other drugs to lipid lowering treatment and reported that Rhabdomyolysis may present as fatigue, low back pain or shortness of breathe and also reported multiple organ failure including hepatotoxicity [103-107].

Statin induced myopathy in competitive cyclist, dermatomyositis (inflammatory myopathy), myositis, myonecrosis, dysphagia, dysarthria, dyspnea and rippling muscle disease comprising stiffness, myalgias were also reported [108-113].

Another study Of 96 patients in French pharmacovigilance database reported that 63 patients exhibited tendonitis and 33 reported tendon rupture with statin use [114]. Accepting above study statin related tendinopathy has occurred in two more cases [115,116]. Since statin have both prooxidant and antioxidant effects, either effect may dominate in individual which cause statin to effect muscle, kidney [117]. In addition to this being inhibitor of cholesterol essential for vitamin.D synthesis statin indirectly cause vitamin-D deficiency leading to Muscle related problem-myopathy and mitochondrial defects [118,119].

Adverse events related to dose/LDL reduction

Recommended therapeutic doses, which typically reduce LDL-C by 30% to 45%, are atorvastatin 10 to 20 mg, fluvastatin 40 to 80 mg, lovastatin 40 mg, pitavastatin 1 to 4 mg, pravastatin 40 mg, rosuvastatin 10 mg and simvastatin 20-40 mg [120]. Choosing a statin and a dosage that can correct each phase of the patient's dyslipidemia is vital in achieving optimal outcomes.

In the 6-week Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial, 2431 patients with hypercholesterolemia were randomized to 1 of the 4 most commonly prescribed statins at varying doses [121]. At a dose of 20 mg/day, treatment with rosuvastatin resulted in significantly greater reductions in LDL-C (52%), as compared with atorvastatin (43%), simvastatin (35%), and pravastatin (24%). These 4 statins also had varying effects on HDL-C and triglyceride levels.

Although some text advises to LDL-C and aggressive statin therapy, the USFDA states all statin should be prescribed at lowest dose that achieves goals of therapy [122-126].

Silva et al in their Meta analysis studied that intensive dose therapy with statin lead to discontinuation due to AES [122,127] but moderate dose statin do not lead to more discontinuation due to adverse events than placebo [128].

Some studies have showed Creatine Kinase elevation, LFT transminase alanine aspartate aminotransferase elevation but some do not show Creatine Kinase elevation related to dose [122,127,128].

One Meta analysis of RCT said that LDL-C reduction was not associated with Rhabdomyolysis risk [129] but inversely related to cancer risk. However lesser LDL-C reduction for same dose may signal a less favorable oxidant/antioxidant effect [130], which may be associated with higher risk of statin adverse event [131].

The Cholesterol Treatment Trialists' meta-analysis of 14 randomized trials involving 90,056 participants confirms the efficacy and safety of lipid-lowering with statins [132]. Reduction in LDL-C reduces all-cause mortality by 12%, with corresponding reductions in nonfatal myocardial infarction (26%), major coronary events (23%), revascularization (24%), and stroke (17%) and there was no evidence of increased risk of cancer or rhabdomyolysis with statin therapy [133].

SEARCH trials of 12,064 subjects were randomized to 20 to 80 mg simvastatin there were 49 cases of definite myopathy in simvastatin 80 mg group and 2 in 20 mg groups [134].

Rosuvastatin 20 mg increased Diabetes mellitus in JUPITER trial [54] and frequency of occurrence of proteinuria is dosing related [135]. The different candidate from same class produces therapeutic effects at different doses due to variation in their pharmacokinetic and pharmacodynamic properties.

Drug Interaction

With other lipid lowering drugs: Although combinations of statin with all lipid drugs may pose risk, there are comparatively few reports of Rhabdomyolysis with statin in combination with niacin [136-139].

Hazardous factors

A nested control studies of a cohort of new users of lipid lowering medications found odds of Rhabdomyolysis for those over age 65 through impaired clearance, increased polypharmacy with more potential drug interaction [140-142].

Drug levels may be increased by impaired hepatic clearance i.e., fatty liver is associated with reduced CYP3A activity and hepatic steatosis (Mitochondrial dysfunction) [143,144].

This alone or with amiodarone has aggravated hypothyroidism. (Both produce through mitochondrial toxicity), hyperkalemia, lactic acidosis and melas syndrome [145-149].

Adverse events related to impaired mitochondrial function by statin

Even if cholesterol is the target of statins, CoQ10 also is affected which produced within the mevalonate pathway and is involved in the electron transport during oxidative phosphorylation in mitochondria [96-100]. A reduction in CoQ10 levels has been recommended to intervene statin myopathy as an end result of its proposed ill effect on mitochondrial function [99,150]. Statins have been associated with a decrease in CoQ10 synthesis that leads to impaired oxidative phosphorylation and impaired energy production and increased carbohydrate metabolism [96-100].

Oh et al., [151] linked the risk of statin myopathy with genetic impairment in co enzyme Q10 production. Parallel to this study another with simvastatin 80 mg Vs atorvastatin 40 mg Vs placebo showed reduced muscle co enzyme Q10 and mitochondrial DNA [152].

Muscle and brain are affected in co enzyme Q10 deficiency mitochondrial syndromes. One trial with subjects of younger and older age showed findings are evidence for mitochondrially based effect medication and trials in Alzheimer samples advocate possible trends to cognitive benefits, although those appeared to fritter away at one year [153-155].

Statin is toxic to muscle satellite cells, the stem cells for muscle that have regenerative potential [156-158]. Statin reduce co

enzyme Q10 that protects against neuro-degeneration retarding Parkinson's in human. Low LDL-C has been linked to risk of Parkinson [117,159,160] and Amyotropic Lateral Sclerosis (ALS) or ALS like syndrome leading to muscle weakness reported based on pharmacovigilance data [114,117].

Usually cholesterol carries anti oxidant, essential for protection against polyneuropathy and disturbances in synthesis cause the peripheral neuropathy. Many case reports showed multiple mononeuropathy [161] with statin which related to impaired mitochondrial function.

Gynecomastia [162], sexual dysfunction [163], testicular pain [164] associated with statin use. Since cholesterol is the biochemical precursor to testosterone and other sexual hormone. Obstruction in production by statin leads to this abnormality. In one study it was reported to improve sexual benefits of sildenafil in some subjects through endothelial function benefits which may rely [165] on anti oxidant effect of statin predominate over pro oxidant effect [166].

High dose statin leads to proteinuria and hematuria and renal tubule toxicity [120,167]. But it has reported to have reduced proteinuria in some groups and may not do so in some other groups [168,169]. It has been proved that muscle mass correlates with creatine and statin can reduce muscle mass, but it is unclear that extent to which the creatine reduction was driven by benefit to kidney Vs harm to muscle [170].

Observation study showing women on statin are more aggressive [171], the suggestion linked to this cause may be low serotonin, altered omega 3 and 6 ratio, impaired all energetic and oxidative stress [172,173]. This offers the possibility that benefits may dominate in some persons through benefits to endothelial function, flow and anti inflammation reliable with bidirectional effect suggested in randomized clinical trials [174].

Dyspnea, interstitial lung disease, pleural effusion are pulmonary related adverse events, reason attributed for this is statin accelerate aging effect on diaphragm mitochondrial cellular respiration affecting major muscle of breathing[175-178].

Heart muscle like other muscle may be affected in myopathy. One observational study reported that statin adversely affected cardiac diastolic function that was partially reversed by co enzyme Q 10 administration and statin lead to average improvement in heart failure or left ventricular systolic function in some studies [179,180].

Statin produced heart block, lactic acidosis and hyperkalemia [150,181-183]. Mitochondrial dysfunction induced high lactate which causes heart block.

RCT showed increase in haemorragic stroke with low cholesterol this may due to statin anti thrombotic and anti plate effect [184,185].

Metaanalysis of randomized trials in samples of generally middle age persons show average neutrality of statin on cancer and one affirmed an interaction on cancer risk [186,187]. Lower LDL-c signal reduce coenzyme Q10 and anti oxidant (transported by cholesterol) carrying capacity may be attributed for above risk.

Autoimmune risk, pancreatitis, contact dermatitis, Ichthyosis, phototoxicity, dry mouth, ulcerative colitis, Psychiatric symptoms like depression, paranoia. anxiety, psychosis are some other rare reported for statin adverse events and reason is reduction of vitamin D essential for muscle strength (through decreased production of cholesterol [188-204].

Hydrophilic/Lipophilic Statin Effects

Statin necessary for dyslipidemia and ischemic heart disease encompass many subtypes based on structural difference, resulting in different pharmacokinetics and efficacy. While different types of statins have different efficacy no standard exists for selecting a statin in clinical background. Statins are classified into hydrophilic and lipophilic groups based on tissue selectivity. Hydrophilic statin such as pravastatin and Rosuvastatin have less tissue assimilation except for liver and less side effects due to lower dependence on the cytochrome p450 enzyme [205]. Several studies have compared lipophilic, hydrophilic statins in clinical surroundings [206-210].

In a sub analysis of multicenter study for aggressive lipid lowering strategy by HMG-CoA reductase inhibitors in patients with acute myocardial infarction (MUSASHI AMD DATABASE), hydrophilic statins were exposed to be greater to lipophilic statin for preventing new Q waves and reducing cardiovascular events in normocholesterol patients with AMI, then size of inflammation was reduced by hydrophilic statin compared with lipophilic statin [208]. In study of patients with coronary artery disease, no significant difference in incidence of all cause events was observed with respect to statin lipophilicity [209]. Another study comparing the two types of statin cognitive impairment associated with statin use in 24,595 patients was significantly different in the 2 types of statin where the lipophilic but not hydrophilic statin induced cell death in gynecological cancers expressing high levels of HMG-CoA reductase and enhanced phagocytosis in human peripheral blood.

All studies compared the statin but didn't mention which statin is preferred for patients with a acute myocardial infarction. The study by Min Chul Kim et al in comparison of clinical outcomes of hydrophilic and lipophilic statins in 1124 patients (317-rosuvastain or pravastatin-hydrophilic; 807-atrovastatin or simvastatin or pitavastatin- lipophilic) with acute myocardial infarction (AMI) concluded that although short-term cardiovascular outcomes were better in lipophilic statin, one year outcomes were similar in patients with AMI with both the statin. So the type won't influence one year outcomes in patients with AMI [210].

FDA Recommendations for Statin Use

In march 2010, FDA was reviewed the safety of simvastatin from large clinical seven year trial [134] and Adverse drug event reporting system relating to myopathy and concluded that patients taking 80 mg simvastatin have increase risk of muscle injury compared to patients taking lower doses of other drugs of same class. In august 2011 FDA [211] has revised the drug labels for simvastatin, Simcor and Vytorin to include the new dosing restriction for the use of 80-mg dose of simvastatin. (i.e.,) patients who are unable to adequately lower their level of LDL-C on simvastatin 40 mg shouldn't be given the higher 80 mg dose of simvastatin; instead they should be placed on alternative LDL-c lowering treatment. FDA also included new contraindications for using simvastatin with certain medicine which is given in Table 2. This also recommended to patients and health care professionals to report if patients experienced muscle pain, tenderness or weakness, dark or red coloured urine or unexplained tiredness.

Table 2: FDA recommendations for statin use.

New Simvastatin label (215)	New lovastatin label (216)
Contraindicated with simvastatin:	**Contraindicated with lovastatin:**
Itraconazole	Itraconazole
Ketoconazole	Ketoconazole
Posaconazole (New)	Posaconazole
Erythromycin	Erythromycin
Clarithromycin	Clarithromycin
Telithromycin	Telithromycin
HIV protease inhibitors	HIV protease inhibitors
Nefazodone	Boceprevir
Gemfibrozil	Telaprevir
Cyclosporine	Nefazodone
Danazol	
Do not exceed 10 mg simvastatin daily with:	**Avoid with lovastatin:**
Verapamil	Cyclosporine
Diltiazem	Gemfibrozil
(Note: These drugs are contraindicated with Simcor as Simcor is only available with 20 mg or 40 mg of simvastatin.)	
Do not exceed 20 mg simvastatin daily with:	**Do not exceed 20 mg lovastatin daily with:**
Amiodarone	Danazol
Amlodipine (New)	Diltiazem
Ranolazine (New)	Verapamil
	Do not exceed 40 mg lovastatin daily with:
	Amiodarone
Avoid large quantities of grapefruit juice (>1 quart daily)	Avoid large quantities of grapefruit juice (>1 quart daily)

In Feb 2012 the FDA has improved important safety label changes for the statins [212] which include following

- Labels have been revised to remove the need for routine periodic monitoring of liver enzyme (Serum alanine aminotransferase-ALT) in patients taking statin. This conclusion was made after findings of National lipid association's Liver Expert panel and safety task force recommendations [213,214], Drug induced liver injury network (DILIN) liver injury severity scale (reported to AERS database) and DILIN and Acute Liver failure study Group (ALFSG) [215], the ineffectiveness of routine periodic monitoring of liver enzyme in detecting the serious liver injury.
- FDA reviewed AERS database and clinical trial reports and stated information about adverse events like increased blood sugar and glycosylated hemoglobin (HbA1c) levels and reversible cognitive effects has been added to statin labels [13,55,216-221].
- Lovastatin label has been extensively updated with new contraindications that can increase the risk of muscle injury subsequent to the label revision to the simvastatin containing products in 2011 (Table 2) [134,221].
- Patients should be aware of unusual fatigue or weakness, loss of appetite, upper belly pain and dark coloured urine or yellow of the skin or whites of eyes.
- Health care professional should perform liver enzyme tests before initiating statin therapy and should be discontinued in case of liver problem.

In Feb 2010 Rosuvastatin was at first indicated for use as an adjunct to diet to increase HDL and reduce total cholesterol, LDL, apolipoprotein B, non-HDL cholesterol and triglyceride levels in patients with hyperlipidemia and mixed dyslipidemia.With data support from JUPITER trial (19-n) the FDA made approval to rosuvastatin , the first statin to receive the additional indication for primary prevention of cardiovascular disease in healthy adult patients who have an increased risk for CVD, high C-reactive protein levels and the presence of one additional CVD risk factor.

Conclusion

Many studies found that the statin facilitate lower risk and higher risk patients in cardiac related issue and these same studies revealed that statin cause various adverse effects wherein muscle weakness is major one. The statin not only inhibit liver from making cholesterol and also other organ especially brain which is vital for its activity. Since it inhibit production of Co enzyme Q 10 which is key for muscle health producing energy for body, indirectly inhibit the heart function which is largest muscle in our body and statin supposed to be doing just opposite for which it is indicated. Statin found to turn on gene

atrogen-1 and activates it to destroy key muscle protein. This result in side effect cardiomyopathy which is a known adverse effect but often not reported in statin therapy. The combination of Co enzyme Q 10 deficiency and atrogen-1 activation is the actual reason behind this problem. The value of statin in preventing heart disease has been clearly recognized. Their benefit is uncertain, but they need to be taken with concern and knowledge of their side effects. The statins because of its few demerits shouldn't go into the withdrawn dug list. The researchers have to concentrate in developing novel drug delivery system to circumvent the demerits of statin. Thereby the drug might be used safely in patient group.

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