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Effect of Statins use on Cardiac, Diabetes, Kidney and Liver Function – An update

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ABSTRACT

Researches done on the use of statins during the last two decades have shown conflicting results in their effects on DM, Cardiac, liver and Kidney functions. Six forms of statins are being prescribed as a preventive measure to reduce the incidence of cardiovascular morbidity and mortality; but statin use have also shown alternations in DM, liver and Kidney function. The latest observations relates to cancer prevention/induction. Statins prescriptions are done mostly for elderly patients in order to reduce lipid profile mostly Total cholesterol and LDL levels. Studies have shown that statins use affects muscular function, induce prediabetes, and alter liver enzymes and affects mitochondrial functions. They may also interact with other medications. Some merits shown in the use of statins include prevention of MCI and strokes. Among the statins used, atorvastatin was found to be very beneficial with minimal side effects with greater beneficial function in maintaining other organ functions. This review article highlights the research findings on the use of statins and its merits and demerits during the last two decades. More clinical trials with large population are required to establish the type of statins to be required for each type of patients and clinical conditions.

Keywords: CVD, CHD, Statins, DM, MCI, AES.

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INTRODUCTION

Patients treated with statins may have adverse effect (AEs) in many disease conditions. Available evidence supports that statins use may be associated with mitochondrial dusfunction and underline many non-muscle AEs such as congnitive loss, neuropathy, pancreatic and sexual dysfunction. Low awarness exists among physicians about such AEs when statins are used. Hence physicians have a role to play in treatment decisions, modification and at improved quality of patient care and to reduce patient morbidity. It is important for every physician to note down the AEs that may occur when statins are prescribed for patients and the risk/ benefit ratios of statin in low risk populations should be noted down and closely monitored. (Golomb BA, Evans MA (2008); Kmietowicz Z (2014).

Unless one make access to raw research data, it will be difficult to understand the AEs due to statins use since some studies have shown mirror image data between statins use and placebo patients since the rate of AEs may vary many fold. Such observations should be analysed by an expert third party.(Wise J (2014).Cochrane review done in 2011 has revealed the role of statins therapy in primary prevention of Cardio Vascular Disease (CVD) has predicted a risk ratio of 1.03 for muscle pain due to the use of statins compared to placebo.(Taylor F et al., 2013).

In clinical trials, very low AEs of statins use have been predicted compared to placebo making clinical interpretation difficult. The greatest AEs was noted in patients using atorvastatin compared to those using fluvastatin. Similar odds of AEs were observed in patients using simvastatins, pravastatins and lovastatins. Some clinical trials have predicted non urgent AEs such as mylgia and elevation in liver functions in about 1/3rd of populations. A greater odds AEs exists between statins use and placebo.(Gøtzsche PC., 2013).

A significant number of patients are being referred to tertiary care facilities and specialists since the proportion of patients with significant statins associated AEs are on the increase. In order to prevent cardiovascular risks, all patients should be treated optimally, safety and confidently with statins and it should be the priority and ultimate goal of the treating physicians.(Mancini GB, Baker S, Bergeron J, et al.,2011).

Some clinical trials have predicted that statin attributable symptoms, although asymptomatic showed elevation of about 0.4% in liver enzymes. Minority of patients have reported some symptoms genuinely due to statins comparable to non-statins users. Development of new onset Diabetes mellitus (DM) was observed due to statins use and placebo and such events occur in just 1 in 5 new cases. However, higher statins use may induce a detectable effect, but the proportions is

variable. In some cases, the asymptomatic elevation in liver enzymes may be due to higher dose of statins.(Finegold JA et al., 2014).

Statins and Cardiovascular Disease:

Experimental and epidemiological studies have firmly established that CVD is the leading cause of morbidity and mortality worldwide and elevations in blood lipid levels are the major risk factor. Good association exists between CVD and increase levels of Low Density Lipoprotein cholesterol (LDL-c). The current strategies for reducing LDL-c level is based on the use of statins, bile acid sequestrates cholesterol absorptions, fibrates, nicotinates or omega-3 fatty acids. All these may have various mechanism of actions. As of date, the widely prescribed lipid lowering agents are the 3-hydroxy-3-methylglutaryl-CoA (HMG-COA) reductase or statins. (Egom EE et al., 2016) Uncontrolled Type 2 Diabetes Mellitus (T2DM) is the leading cause for acquiring CVD, but the role of statin to prevent such incidence has not been addressed adequately. A study has shown significant reductions in LDL-c and prevention of CVD when atorvastatin 10mg /day was used (Helen M Colhoun et al., 2004).

Extensive research have been carried out on the effect of long term use of statin, to assess the risk of major cardiovascular events such as Coronary Heart Disease (CHD), Myocardial Infraction (MCI) and strokes. The risk of statin is based on the Individual vascular events, satisfactory reduction of LDL-c and an increase in High Density Lipoprotein Cholesterol (HDL-c). The serious effects identified due to long term consequences of using statin are myopathy, increase in Creatinine Kinase of Muscle-Brain (CK-MB), onset of DM and haemorrhagic strokes. Large scale studies from randomised trials are required to clearly rule out adverse effects on the long term use of statin. Such studies will definitely find out the merits and demerits of long term statin use. Under use, however may lead to increased side effects leading to CVD, MCI and stroke and in case of inadvertently stopping the use of statin mid way may be devastating.(Collins et al., 2016).

The available forms of statins which are approved for use in the US include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pravastatin. Use of different forms of statin have revealed statistically significant differences between simvastatin and pravastatin. Dose level comparison has revealed an increase in transaminases levels when atorvastatin, fluvastatin, lovastatin and simvastatin were used. Simvastatin at higher dose may increase CK-MB. Although adverse effects of statin therapy are not common, statins are not a factor for cancer induction, but higher odds risks were observed for onset of DM. Among the various statins simvastatin and pravastatin have been found to be safe and tolerable compared to other statin forms. (Naci H, Brugts J, Ades T 2013).

Statins have been prescribed extensively for elderly people in order to reduce the risk associated with CVD morbidity and mortality even when they have some risk for CVD. Long term use of statins may induce drug-drug interactions (DDIs) when an individual takes other drugs along with the statins. Under such conditions, myopathy and hepatoxicity may develop. The causes of DDIs include poly pharmacy and pharmacogenetics variability. Hence patients receiving multiple drugs along with statin must be regularly monitored for adverse cardiac function. Clinicians should be aware of such effects when statins are used so that patients under their treatment used to be fine tuned for lipids lowering thereby providing the patient's evidence based cost and safe clinical support. (Bellosta, S; Corsini, A 2012).

Use of atovastatin has shown significant reduction in mild MCI, Cardiac revascularization and has shown beneficial effect in the combined end point of preventing cardiac death as well as reduction in liver enzymes irrespective of the age of the patient. However, in patients aged 65 – 78 years, serious adverse effects were observed compared to people <65 years. The efficacy and safety of aggressive lipid management could be achieved in older CHD patients when atorvastatin is used. (Koren MJ et al., 2009). Use of atorvastatin for just 3 months has shown significant reduction in lipids, oxidised LDL-c, and an increase in adiponectin. However, no significant correlation observed between adiponectin and LDL-c, Triglycerides (TGs) and HDL-c. Further, no side effects such as myalgia and gastro—intestinal disorders were observed. All these observations were seen in Ischaemic Heart Disease (IHD) patients treated with atorvastatins. (MiyagishimaKet al., 2007).

In a study atorvastatin has shown changes in LDL-c, Total Cholesterol (TC), TGs, HDL-c, VLDL-c, apoIioprotein-B and some patients have achieved target figures as per National Cholesterol Education Program (NCEP) guidelines levels after just 6 weeks of treatment. Atorvastatin has shown greater reduction compared to simvastatin. All treatment groups have shown decrease in LDL-c / HDL-c ratio compared to baseline levels. A higher proportion of patients showed higher reduction with treated atorvastatin than simvastatin. (Karalis DG et al.,2002).

To prevent CVD in subjects with T2DM, statin is the drug of choice. A statement from American Diabetic Association (ADA) as well as American Heart Association (AHA) recommends the use of statin along with life style therapy irrespective of baseline lipid levels in all patients above 40 years even when there is no overt CVD. It further stress the use of statin for 40 – 75 years old adult with DM regardless of their CVD risk if LDL-c levels becomes >70mg /dL. (Bo Kyung Koo, 2014).

Although studies have established the effects of atorvastatin on serum lipids levels but its effects on other serum biomarkers remain uncertain. Some outcome on the effects of atorvastatin therapy

on many parameters such as lipid profile, glycemic control, liver enzymes have been observed in patients with Ischemic Cerebrovascular accident without clinical evidence of DM, heart failure, renal failure or hepatic disorders. (Roxana Sadeghi et al., 2014). All atorvastatin drugs are inhibitor of HM-G-CoA reductase. Placebo controlled trials have shown significant dose dependent reduction in LDL-c, TC and TGs. Alternate day dosing of atorvastatin is an efficacious and safe to daily dosing to achieve the above target. (Jafari M et al., 2003).

Statins are the generally prescribed drug and confer the benefit to a wide range of patients in the primary and secondary prevention of CHD. Greater than 25% sometimes more in the reduction of TC and >30% in LDL-c were recorded when a fixed dose of simvastatin at 40mg, atorvastatin at 10mg and rosuvastatin at 5 & 10 mg respectively were used. (Edwards JE, Moore RA,2003). Drug like fluvastatin, pravastatin, lovastatin and simvastatin have only 30%, 50%, 60% and 85% effects in lowering TC, LDL-c, non-HDL-c and RLP in the fasting and fed state compared to atorvastatin at the same dose in the same group of patients (Schaefer EJ et al., 2004).

In hyper cholesterolemic patients, atorvastatin shows beneficial effect in reducing HDL-c and apolipoprotein-B, but significant increase in fasting insulin and HbA1c and such observations was found to be in consistent with IR and glycemia. (Kwang Konkoh et al.,2010). Rheumatic Heart Disease (RHD) is a well-known inflammatory process leading to progressive calcification and thickening of leaflet overtime. However, slowing down the development of RHD retrospective by statins therapy is still controversial. Studies have shown that medical therapy is beneficial for patients with aortic stenosis as well as for Rheumatic Value Disease (RVD). However, randomized clinical trials have shown negative results. Medical therapy may play a role in controlling RHD affecting the valves. (Nalini M. Rajamannam et al., 2009).

Irrespective of statins use, TGL/LDL-c ratio was found to be constant. All statins may decrease TGL levels but more so in hypertriglyemic patients. Increasing statins dose was found to decrease hyperlipidaemia. Simvastatin was found to be more effective compared to atorvastatin (Evan A Stein et al., 1998).

Decreasing cholesterol with statin was found to reduce the incidents of stroke especially in high risk populations. Compared to Aspirin and anti hypertensive treatment, use of statin is a better option to prevent stroke. Studies based on increasing HDL-c and decreasing LDL-c based on TGL lowering drugs are needed. (PierreAmarenco et al.,2009).

Past research did not establish a relation between hypertriglyceredemia and CHD: however, recent studies have firmly established that hypertriglyceredemia has an independent risk factor for coronary risks and to reduce such risk lowering of LDL-c and increasing HDL-c should be the

target in treatment modalities. In men with established CHD, Gemfibrozil use may benefit in reducing coronary risk (Paul Cullen, 2000).

For patients with hypercholesteraemic and dysbetalipoproteinemia use of statins therapy should be advocated for reducing LDL-c. Many clinical trials have shown the efficacy of statins in decreasing VLDL-c. (Henry N Ginsberg, 1998).The cholesterol lowering effect of statins was due to pleiotropic property and it shows benefit in preventing CAD beyond the reduction of LDL-c levels. More clinical trials are required in establishing a firm relationship between statin use and CAD. (Davignon J , 1999).

In a study, among the various statins tested, atorvastatin was significantly more effective in lowering LDL-c and increasing HDL-c and simvastatin showed effect in decreasing TGs. The order of effect in LDL-c is 33, 50, 60 & 85% for fluvastatin, pravastatin, levastatin and simvastatin of the efficacy of atorvastatin. (Ernst J Schaefer et al., 2004). Statin use also decreases the mortality rates in patients with CAD and this observation was based on decrease in ventricular arrhythmias. Statin therapy was found to be very effective on recurrent ventricular arrhythmias linked to CAD particularly after implant (John H. Chiu et al.,2005).

Early use of pravastatin is recommended to reduce the incidents of late potentials following thrombolytic therapy in AMI and also useful in reducing ventricular arrhythmias in hospital patients. These beneficial effects were based on the prevention of early MCI, plague stabilization as well as regulation of platelets functions (MeralKayikcioglu et al., 2003).

The first action of statins is to reduce LDL-c thus preventing the progression to coronary atherosclerosis; however no relationship has been established between changes in HDL-c. It is generally assumed that statin therapy is associated with regression of coronary atherosclerosis by decreasing LDL-c and increasing HDL-c by 7.5%. However more studies should be done whether these benefits shows reductions in clinical events and improved outcome (Stephen J. Nicholls, et al., 2007).

Inhibitors of statins have shown to alter endothelial dysfunction. The autoimmune balance in sympathoexcitory state in the CNS may be due to Nitrous oxide. (Rainer U et al., 2003). Both potential harm and benefit from statin therapy have observed in severe heart failure patients, however solid relationship have not yet been established in clinical trials. Propensity score analysis predicts 48% lower risk of death. Further investigations on the potential benefits of statins in patients with severe HF appears to be warranted. (DariushMozaffarian, et al.,2004).

Conflicting opinions still exist on the use of statins about the risk of developing DM. Although some risk have been found, its effect is very small compared to its benefits in reducing CHD.

Hence clinical practise in treating CHD with statin therapy should not be changed (NaveedSattar, et al.,2010).

It is well known that DM is a risk factor for CVD. Many trails have predicted that statin therapy will accelerate DM since statin may affect multiple pathways of glucose metabolism. Many clinical trials done with statin did not adequately addressed this issue. The US task force recommended statin use for primary prevention of CVD. As of date the number of patients receiving statin therapy has increased exponentially. (YogitaRochlani,et al.,2017).

Aspirin was the first block buster used as the preventive CVD drug, but now it is replaced by statins. However, majority of patients are prescribed both as a better preventive measure for CVD. As of date, the state of art medicine for preventive measures for CVD are statin and aspirin both of which have many intriguing properties. Majority of placebo control trails proved the benefits of statin in reducing MCI, CHD and overall mortality. However, much is left to understand since studies done so far have predicted that only 40% of patients treated with statin showed reduction in cardiovascular event. (Thomas F, 2008).

Dyslipidaemia is a major CVD risk factor. Some studies have proved that treatment with fibrate, statin or other lipid lowering drugs prevents primary and secondary CV risk. Generally all lipid lowering drugs have side effects; however fibrate statin combination therapy affords clinical benefits that are superior to treatment with fibrate alone. Hence it is important to carefully monitor the treatment. (Choi HD, et al.,2015).

Statins and Diabetes Mellitus:

Studies have revealed new onset DM in patients using statins therapy. Some form of statin affect the secretion of insulin by combined effect on calcium channels in β-cells of pancreas either directly or indirectly. They may also reduce the glucose transporter 4 response leading to hyperglycaemia and hyper insulinemia. They may also decrease the levels of coenzyme Q10 and some phosphatases which may lead to reduced intercellular signalling, Some forms of statins may cause decrease in circulating leptin levels leading to β-cell inhibition which affects insulin secretion and hence assessment of onset of DM is an important aspects.(Brault, Marilyne et al., 2014).

The increased risk associated with statin therapy in T2DM patients are due to major risks already present in such patients and it accounts to approximately to 25% of such cases compared to placebo. In patients with major T2DM risk factors, CVD have been prevented due to statin therapy as it controls cholesterol level, the chief architecture of CVD inducer. It is further stressed that life

style management and other preventive measures to be adapted to control the risks associated with both T2DM and CVD in all patients receiving statins therapy.(Maki KC et al., 2018).

Although studies on the use of statin have been done mostly to control glycemic level in DM on CVD, no clear conclusions have not yet been shown. In all statin trial studies, although it predicted the increase in new onset DM, the rise is clearly outweighed by the CVD benefits observed in all statin trials, but such trials have recommended the monitoring of glycemic control after commencing statin therapy. Studies have established that atorvastatin is the most widely used statin worldwide, however rosuvastatin was found to be more efficacious. But these observations may be against the background of the effects of other statins on the metabolism of glucose in non-diabetic patients. (Ahmed Abbas et al.,2012).

Since T2DM shows dyslipidaemia, statins have a major role in preventing the long term complications in DM and is mainly recommended for those DM patients with normal LDL-c levels. It is chiefly accomplished by the down regulation of glucose transporters by the statins. Although statins can have diabetogenic risk, they have long term beneficial effect over weighing its risks. However, in elderly DM patients with metabolic syndrome, the risk for DM increases and hence statin use must be undertaken with more caution. (Bharti Chogtu et al., 2015).

Hyperlipidaemia is a common finding in all T2DM patients. Although statins are widely used to control hypercholesterolemia, only atorvastatin has been reported to show adverse effect on glucose metabolism. It may increase HbA1c, but not fasting TGs and such effect was found to be higher in non obese group of DM patients. Such effect was based on atorvastatin action of alternating adipocyte maturation which impairs glucose tolerance (M. Nakata, et al., 2006).

Statins are said to reduce cholesterol biosynthesis as well as pharmacodynamics effects. Statin therapy has shown increasing concern about to incidents of raised DM cataracts as well as frequent muscular side effects. Based on the low cost of statin, those concerns may have little effects. (Cesare R.Sirtori, 2014).

Statins and Kidney Diseases:

The frequent cause of death found in CVD patients are due to early Chronic Kidney Disease (CKD) which was found to be similar to the one that occurs in CAD. People with CKD not requiring dialysis may benefit by using statins and about 20% of people have shown improvement both in CVD and CAD. However, it has been found out that statin related effects on stroke and kidney function is uncertain. Statin treatment may have an important role in the primary prevention of Cardio Vascular events and mortality in people who have CKD. (Palmer SC et al., 2014).

Statins are found to interact with other medications and it vary due to the form of statin used and therefore it is important for patients and clinicians to be aware of common interactions of statins with other medications. Recent studies predict that statins use may induce Acute Kidney Injury (AKI). Further recent observational data predicts that statins use may contribute to memory loss and confusion, but it has not been established in randomized controlled trials. Hence it is important to review the common effects of statin used so as to strengthen the understanding between patients and clinicians. (Katz DH et al., 2014).

Clinical trial outcome in certain implant patients the effect of statin therapy was assessed immediately after stenting and stent length was found to be an independent predictor of minimal diameter. (Dirk H Walter et al.,2000).

Statins and Liver Disease:

Recently it has been shown that patients with Non Alcoholic Fatty Liver Disease (NAFLD) may have greater cardiovascular risk. Substantial evidences are available to show that CVD is an important cause of morbidity and mortality in such patients and hence aggressive treatment with lipid lowering drugs like statins is the need of the hour. Statins therapy are not suitable for decompensated and Acute Liver Failure (ALF) patients due to contraindications for lipid lowering therapy. Hence patients with liver disease may not get benefits due to statin therapy since the risk involved is more than the benefit in case of serious liver injury. (Tandra S et al.,2009).

Many recent research findings suggest that statin exhibit chemo preventive action against cancer which was contrary to previous observations of cancer over the carcinogenicity of statins. However, some studies have shown associations between statins use and cancer incidents overall or as a particular organ. Strong research evidence is lacking on the effect of statin on cancer prognosis or prevention except some consistent evidence that statins are associated with reduced risk of advance / aggressive prostate cancer. However, without clinical trials, use of statins to prevent other forms of cancer should be undertaken with caution as studies have not established its safe use. Further exploration of clinical trials needs to be undertaken for the safe use of statins for prevention of Cancer & CVD. (Denise M. Boudreau et al.,2010).

Statins intake and dose must be cautiously implemented in the prevention of CVD by observing in the reduction of both TC and LDL-c. However, statins use has become the subject of male infertility. (Hanae Pons-Rejraji et al., 2014) Some pre-clinical trials have shown that inhibitors of HMG –CoA are said to positively affect bone remodeling balance. Some observations and secondary analysis study involving lipid lowering trials have shown consistent results about the effect of statins on bone mineral density and fracture risk. (Henry G. Bone Douglas et al., 2007).

Many studies have firmly established the benefits of statin therapy to reduce cholesterol and its fractions. However, its benefits in renal function maintain versatile. All statin therapy studies have significant improvement for CVD, but not so with patients with diabetes and hypertension and kidney disease. Mean reduction in albuminuria and protein urea where observed due to statin therapy. Hence, statin therapy may be beneficial for population with CVD & DM linked to renal impairment. (Sabrina Sandhu et al.,2006).

One of the most adverse effects of statins is linked to hepatic dysfunction. Discontinuation of statins, with some cases are based on fear of serious hepatic adverse effects, however the trends has now changed based on actual risk, monitoring and safety of use in those with pre-existing hepatic disorders. It is also recommended that statins use should not be avoided in patients with Nonalcoholic fatty liver disease (NAFD) and Nonalcoholic steatohepatitis (NASH), cirrhosis as well as CLD. Physicians judgement on the use of statins is more important. (Jimmy JoseStatins, 2016).

Recent studies have demonstrated that stain use will reduce liver enzymes especially both Alanine Transaminase (ALT) & Aspartate Transaminase (AST). However, no solid conclusion has been arrived. Trials with large number of patients only would be able to establish the beneficial effect of statins for patients with liver problem especially NASH. Since statin use could improve the adverse outcome of other conditions such as hyperlipidaemia DM, Metabolic Syndrome, their use in patients with NASH may be justified (Eslami L, et al.,2013).

Statin therapy is generally used for improving hyperlipedemic status associated with both primary and secondary CHD. It may also be useful for other diseases not linked to hyperlipidaemia. Current clinical trials have shown the efficacy and safety of statins in a variety of other diseases like rheumatoid arthritis (RA), Venus thromboembolism, liver disease, Polycystic Ovary Syndrome (PCOS) and age related muscular degeneration. However, more evidence must be made available by large scale studies before accepting the beneficial effect of statin for the above mentioned diseases. (Nicola FerriAlberto Corsini,2014).

Statins and Muscular problems:

In clinical practice approximately 10 – 25% of patients treated with statin experienced muscle problems; however such predictions are rarely reported. The % of problems were found to be higher for statin treated patients compared to placebo group. However, the difference is small predicting high background rate of nonspecific muscle problems in both groups. Statin associated myalgia could not be distinguished in such a study. (Ganga HV, et al.,2014).

Although, statin therapy reduces the risk associated with CVD, some side effects such as muscle cramping, soreness, fatigue, weakness rapid muscle breakdown all of may which leads to death. However, the mechanism of which statin affect muscle problems has not yet been well documented. Exercise and physical therapist have a role in identifying such a side effect. (Stephanie L, et al.,2010).

Studies show that stain treatment may cause mitotic effects ranging in severity from myalgia's to rhabdomyolysis. Recent studies suggest that statin is associated with the development of a unique form of immune mediated myopathy. It is therefore important to be aware of these consequences of statin therapy since such patients may require immune suppressive therapy. (Mammen AL, Amato AA, 2010).

In some large clinical trials statin associated muscle problems where predicted only in about 1 – 5% of patients but it may be more. Observational studies shows a prevalence of around 10% although muscle problems may start any time during statin therapy but it usually starts after six months. The identified risk factors are multiple drug treatment, alcohol abuse, hypothyroidism and family history of muscle problem associated with statin therapy. The benefit of Co- enzyme Q10 has not yet been conclusively proved if recurrent elevation of Creatinine Kinase (CK) along with muscle problem is identified, better to switch over to other cholesterol lowering drugs. (Janssen SP, et al., 2010).

A study has shown that stain therapy are associated with skeletal muscle complaints myositis, rhabdomyolysis, increase in CK levels myalgia, muscle weakness and cramps. The mechanism of statin induced muscle injury has not yet well established. Recent evidence suggests that statin reduce the production of small regulatory proteins that are important for myocyte maintenance. (Thompson PD, et al., 2003).

CONCLUSIONS:

This review article gives a condensed summary of the effects of various forms of statins therapy to reduce the incidence of mostly cardio vascular morbidity and mortality. Among the six brands of statins currently used each brand has its own effect on the prevention of CVD notably by reducing the lipid profile levels. However, prolonged use of statins have shown conflicts results on the induction of prediabetes, elevation in liver enzymes, alterations in kidney functions, mitochondrial, muscular and sometimes cancer induction. The alterations in the functioning of organs like liver and kidney and cancer may be due to its interactions if other drugs are being taken along with statins. Although conflicting results are available from clinical trials, the merits of statins use

outweigh its demerits and dose adjustment of statins based on the patient's clinical conditions may overcome the side effects of statins in altering other organ functions. More clinical studies are required with large populations to establish the use of a suitable brand of statin for each individual based on his/her clinical condition.

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