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# Statins Overview: Balancing Benefits, Risks, and Safety in Special Populations

**Rajeswari M*, Sechana K, Sushmitha A, Sai Nath R, Sarika Goud B , Aravind B**

**Corresponding Author: Rajeswari M*
*Department of Pharmacy Practice, Malla Reddy Institute of Pharmaceutical Sciences, Hyderabad , India*
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**Abstract**
**Introduction:** Satins have cholesterol lowering, anti-inflammatory, anti-oxidant, Plaque stabilizing capacities and are indicated for treatment of MI, Stroke, Hyperlipidemia by FDA. Satins are used for various conditions in different populations. This article revies the usage of statins in patients with comorbid conditions according to the respective Standard Guidelines, adverse effects specific to the patient population and strategies recommended to mitigate the risk of adverse event.
**Discussion:** Initiation of statin therapy to patients should be taken post assessment of patient for risk of ASCVD. According to ADA Guidelines & AHA Guidelines, statins are to be prescribed for patient who are at risk for ASCVD or having history of ASCVD. Statins treatment should be initiated with a target of LDL cholesterol reduction to less than 70mg/dl in diabetic population who are at risk for ASCVD. Rosuvastatin performs better than Atorvastatin due to its prominent pharmacokinetic characteristics. Diet and life style changes along with right statin therapy with right dose for right patient works efficiently.
**Conclusion**
Statins are gold- Standard medicines for individuals at risk for ASCVD and MI for both primary and secondary prevention, although extended treatment may result in adverse effects and drug interactions. High – Intensity statins used for greater than eight weeks results in myopathy, Rhabdomyolysis and hyperglycaemias. Satin induced myopathy can be managed by adding ezetimibe as adjuvant. Pravastatin has proven its efficacy over other statins in paediatric population but further research is needed to utilize pravastatin as safer alternative.
**Key words:** Statins , Hyperlipidemia, Atherosclerotic Cardiovascular Disease, Diabetes Mellitus, Myocardial Infraction

## I. INTRODUCTION

Statins are 3-hydroxy -3 methyl glutaryl coenzyme-A reductase inhibitor. They have cholesterol lowering ,anti-inflammatory , antioxidant ,plaque stabilising capacities and can also improve endothelial funtion.[1]
According to FDA the statins are indicated-

- As An adjunct therapy to diet to reduce MI , Stroke without CHD with multiple risk factors.
- To reduce the risk of fatal and non- fatal stroke in CHD patients.
- For treatment of Familial , non Familial and mixed hyperlipidemia .

Hyperlipidemia

Hyperlipidemia is abnormal rise in body fats(lipids) which are diagnostically characterised as rise in blood LDL , Triglycerides are cholesterol levels.[2]It can be caused due to various causes like genetic, familial hyperlipidemia or lifestyle induced hyperlipidemia or obesity.

A 2014 study by the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) found that 79 percent of participants showed abnormalities in one of the lipid parameters, whereas 13.9% had hypercholesterolemia, 29.5% had hypertriglyceridemia, and 72.3% had low HDL-C and 11.8% had high LDL-C values.[3]

According to recent studies, 15-20% of individuals in rural areas and 25-30% of subjects in cities have high cholesterol. Compared to countries with high incomes, this prevalence is lower. In India, borderline elevated low HDL cholesterol, elevated triglycerides, and low LDL cholesterol are the most prevalent forms of dyslipidemia. According to studies, urban populations have seen increases in total cholesterol, LDL cholesterol, and triglyceride levels over the course of 20 years [4]

.In developed countries like the US 3% of adults have LDL-C >190 mg/dl. 1% drop in serum cholesterol reduces the risk of CHD by 2%. People having genetic predisposition , familial hyperlipidemia, Diabetes Mellitus, Renal disease are at high risk.[5]

**Food and Lifestyle Recommendations for Hyperlipidemic populations[6,7,8]**

Food and lifestyle changes act as adjuvant therapy with statins to show improovement in hyperlipidemic condition and reduces the risk of ASCVD risk.

The following instructions will be useful to plan low calorie diet.

When looking at food labels per 100g you should aim for:

- Less than 3g of fat per 100g of the food – this is a low fat product
- A medium fat product would contain 3.1-17.4g fat per 100g
- A high fat product would contain over 17.5g fat per 100g

Saturated fats can raise triglyceride levels. They can be found in fried foods, red meat, chicken skin, egg yolks, high-fat dairy, butter, lard, shortening, margarine, and fast food. Alternatives include:

- Lean proteins such as skinless white chicken meat and fish
- Low-fat dairy
- Egg whites
- Legumes
- Olive oil, canola oil, and peanut oil

Trans fats are hydrogenated fats that can be found in some packaged and fried foods. Trans fats have been banned, with exceptions, from the food supply in the U.S.

Refined Grains and Starchy Foods

Refined or processed grains are typically made from white flour, which can increase triglycerides. They also often have added sugars. If possible, try to limit:

- Enriched or bleached white bread, wheat bread, or pasta
- Sugary cereals
- Instant rice
- Bagels
- Pizza
- Pastries, pies, cookies, and cakes

Starchy foods can also raise triglycerides. Try to choose foods with 100% whole grains and opt for long-grain rice instead of instant rice. If possible, eat non-starchy vegetables such as spinach, instead of starchy ones like potatoes.[6]

Alcohol

Alcohol consumption can raise triglyceride levels.[4] Decreasing your alcohol intake can help lower these levels.

High-Calorie Foods

Be mindful of your intake of high-calorie foods if you are trying to lower your triglyceride levels. As some high-calorie foods are nutrient-rich, like nuts and avocados, but still can rise lipid levels in body.

**Statin use in Diabetic Population- ADA 2023 Guidelines[9]**

Patients with Diabetes above 40 years of age and without ASCVD risk should be initiated with moderate dose statin Therapy. Patients above 40 - 75 years with high cardiovascular risk and ASCVD risk high intensity statin therapy should be initiated with the goal of LDL cholesterol <70 mg/dl .

**Management of Statin Induced Myopathy**

Daily dose of statins should be titrated and given 3 times weekly and combine Ezetimibe non-stain agent to treat hyperlipidemia.

Treatment with ezetimibe in addition to statins was more effective than treatment with statins alone in reducing the risk of ASCVD and MI.[10]

**Statin induced Hyperglycemia**

Statins can cause blood glucose levels to rise or increase the risk of developing diabetes. Statins are diabetogenic medicines that vary in dosage. The propensity to cause hyperglycemia is 25%, 15%, and 7% for rosuvastatin 20 mg, atorvastatin 80 mg, and pravastatin 40 mg, respectively. The chance of developing diabetes at a new onset may rise after using high-intensity statins continuously for seven months.[11]

Because statins prevent the synthesis of new cholesterol, oxidation of beta-carotene is the mechanism behind statin-induced hyperglycemia. Along with inhibiting calcium-mediated pancreatic insulin release, it can also change the expression of the beta cell glucose transporters GLUT-2 and GLUT 4.[12,1]

The pharmacokinetic parameters and mechanism of action of statins vary; for instance, atorvastatin, rosuvastatin, fluvastatin, and pitavastatin are synthetically derived, whereas pravastatin, lovastatin, and

simvastatin are derived from fungi, and simvastatin is semi-synthetically. The lipid-lowering effects of statins are not recognized or apparent until 4-6 weeks after treatment commences, and their half lives range from 1 to 14 hours. The half-lives of atorvastatin and rosuvastatin are lengthy.[14]

Before prescribing statins, it is important to take into account the functions of the liver and kidneys because statins are metabolozed and excreted through bile, urine, and feces,. For example, simvastatin and lovastatin are excreated by the kidneys, so patients with renal dysfunction should not receive a prescription for them, but patients with hepatic dysfunction can.[14]

Both atorvastatin and rosuvastatin increase HBA1C levels and deteriorate glycemic control, which in turn causes and worsens diabetes mellitus. Atorvastatin is taken 5 mg/month or 20 mg/day.[15]

In some studies it was found that in order to lower cholesterol levels in some patients, pravastatin was initially administered. Later , the patient was switched to 40 mg of atorvastatin. However, within a day, the patient experienced symptoms such as increased thirst and polyuria , and after a week, their FBS and PLBS levels increased. Following this, the patients were switched back to pravastatin and their sugar levels returned to normal.

Before prescribing statins, the study recommends non- pharmacological treatments such as healthy diet, regular exercise and weight loss. If these treatments are not successful in achieving a normal lipid profile, hydrophilic statins should be used instead of lipophillic statins and ezetimibe , a secondary lipid lowering medication should be added.

Hence either of the ways rousvastatin and simvastatin pose the greater risk of hyperglycemia than pravastatin.

**Statin use in Primary and Secondary Prevention of MI [16]**

According to (ACC/AHA) American College Of Cardiology/ American Heart Association 2019 guidelines gave a clarity on the primary prevention of cardiovascular disease to use of statins for primary prevention in those up to 75 years.

Increased risk of ASCVD due to rise in age and leads to death in older adults, about 60% of deaths in those aged who are greater than or equal to 85 years.

In this review, they compared the seven major North American and European guidelines on cholesterol management released in the past 5 years, with respect to primary prevention of cardiovascular disease (CVD) in older adults.

The study's literature review concluded that pravastatin and placebo groups, which included older adults with and without baseline ASCVD in the age group of 70-82 years, were compared. The results showed that the pravastatin group experienced a reduction in myocardial infarction and coronary deaths, as well as an approximate 34% decrease in LDL-C after 3.2 years of follow-up.

In this seven major cholesterol guidelines they choose different paths in one of key area is to develop methods to estimate ASCVD risk

The Risk Estimator is intended for use in those without ASCVD with a LDL-cholesterol <190 mg/dL.The information required to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status.

**Statins use in Paediatric Populations for Familial Hyperlipidemia**

In the United State the leading cause of mortality is Cardiovascular disease. Some of the highly prevalent clinically silent disorders are Atherosclerosis, dyslipidemias such as familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). In 2011, National Heart, Lung, Blood Institute (NHLBI) conducted an expert panel on Cardiovascular Health and Risk Reduction in children and adolescents, for universal lipid screening in the pediatric population. Lipid screening results in a large number of children with previously unrecognised dyslipidemia Statins are the most important potent classes of lipid lowering drugs for cardiovascular risk reduction.[17]

Children with average LDL-C ≥190 mg/dl have a high FH and require pharmacotherapy, diet, exercise can maximally reduce lipids by ~10-20%. Fasting TG levels stays elevated ≥160 mg/dl about 6 months of lifestyle modifications or interventions. Once lipid profile has been repeated within a 2 week to 3 month period and recommended to start statin therapy with diet and lifestyle changes.

In children ≥10 years.

1)LDL ≥ 190 mg/dl

2)LDL ≥ 160 mg/dl + positive family history (or) 1 high risk factor (or) 2 moderate risk factors

3)LDL ≥ 130 mg/dl + 2 high risk factors (or) 1 high risk factor and 2 moderate risk factor (or) Clinical CVD

The drugs like:

1) ATORVASTATIN 5-10 mg Lipophilic

2) FLUVASTATIN 20 mg Lipophilic
3) LOVASTATIN 10mg Lipophilic
4) PRAVASTATIN 5-20mg Hydrophilic

Statins are the only available in pill form. In children Simvastatin an oral suspension, liquid preparations are not readily available which can be an issue with sensory issues or difficulty swallowing a pill. Disintegrating formulation of Simvastatin is available, and is helpful in younger children. Lovastatin and Fluvastatin are rarely used in children and should not be crushed. Fluvastatin is available as a capsule but the contents are not to be separated as per manufacturer's instructions. Paediatric dyslipidemia could be because of monogenic, secondary or polygenic causes.[18]

**SPECTRUM OF STATIN THERAPY IN HYPERLIPIDEMIC CHILDREN [19]**

In children the recommended first choice in treatment for hypercholesterolemia is 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Statins). Statins are not only effective in reducing low-density lipoprotein cholesterol levels in children with familial hypercholesterolemia; it also improves endothelial function and reduces the thickening of intima media complex of carotid arteries. Statins are safe at longer term in children as plasma levels of liver enzymes, liver function, creatinine kinase levels, and muscle function and sexual development.

The target of the Paediatric population for lipid reduction include children with Homozygous (or) Heterozygous familial hypercholesterolemia (FH). FH is an autosomal dominantly inherited metabolic disease caused by mutations in the low-density lipoprotein (LDL) receptor gene. The elevated level of LDL-C and total cholesterol from birth result in early atherogenesis and premature cardiovascular disease(CVD). The recent tracts demonstrated the efficacy of short term and long-term safety of early initiation of statin therapy in children and adolescents with heterozygous FH.

**Efficacy effects of various Statin on lipids and lipoproteins in FH children.**

The reduction of LDL-C levels varied between 17 with 45%, total cholesterol between 13 with 37% and apolipoprotein B100 between 18 with 34% depending on dose and statin high density lipoprotein cholesterol levels between 1 with 11% and elevations of apoAI between 2 with 10% in the statin treated children. Statins are well tolerated by the majority of patients. The most common effects in adults are GI like constipation, diarrhoea, flatulence, dyspepsia and abdominal pain and also includes myalgia, rash, headache, pruritus, fatigue and sleep, mood disorders these disorders are also seen in children.[20]

**STATIN-BEYOND THEIR USE IN HYPERCHOLESTEROLEMIA: FOCUS ON THE PAEDIATRIC POPULATION:**

Statins primarily function by inhibiting 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is a main enzyme involved in cholesterol biosynthesis. Statins possess pleiotropic properties that may be relevant to various paediatric diseases which include anti-inflammatory, anti-angiogenic, pro-apoptotic effects, modulation of cell signalling pathways. The most frequent anticoagulant used in paediatrics, Warfarin as Simvastatin, atorvastatin, rosuvastatin were reported potentiate its effects. The statins like Lovastatin, Simvastatin, Atorvastatin are substrates of Cytochrome P4503A, and the other drugs like antifungal azole, protease inhibitors, cyclosporine, should be avoided with dosage adjustment needed for calcium channel blockers and amiodarone. Fluvastatin, pitavastatin, and rosuvastatin are the substrates of CYP2C9 and cyclosporine should be avoided. The only statin which is not metabolised by CYP isoenzyme is **pravastatin**. The concurrent use of statins and gemfibrozil should be avoided. Pravastatin decreases low-grade chronic inflammation and enhances endothelial function in patients with coronary aneurysms caused by KD.Children with KD-related coronary aneurysms may benefit from statin treatment.[21]

**Statins with Cardiovascular disorder:**

Kawasaki disease, also known as Kawasaki Syndrome, which is an acute febrile illness in children under age of 5, it can have serious complications if left untreated leads to Coronary Artery abnormalities, which leads to coronary artery aneurysms, myocardial contractility, heart failure, myocardial infarction and arrhythmias. Statins have been found to have positive effects on inflammation, endothelial function, oxidative stress. Besides Kawasaki disease, statins showed potential benefits in chronic vasculitis such as Behcet's and rheumatoid arthritis due to anti-oxidant, endothelial-repairing properties.

Children with acute Kawasaki disease and CAA were given atorvastatin, which proved to be safe and well-tolerated. Given that this patient population may benefit from the medication's well-known anti-inflammatory and immunomodulatory actions, a Phase III efficacy trial is necessary.In order to ascertain the PK surrounding the first dosage, this study evaluated the safety and tolerability of a 6-week course of atorvastatin in children with acute Kawasaki illness and CAA. In this group of young patients, atorvastatin at doses between 0.125 to 0.75 mg/kg/day was safe and well tolerated. Based on this multiethnic population trial, individuals with

acute Kawasaki disease with CAA tolerated 0.75 mg/kg/day of atorvastatin for six weeks with good quality of life.[22]

**Statins with Oncologic disorders:**

In children, medulloblastoma is the most prevalent malignant brain tumour with 20% of all childhood brain tumours. In humans, phase 1 study conducted in children with relapsed/ refractory solid and CNS tumours reported that plasma interleukin-6 (Il-6) concentrations consistently decreased overtime, and returning to normal values in all the patients after 3*weeks of simvastatin, with combination of topotecan and cyclophosphamide on day 1-5. [23]

| Parameters | Atorvastatin | Pravastatin | Rosuvastatin |
|---|---|---|---|
| Fraction absorbed (%) | 30 | 34 | 50 |
| Bioavailability (%) | 12 | 18 | 20 |
| Effect of food on bioavailability (%) | 13 | No | No |
| Protein binding (%) | >98 | 43-55 | 88 |
| Hepatic extraction (%) | >70 | 46-66 | 63 |
| Systemic metabolites | Active | Inactive | Active (minor) |
| Systemic clearance (ml/min) | 291. | 945 | 805 |
| t 1/2(h) | 15-30 | 1.3-2.8 | 20.8 |

Fig1- Pharmacokinetics of Statins

**Insights on Pravastatin…**

Pravastatin, one of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) widely used in the management of hypercholesterolaemia, has unique pharmacokinetic characteristics among the members of this class. Many *In vivo* and *In vitro* human and animal studies suggest that active transport mechanisms are involved in the pharmacokinetics of pravastatin.

The oral bioavailability of pravastatin is low because of incomplete absorption and a first-pass effect. The drug is rapidly absorbed from the upper part of the small intestine, probably via proton-coupled carrier-mediated transport, and then taken up by the liver by a sodium-independent bile acid transporter. About half of the pravastatin that reaches the liver via the portal vein is extracted by the liver, and this hepatic extraction is mainly attributed to biliary excretion which is performed by a primary active transport mechanism. The major metabolites are produced by chemical degradation in the stomach rather than by cytochrome P450-dependent metabolism in the liver. The intact drug and its metabolites are cleared through both hepatic and renal routes, and tubular secretion is a predominant mechanism in renal excretion.[24]

The dual routes of pravastatin elimination reduce the need for dosage adjustment if the function of either the liver or kidney is impaired, and also reduce the possibility of drug interactions compared with other statins, which are largely eliminated by metabolism. The lower protein binding than other statins weakens the tendency for displacement of highly protein-bound drugs. Although all statins show a hepatoselective disposition, the mechanism for pravastatin is different from that of the others. There is high uptake of pravastatin by the liver via an active transport mechanism, but not by other tissues because of its hydrophilicity, whereas the disposition characteristics of other statins result from high hepatic extraction because of high lipophilicity.

These pharmacokinetic properties of pravastatin may be the result of the drug being given in the pharmacologically active open hydroxy acid form and the fact that its hydrophilicity is markedly higher than that of other statins. The nature of the pravastatin transporters, particularly in humans, remains unknown at present. Further mechanistic studies are required to establish the pharmacokinetic-pharmacodynamic relationships of pravastatin and to provide the optimal therapeutic efficacy for various types of patients with hypercholesterolaemia.[25]

## II. DISCUSSION

Statins are promising medications that are essential in preventing MI and ASCVD in individuals who are at risk, as well as lowering morbidity and enhancing quality of life. Additionally, statins can create several drug-drug interactions, alter metabolic pathways, and worsen the quality of life by increasing the risk of diabetes mellitus, and other adverse effects. These effects are brought on by the dynamic pharmacokinetic and pharmacodynamic features of statins.

When pharmacokinetic characteristics of Atorvastatin and Rosuvastatin are compared, Rosuvastatin performs better than Atorvastatin due to reduced protein binding, increased absorption, decreased t1/2, and optimised systemic clearance. In this instance, pravastatin's pharmacokinetic characteristics—which include a shorter half-life (t1/2), inactive systemic metabolites, and reduced protein binding—elucidate its efficacy in the literature.

Furthermore, as was already noted, pravastatin has been shown to be effective in treating familial hyperlipidemia in paediatric populations. It also lowers the risk of ASCVD in people with diabetes and has less ability to cause hyperglycemia.

While statins are effective medications, they must be used with extreme caution along with constant monitoring to ensure that no adverse reactions occur. Adopting the recommended parameters for statin therapy is essential to prevent side effects such as hyperglycemia, myopathy, and rhabdomyolysis. The added benefit of ezetimibe to statin therapy has been established to be beneficial of both risk reduction and CVD death prevention.In order to prevent statin-induced side effects and find safer alternatives, research on pravastatin's efficacy over currently available, widely prescribed statins is required.

## III. CONCLUSION

Statins are safe to use in individuals at risk for ASCVD and MI for both primary and secondary prophylaxis, although extended treatment may result in adverse effects and drug interactions. By choosing the right statin for each patient, the likelihood of statin side effects is decreased. When using high-intensity statins for longer than eight weeks, the predominant side effects of the drug are myopathy, rhabdomyolysis, and hyperglycemia.

Of all the statins, pravastatin has been proven to be both safe and effective in paediatric populations for treating familial hyperlipidemia.

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