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# A SHORT REVIEW ON HMG CoA REDUCTASE INHIBITORS

**[1]Riyas Mon O.P, [2]Basim Abdul Bari Palliparambil, [3]Muhammad Jameel K.A, [4]Sabah Abdul Nazir, [5]Mohammed Shifan, [6]Muhammed Fayas B**

[1]Pharm D 5th year student, Jamia salafiya pharmacy college, Pulikkal, Malappuram. Kerala
[2]Pharm D 4th year student, Jamia salafiya pharmacy college, Pulikkal, Malappuram. Kerala
[3]Pharm D 4th year student, Jamia salafiya pharmacy college, Pulikkal, Malappuram. Kerala
[4-6]Pharm D 5th year student, Jamia salafiya pharmacy college, Pulikkal, Malappuram. Kerala

**Abstract:**

*HMG CoA reductase inhibitors are the first line and more effective treatment for the patients with elevated LDL cholesterol level and to prevent high cholesterol associated disease conditions such as coronary artery disease. The purpose of this article is to clarify the mechanism of action, benefits, pharmacokinetics, dose, adverse reaction and indications of statins. They can inhibit the enzyme HMG CoA an enzyme responsible for conversion of HMG CoA (3-hydroxy-3-methylglutaryl-CoA) into mevalonic acid in the pathway of cholesterol biosynthesis. The action of statins results in a reduction in intracellular levels of cholesterol, an increase in expression of hepatic LDL receptor, and enhanced receptor- medicated catabolism and clearance of LDL-Cholesterol from serum. The overall effect is a reduction in triglycerides, low density lipoprotein (LDL), very low-density lipoprotein (VLDL) and total protein with an increase in high density lipoprotein (HDL) level in the body. An overwhelming amount of data that confirm the morbidity and mortality benefit of statin therapy in high-risk CVD conditions have been reported, both in the primary and secondary prevention settings. Within the statin class, atorvastatin is a stronger medication. At 10 mg/day, 40 mg/day, 45 mg/day, and 80 mg/day, atorvastatin reduces LDL cholesterol by 33%, 40%, 45%, and 50–55%, respectively. Among the medications in the statin class, atorvastatin is the most effective. When compared to other statins, this more recent and well-liked one has the strongest LDL-lowering activity. Moreover, its plasma half-life is longer. Muscle aches, changes in liver function tests, and digestive issues are the most frequent side effects of statin medication. Hepatitis, sleeplessness, nightmares, rashes, and concentration problems are less frequent. These statins showed the best tolerability and hazard profile when it comes to discontinuations because of adverse events, myalgia, transaminase elevations, and CK elevations. The only significant reaction is myopathy, which is uncommon. When compared to other conditions, headaches and digestive problems are typically minor. Clinicians have long utilized statin medicines to treat hypercholesterolemia, hyperlipoproteinemia, and hypertriglyceridemia in addition to diet and exercise.*

*Keywords: HMG CoA reductase inhibitors, statins, anti-hyperlipidemic agent, Cholesterol lowering agents, Lipid lowering agents.*

**Corresponding author:**
**Riyas Mon O.P,**
*Pharm D 5th year student,*
*Jamia Salafiya Pharmacy College,*
*Pulikkal, Malappuram. Kerala*

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## INTRODUCTION:

HMG CoA(3-hydroxy-3-methylglutaryl) reductase inhibitors also known as Statin drugs. They can inhibit the HMG CoA an enzyme responsible for conversion of HMG CoA (3-hydroxy-3-methylglutaryl-CoA) into mevalonic acid in the pathway of cholesterol biosynthesis. This class of compounds are the most efficacious and best tolerated hypolipidemic agents. Therapeutic doses of statins reduce the cholesterol synthesis in by 20-50%. Systematic review demonstrates that, among patients with coronary artery disease, the provision of more intensive statin monotherapy (compared with less intensive statin therapy) reduces LDL cholesterol levels by a further 0.72 mmol/L [1]. The action of statins results in a reduction in intracellular levels of cholesterol, an increase in expression of hepatic LDL receptor, and enhanced receptor- medicated catabolism and clearance of LDL-Cholesterol from serum. The overall effect is a reduction in triglycerides, low density lipoprotein (LDL), very low-density lipoprotein (VLDL) and total protein with an increase in high density lipoprotein (HDL) level in the body. The use of statins by people at low cardiovascular risk reduced the relative risk of death from any cause by 10% [2].

Results of the recent JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) [3] have renewed enthusiasm for the use of statins in people without a history of coronary artery disease and have generated further controversy as to whether high-potency statins such as rosuvastatin and atorvastatin lead to better clinical outcomes than low-potency statins such as pravastatin, simvastatin, fluvastatin and lovastatin.

### Benefits of statin therapy

An overwhelming amount of data that confirm the morbidity and mortality benefit of statin therapy in high-risk CVD conditions have been reported, both in the primary and secondary prevention settings [5]. A dose dependent effective is seen with all statin therapy. With lovastatin a mean reduction of low-density lipoprotein (LDL) cholesterol by 25% at 20 mg/day, 32% at 40 mg/day and 40% at 80 mg/day has been measured.

### Potent drug among statins

Atorvastatin is more potent drug in the statin class. The reductions in LDL cholesterol by the atorvastatin are 33% at 10mg/day, 40% at wo mg/day, 45% at 40mg/day and 50-55% at 80 mg/day.

### How the statin reduces cholesterol

Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell [6].

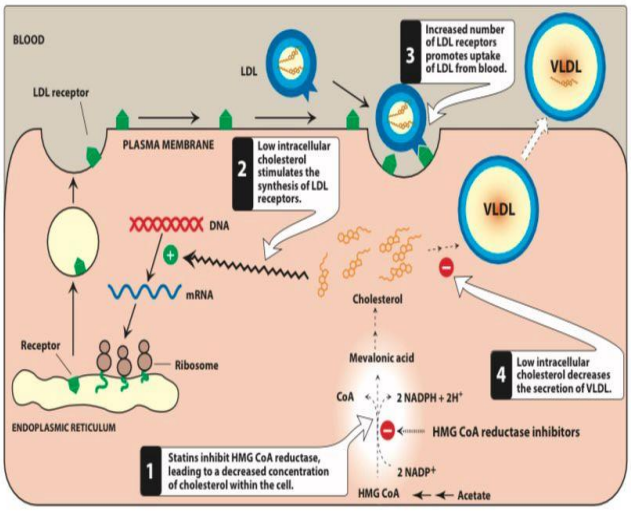


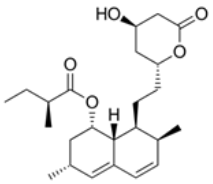

**Figure 1: MOA of Statins**

Inhibition of this enzyme (rate limiting enzyme in the cholesterol biosynthesis) results reduced biosynthesis of the cholesterol in body and reduces the risk associated with high level of cholesterol.

### FDA approved HMG CoA reductase inhibitors [25].

1. Lovastatin
2. Simvastatin
3. Pravastatin
4. Atorvastatin
5. Rosuvastatin
6. Pitavastatin
7. Fluvastatin

### 1. Lovastatin




1979 saw the patenting of lovastatin, and 1987 saw its approval for use in medicine. It is on the World Health Organization's List of Essential Medicines [8]. It is the first clinically used statin. Its use is recommended with life style changes to control cholesterol level.

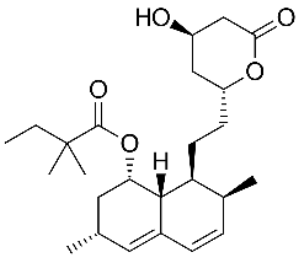
### Pharmacokinetics

- Absorption of lovastatin is incomplete and 1st pass metabolism in extensive [7].
- 95% of protein binding.
- Bile is the main excretion route of elimination

- 10% excretion through renal route

**Dose**
10-40 mg/day with maximum dose of 80 mg/day [7].

**2. Simvastatin**

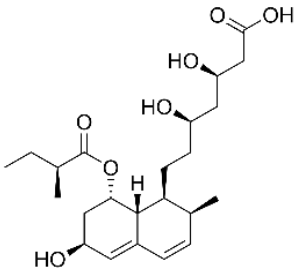


It functions by reducing the amount of cholesterol that the body produces, which lowers the risk of cholesterol accumulating on artery walls and obstructing blood flow to the heart, brain, and other organs. It is twice potent than lovastatin [7].

**Pharmacokinetics**
- Oral absorption is good
- Extensive 1st pass metabolism from GIT
- 2-3 hours of plasm half-life.

**Dose**
5-20 mg/day with maximum of 80 mg/day [7].
Simvastatin may be best avoided in individuals with genetically poor OATP1B1 function or CYP3A4 activity and in those with the combination of decreased OATP1B1 function and CYP3A4 activity [9].

**3. Pravastatin**

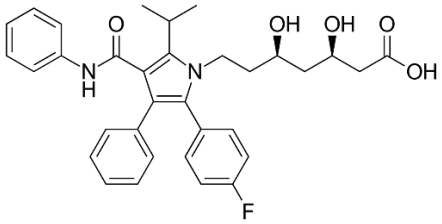


A drug called pravastatin is used to treat and manage mixed dyslipidemia, hyperlipidemia, and primary hypercholesterolemia [4]. It equipotent to lovastatin at low doses. Cholesterol lowering effect is less at higher doses(40mg/day)

**Pharmacokinetics**
- After oral treatment, pravastatin is absorbed 60–90 minutes later.
- 17% bioavailability
- 1-3 hours of plasma half-life.

**Dose**
10mg tablet & 20mg tablets are available

**4. Atorvastatin**



It is the most potent drug among statin class of drugs. This newer and most popular statin have highest LDL lowering activity compared to other statins. It has higher plasma half-life also.

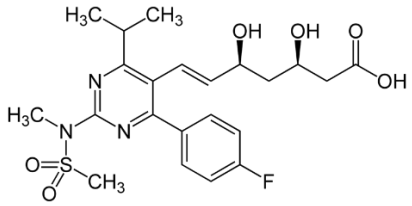
Atorvastatin is rapidly absorbed after oral administration with a peak plasma concentration at 1 to 2 hours. The bioavailability is low at 14% due to extensive first-pass metabolism.[10].

Atorvastatin has been shown to reduce total cholesterol in patients with homozygous or heterozygous familial hypercholesterolemia, mixed dyslipidemia, isolated hypertriglyceridemia, or nonfamilial hypercholesterolemia.

**Pharmacokinetics**
- Bioavailability is low at 14% due to extensive first-pass metabolism.
- 98% of plasma protein bound.
- Volume of distribution is about 380L
- metabolized by cytochrome P450 3A4 (CYP3A4)
- get eliminated through bile route.

**Dose**
10-40 mg/day with maximum dose of 80mg/day

**5. Rosuvastatin**



Another more recent and widely used powerful statin is this one.10 mg rosuvastatin is nearly equal to 20 mg of atorvastatin [7]. In combination with diet, exercise, and weight loss, rosuvastatin lowers the risk of heart attack, stroke, and the need for heart surgery in patients

with heart disease or at risk of developing heart disease. Rosuvastatin is available as an oral tablet (Crestor) and capsule (Ezallor).

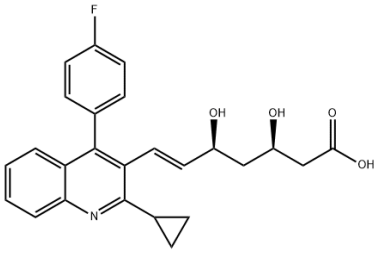
**Pharmacokinetics**

- Rosuvastatin's absolute bioavailability is 20%
- Estimated absorption is about 50%
- At a median of 5 h rosuvastatin achieves maximum plasma concentration [11].
- The majority of the drug dose was excreted unchanged
- Primarily eliminated in the faeces (90%) compared with 10% renal excretion [12].

**Dose**

Start the dose with 5mg once daily, if needed increase the dose upto 20mg/day with maximum dose of 40mg/day [7].

**6. Pitavastatin**




Pitavastatin is a novel potent HMG-CoA reductase inhibitor that has shown a strong effect on lowering plasma total cholesterol and triglycerides in body. No specific advantages compared to other statins have been demonstrated.

**Pharmacokinetics**

- The plasma concentration of pitavastatin is increased in patients with liver cirrhosis [13].
- 60% bioavailability after oral administration
- The half-life was shortened from 9.7 to 4.9 hours, which suggest a reduction in the apparent volume of distribution.
- Tmax is 1 hour
- 96% plasma protein binding
- Hepatic metabolism and excreted through bile route.

**Statins associated adverse reactions**

Gastro-intestinal symptoms, alteration in liver function tests and muscle aches are the common harm effect associated with statin therapy [14].

Less common are hepatitis, insomnia, nightmares, rashes, and difficulty in concentrating. When it came to discontinuations due to adverse events, myalgia, transaminase elevations, and CK elevations, these statins had the best tolerability and hazard profile [15].

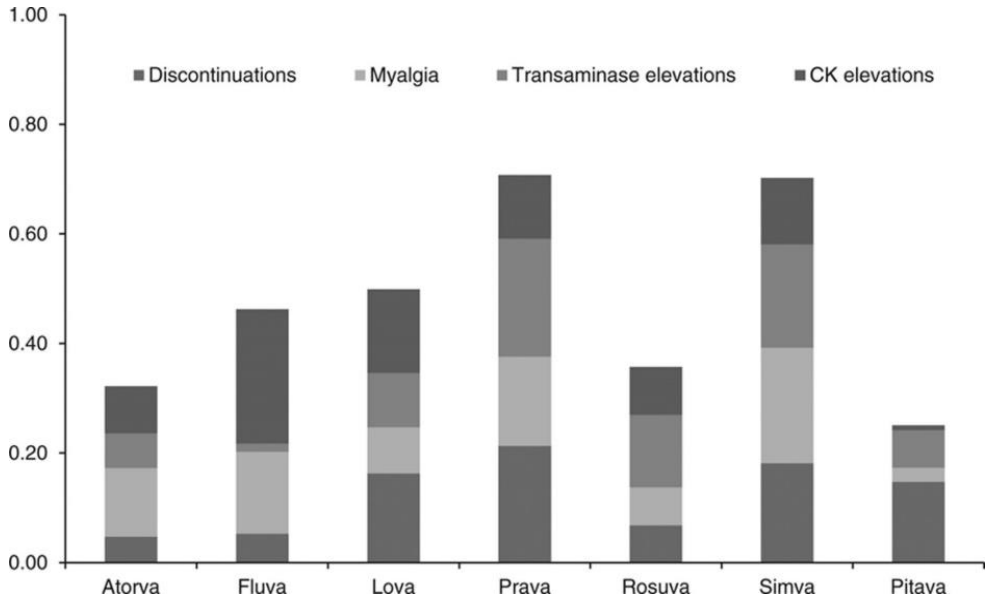



**Figure 2: Individual statins were ranked according to their overall likelihood of being the best treatment in terms of discontinuations due to adverse events, myalgia, hepatic transaminase elevation, and CK elevation in participants in placebo-controlled and active-comparator trials [15].**

Myopathy is the only serious reaction, but rare (<1 per 1000). Gastrointestinal disturbances and headaches are usually mild compared to others. A well-known adverse effect of statin therapy is rhabdomyolysis, and the risk is increased when medications that inhibit cytochrome p450-3A4 are used concurrently [16].
Examples of cytochrome p450-3A4 inhibitors are listed below;

**Table 1: examples of cytochrome p450-3A4 inhibitors** [16].

| Drug class | Examples |
|---|---|
| Antibiotics | Clarithromycin, Erythromycin, Telithromycin |
| Antifungals | Clotrimazole, Itraconazole, Fluconazole, Ketoconazole, Voriconazole |
| Protease inhibitors | Atazanavir, Darunavir, Lopinavir, Ritonavir, Tipranavir |
| Calcium channel blockers | Diltiazem, Verapamil |
| Others | Amiodarone, Ciclosporin, Ranitidine, Sertraline, Tamoxifen |

The development of muscle complaints, also referred to as statin-associated muscle symptoms (SAMS), is the main adverse reaction that restricts the use of statins [27].

**Indications for statins**
The primary and secondary prevention of coronary artery disease is the principal application of these medicines.

FDA approved indications for statins are,

a) Hyperlipidemia and mixed dyslipidaemia [17].
b) Type III hyperlipoproteinemia [18].
c) Atherosclerosis [19].
d) Hypertriglyceridemia [20].
e) Primary prevention of ASCVD (atherosclerotic cardiovascular disease) [21].
f) Secondary prevention in patients with clinical ASCVD [22].
g) Paediatric patients with familial hypercholesterolemia [23].
h) Adult patients with homozygous familial hypercholesterolemia [24].

As an addition to diet and exercise, statin drugs have long been used by clinicians to treat hypercholesterolemia, hyperlipoproteinemia, and hypertriglyceridemia.

**Additional information about statins**
FDA recommends that healthcare professionals should:

- Only continue simvastatin 80 mg treatment in patients who have not shown signs of muscle toxicity after 12 months or longer [26].
- Don't start 80 mg of simvastatin on new patients.
- Patients who require starting a medication that interacts with simvastatin should be switched to a statin that has a lower risk of drug-drug interactions.

During the acute stage of an ischemic stroke, this treatment should be continued. Withdrawing off statins is linked to a higher risk of dependence or mortality after 90 days [28].

## CONCLUSION:

In conclusion, the most widely used lipid-reducing medication in patient care settings is statin therapy, which is capable of significantly lowering blood cholesterol levels. Statins reduce the cholesterol level by inhibiting the HMG CoA, a rate limiting enzyme in the cholesterol biosynthesis pathway and reduces the cholesterol related disease in patients. Atorvastatin is the most commonly preferred statin in clinical settings with maximum dose of 80mg/day. Myopathy is the serious and rare adverse effect associated with statin therapy compared to other common adverse effect such as gastrointestinal disturbances and headache. The primary and secondary prevention of coronary artery disease is the principal application of these medicines. As an addition to diet and exercise, statin drugs have long been used by clinicians to treat hypercholesterolemia, hyperlipoproteinemia, and hypertriglyceridemia.

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