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REVIEW ARTICLE ON STATIN AND DRUG INTERACTIONS ASSOCIATED WITH STATINS.

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ABSTRACT
Statins are the most preferred antihyperlipidemic drug. In the present review the chemistry, pharmacokinetic, pharmacodynamic, ADR and most common drug-drug interaction are discussed. Statins inhibit HMG CoA to show its pharmacological action and most of them are metabolised by CYP450. These drugs are reported for ADRs like renal, musculoskeleton, hepatic, gastric and pregnancy problems. There are also found to show drug-drug interaction with drugs like warfarin, fibrates, Azoles, macrolides, amaidirone, rifampicin, clopidogrel, digoxin and Phytoin

KEYWORDS:- Statins, HMG CoA, pharmacokinetic & pharmacodynamics, ADR, Drug interaction.

INTRODUCTION OF STATINS

Statins are HMG coA reductase inhibitors introduced in 1970s which are the best tolerated hypolipidaemic drugs. It reduces the LDL and total cholesterol levels. It was first discovered by the Japanese microbiologist **Akira Endo,** in the fermentation broth of pencillinium citrinium Pen-51, which was isolated from rice sample during his search for antimicrobial agent. In July 1973, three active metabolites were isolated from the culture broth which showed potent activity to inhibit cholesterol synthesis both invivo and invitro. Of these three, the most active product is ML-236B, which was later referred as compactin. Due to structural similarities between the compactin and HMG coA, it is used as competitive inhibitor of HMG coA reductase.[1]

Joseph Goldstein and Brown demonstrated that the familial hypercholesterolemia patients with their cultured fibroblasts found, regulation of HMG CoA reductase was partially or completely lost resulting in high reductase activity even in the presence of LDL. Inhibition was 50%. Studies on compactin was done at Osaka university hospital in Osaka in February 1978 on a 18 year old woman with severe hypercholesterolemia & her cholesterol levels dropped from 1000 mg/dl to approx. 700mg/dl by the use of compactin at a daily dose of 500mg.Thes treatments lead to clinical development of compactin & it was given to patients of severe hypercholesterolemia because of its excellent safety profile[1]

The statins that are available in the market are atorvastatin, fluvastatin, simvastatin, pravastatin, rosuastatin, etc. Lovastatin was the first statin used with fewer adverse effects and was first approved for use by FDA. Simvastatin was the second most potent statin used clinically. And it is more effective than other statins in raising HDL cholesterol. Simvastatin which differs from lovastatin in an additional side chain methyl group was approved for marketing in Sweden in 1988, and then worldwide. In 2005 one of the statin drugs Lipitor was the most prescribed drug in the country. Of these statins Cervistatin is the most potent but withdrawn from the market in August 2001 due to risk of serious Rhabdomyolysis nearly 80 times greater than other statins. Other effects of statins include inhibition of platelet function by decreasing the production of thromboxane A2 & decreasing the cholesterol content of platelet membranes thus lowering cholesterol potential. They are also used to reduce CRP(C-reactive Protein) & has a direct role in pathogenesis of atherosclerosis. Fluvastatin is the least expensive statin drug. Pravastatin evidence exist from clinical trials about its ability to prevent heart attacks and mortality rates and it is also least likely to cause interactions with other drugs.[1]

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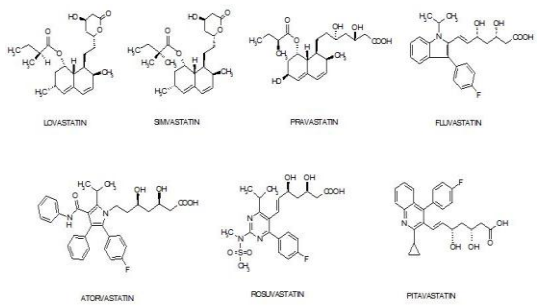
Table 1: statins availability in the market with their dosages.

Generic name	Year of discovery	Dose	Brand names	Available as a prescription Generic drug?
Pravastatin	1991	20mg,40mg	Pravator	No
Fluvastatin	1994	20mg,40mg	Lescol,lescol L	Yes
Atorvastatin	1997	10-40mg/day	Aztor,Atorva	Yes
Cervistatin	1998		Lipobay ,Baycol	Yes
Rosuvastatin	2003	5-40mg/day	Rosyin,rosuvas	No
Pitavastatin	2009	1-4mg/day	Flovas	No

CHEMISTRY AND MECHANISM

The structural model of the statins achieved different functionalities related to each particular component of the molecule. The chemical structure of the statin constitutes two components, the pharmacophore, which is a dihydroxyheptanoic acid segment, and its moiety composed of a ring system with different substituents.The pharmacophore inhibits HMG-CoA reductase enzyme. The stereo activity of HMG-CoA reductase enzyme dictates the sterio chemistry of statins, which presents two chiral carbon atoms, C3 and C5 on their pharmacophore .The moiety generates different structures of the statins. The ring system is a complex hydrophobic structure covalently linked to the pharmacophore, that is involved in the binding interactions to the HMG-CoA reductase. The structure of the ring can be partially reduce naphthalene (lovastatin, simvastatin, pravastatin), a pyrole (atorvastatin), pyridine (cerivastatin), pyramidine (rosuvastatin), quinoline (pitavastatin). Substituents on the rings define the solubility and their pharmacological properties. The statins are commonly grouped into two types: type1 natural or fungal derived statins (lovastatin, simvastatin, pravastatin) and differ from type 2. Type2 statins are synthetic statins. The functional difference between natural and synthetic statins relies on their ability to interact and inhibit the HMG-CoA reductase and on their lipophilicity.Type2 statins form more interactions with HMG-CoA reductase because of their structural characteristics. Lovastatin,simvastatin practically insoluble in water; rosuvastatin sparingly soluble in water and methanol,cervistatin, fluvastatin,pravastatin are soluble in water; Atorvastatin very slightly soluble in water.[12]

Chemical structures of statins.[2,3,4,5,6,7,8]:



Stability: statins should be closed in well closed light resistant containers at 5-30 degree centigrade, they are stsble for 24 months after the date of manufacture when kept under these conditions.[15]

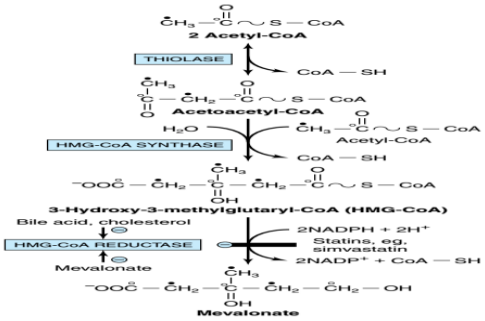


Figure1:Biosynthesis of mevalonate.

Atorvastatin,simvastatin and pravastatin inhibits HMG CoA reductase. The fate of the each of the carbons in the acetyl CoA indicate open and solid circles.

Mechanism: The primary mechanism of statins is the inhibition of HMG-CoA reductase, the rate limiting step in cholesterol biosynthesis which is an enzyme of hepatocyte that converts HMG-CoA into mevalonic acid. They bind to the active and alter the confirmation of the enzyme which leads to changes in the functional structure and ultimately prevents the endogenous production of cholesterol. Due to reduction in the cholesterol concentration in the hepatocytes LDL cholesterol receptor expression is increased which causes the uptake of LDL from systemic circulation.

The other mechanism is inhibition of hepatic synthesis of apolipoprotienB100 and the reduced synthesis and secretion of triglyceride rich lipoproteins and an increase of receptors production for apolipoprotein B/E.[10]

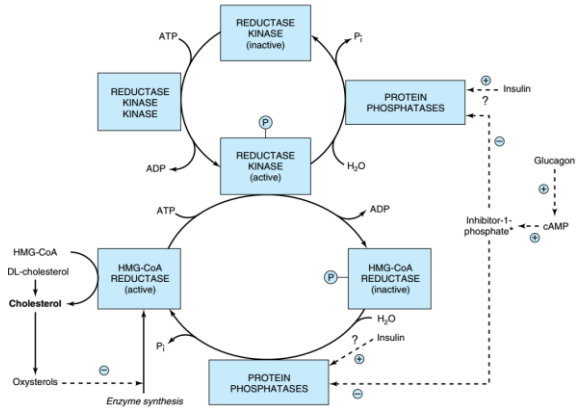


Figure 2: Mechanism of cholesterol synthesis, transport and excretion.

PHARMACOKINETICS

Different statins differ in their potency and maximal efficacy in reducing LDL CH. Lovastatin and simvastatin are administered as prodrugs, then other statins are administered as active hydroxy acid. They absorb rapidly and attains peak plasma concentration levels with in 4hours. However most of the statins are active at midnight because HMG-CoA reductase activity is maximum at night time. But atorvastatin and rosuvastatin need not be taken at that time due to their longer plasma $t_{1/2}$. Food may vary the absorption of statins lovastatin is more effective when taken along with the food, but atorvastatin, fluvastatin and pravastatin bioavailability decreases when taken along with the food. No effect is seen for simvastatin and rosuvastatin**.**

A dose dependent effect is seen with all statins.

- Lovastatin mean reduction of LDL CH by 25% at 20mg per day, 32% at 40mg per day and 40% 80mg per day.
- Atorvastatin mean reduction of LDL CH by 33% at 10mg per day, 40% 20mg per day, 45% 40mg per day, 50 to 55% 80mg per day.

All statins except rosuvastatin and pravastatin are metabolized by cytochrome P450 family of enzymes i.e., CYP3A4 isoenzyme. The first pass effect is efficient in case of statins. Inhibitors and inducers of this isoenzyme increases and decreases statin blood levels. As statins are metabolized by CYP450 system they are more likely to produce muscle toxicity due to drug interactions with many drugs that inhibit CYP450 system. The increased risk of toxic effects is due to increased plasma levels of statins due to drug interactions. Elimination occurs through bile after metabolism by the liver.

- Pravastatin is eliminated by both kidney and liver in unchanged form, but its pharmacokinetic properties are altered in patients with hepatic dysfunction.
- Rosuvastatin is eliminated by both kidney and liver in unchanged form, but its pharmacokinetic properties are not altered in patients with hepatic dysfunction.

  Bioavailability of statins differ greatly 5%-lovastatin, simvastatin-60%, cervistatin-60%,pitavastatin-60%. Lovastatin plasma half life 1-3 hrs, simvastatin 2-3 hrs, pravastatin 1-3 hrs, atorvastatin 18-24 hrs, fluvastatin 1hr, rosuvastatin 18-24 hrs, pitavastatin 12 hrs

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Table 2: pharmacokinetic profile of statins.

Statins	Optimal time of dosing	Bioaviala bilty %	Solubility	Effect of food	Protein binding%	Active metabolites	Eliminati on half life	CYP450 metabolism and isoenzyme	Renal excretio n in %
Pravastat in	Bed time	18	Hydrophilic	Bioavailab ilty decreased	˜50	×	1.8	×	20
Fluvastat in	Bed time	24	Lipophilic	Bioavailab ility decreased	Greater than 98	✓	1.2	✓ 2C9	6
Atorvasta tin	Any time of day	12	Lipophilic	Bioavailab ility decreased	98	✓	14	✓ 3A4	Lessthan 5
Cervistati n	Evening	60	Lipophilic	No effect	Greater than 99	✓	2.5	✓ 3A4,2C8	30
Rosuvast atin	Any time of day	20	Hydrophilic	No effect	90	Minor	19	Limited	10
Pitavastat in	Na	˜80	Lipophilic	Na	96	Minor	11	Limited	Na
Lovastati n	With meals morning and evening	5	Lipophilic	Increased	Greater than 95	×	3	✓ 3A4	10
Simvasta tin	Evening	5	Lipophilic	No effect	95-98	×	2	✓ 3A4	13

Pharmacodynamics

Statins are the most effective drugs with maximum effect in reducing the LDL-C at therapeutic dose. Even though statins are well tolerated and serious adverse events like myopathy that leads to rhabdomyolysis with Cervaststin use made to withdraw it from the clinical use. The other adverse effects that are observed are thrombocytopenia, bone marrow suppression leading to decreased platelet production, kidney failure etc.[12,13]

Adverse effects.[13]

Hepatic effects: Elevation in liver enzymes especially AST,ALT increased serum bilirubin greater than the upper normal limit. Serious hepatotoxicity is very rare, it is reasonable to measure alanine aminotransferase

baseline and there after when clinically indicated. Patients taking 80mg of doses (40mg of rosuvastatin) should check their ALT after 3months. Unless clinically indicated the ALT test is not indicated. Elevation greater than three times the upper normal limit liver enzymes elevation specifically AST,ALT dose related effects of statins occurs in less than 1% of patients with initial treatment, and in 1-3% on higher dose like (eg: 80mg of atorvastatin). This effect is typically transient and asymptomatic, resolving spontaneously even in continued therapy. Increase in serum aminotransferase is also seen in pitavastatin it should be used with caution in patients who consume alcohol. If there is increase in amino transferase concentration during pitavastatin therapy dosage of pitavastatin should be reduced or drug discontinued. For the patients who receive statin therapy liver function test must be performed at 6-12 weeks after initiation of treatment. No need of routine monitoring of LFT in patients receiving statins. Jaundice, malaise and fatigue are the indicative symptoms of hepatotoxicity so patients must be warned of these symptoms. Jaundice has been reported rarely with rosuvastatin therapy. As simvastatin is metabolized pre dominantly in liver and may accumulate in plasma of patients with hepatic impairement the drug should be used with caution who receive who consume alcohol it is contraindicated in active liver disease. Atorvastatin is also associated with frank, clinically hepatic injury which is apparent but is rare occurring in 1:3000 to 1:5000 patients who are treated. The clinical presentation of hepatotoxicity by atorvastatin varies gently from simple cholestastic hepatitis to mixed forms to hepatocellular injury.The common presentation of cholestatic hepatitis tends to mild to moderate in severiety and self limiting. latency to onset of injury is highly variable ranges from 1month to several years. In most of the cases it arises with in starting 6months (atorvastatin) or several months after a dose.

Musculoskeletal effects: The most reported adverse effects of statins are myopathy, rhabdomyolosis with acute renal failure secondary to myoglobinuria, diarrohea, constipation, myotoxicity. Pitavastatin should be used with caution in patients with predisposing factors for myopathy example: renal impairment, age greater than 65 years, untreated hypothyroidism, and also the patients who receive anti lipemic agents as con concomitant therapy for example: fibric acid derivatives. Risk of myopathy in patients receiving rosuvastatin is seen in Asian patients, renal impairment and exceeding the dose range of 5-40mg daily and concomitant therapy with cyclosporine, macrolide antibiotics like erythromycin anti-fungal specially azole anti-fungals and alcohol. A variety of pharmacokinetic mechanism by these drugs increase the risk of myopathy with statins co administered. Discontinue statin therapy if serum creatinine kinase concentration becomes elevated or myopathy is diagnosed. Verapamil, azole anti-fungals, macrolides, alcohol, diltiazem, and grapefruit juice decreases the metabolism of CYP3A4, CYP2C9 isoenzymes which are involved in the metabolism of statins because of this inhibition it leads to increased risk of toxicity.

Renal effects: Dosage adjustments are required in patients with moderate renal impairment and the patients who are undergoing hemodialysis. Pitavastatin should not be used in severe renal impairment. In moderate renal impairment patients the peak plasma concentration or AUC were 60-79% higher when compared to other healthy individuals. In patients undergoing hemodialysis the peak plasma concentration or AUC were 40-86%. A study found that renal disease and failure occurred more frequently in placebo controls than in pravastatin treated patients with rates of 0.8 and 0.5% respectively. Proteinuria and hematuria are reported in patients receiving rosuvastatin in those persons who receive higher than recommended dosages i.e, 80mg and more frequent in patients who receive 40 mg of rosuvastatin, so dosage reduction must be there for patients receiving 40mg of rosuvastatin daily who have unexplained persistant proteinuria during routine urine analysis testing. Modification of dosage of simvastatin is not necessary in patients with mild to moderate renal impairement but dosage adjustment should be there in patients with severe renal impairment under a close monitoring at a dosage of 5mg daily.

Neurological effects: Statins affect the central nervous system by crossing the blood brain barrier as they are highly lipophilic and has potential to cross BBB**.** The actual exposure of brain to statins is determined by the balance between diffusion in and out of the CNS by transporters. Statins interfere with cholesterol synthesis and theoretically alter adrenal or gonadal steroid hormone production. So they should be used in caution with drugs that may decrease the levels of endogenous steroid hormones example ketoconazole, spironolactone, and cimetidine. Statins may also have beneficial effects in alzheimers disease and dementia.

Special categories: pregnancy: The safety has not yet been established in pregnancy. The women who are wishing to conceive should avoid using statins because it may cause fetal harm as cholesterol products are essential for fetal development. If the patient is using statin therapy and she becomes pregnant the therapy should be discontinued.

Lactation: It is secreted in the milk in rats**,** but not known in human. It is contraindicated in patients using pitavastatin, rosuvastatin, simvastatin. But it is excreted in patients using pravastatin. Discontinue nursing or drug taking into consideration the importance of drug to the women.

Geriatric: Pitavastatin is well tolerated in geriatric severity of adverse effects reported in older age people is similar to those in younger adults. Reduction in LDL cholesterol is higher in geriatric patients using

simvastatin than in younger patients. In patients of advanced age risk of myopathy is increased so use with caution in such patients. In patients who receive lovastatin 80mg daily as conventional tablet their mean plasma levels of HMG CoA reductase inhibitory activity is 45% higher in geriatrics than in younger adults. Fluvastatin is well tolerated and a recent report by NCEP expert panel suggest that, CHD risk reduction in geriatric patients is seen, by decrease in serum cholesterol concentration. In trials made on 1900 patients using atorvastatin therapy reduction in LDL cholesterol concentration is slightly higher after 6 weeks in geriatrics than in younger adults.

Pediatrics: Safety and efficacy of simvastatin is not established in children younger than 8years of age, adolescent girls should be advised to use contraceptive methods during therapy to reduce the likelihood of unintended pregnancy. There were no detectable adverse effects on growth and section maturation in adolescent boys and girls who are menstruating. The pediatric patients with homozygous familial hypercholesterolemia clinical or biochemical abnormalities are not seen who receive 80mg dosage daily for 1year. The most common adverse effect observed is influenza and infections. There were no detectable effects on growth or sexual maturation in boys or duration of menstrual cycle in girls. The pediatric patients receiving fluvastatin should be revaluated in adulthood in order to achieve adult treatment goals. In pitavastatin safety and efficacy has not been established in pediatric patients younger than 18 years of age.

Therapeutic Uses.[14]

simvastatin: prevention of cardiovascular events it is given as an adjuvant to dietary therapy in patients with coronary heart disease, hypercholesterolemia, to reduce risk of total mortality by reducing coronary heart disease deaths and to reduce coronary and non-coronary revascularization procedures; dyslipidemias it is used as an adjuvant to dietary therapy to decrease elevated serum total cholesterol apolipoprotein-B, high density lipoprotein (HDL), very low density lipoprotein (VLDL);Homozygous familial hypercholesterolemia.

Rosuvastatin- dyslipidemia- it is used as an adjuvant to dietary therapy in the management of mixed dyslipidaemia, primary hypercholesterolemia to reduce elevated non-HDL, LDL, apolipoprotein-B and triglyceride concentration and to increase HDL in patients with heterozygous familial and non-familial hypercholesterolemia; it is also used in management of hypertriglyceridaemia.

Pravastatin- It is used in reducing progression of coronary atherosclerosis in carotid arteries by reducing, primary hyperlipidaemia and mixed dyslipidaemia, primary dysbetalipoproteinemia who donot respond to diet it reduces total LDL cholesterol, VLDL cholesterol triglyceride, non- HDL cholesterol concentrations; hypertriglyceridemia, diabetic dyslipidaemia, nephrotic hyperlipidaemia.

Pitavastatin- dyslipidaemias, primary hypercholesterolemia or mixed primary hypercholesterolemia to reduce elevated non-HDL, LDL, apolipoprotein-B and triglyceride concentration and to increase HDL in patients with heterozygous familial and non-familial hypercholesterolemia; it is also used in management of hypertriglyceridaemia.

Lovastatin- It is used as primary prevention of cardiovascular events who have normal or moderate elevations of LDL cholesterol and below average HDL cholesterol concentrations to reduce the risk of major acute coronary event (i.e., myocardial infraction, unstable angina) and coronary revascularization procedures risk, primary hypercholesterolemia and mixed dyslipdaemia; reducing progression of coronary atherosclerosis and in both coronary and carotid arteries by reducing intimal medial wall thickness.

Fluvastatin- It is used as primary prevention of cardiovascular event, primary hypercholesterolemia and mixed dyslipdaemia, It reduced total and LDL cholesterol concentrations in patients with hypercholesterolemia associated with diabetic dyslipidaemia, renal insufficiency, nephrotic hyperlipidaemia. It has been shown that fluvastatin also decreases proteinuria in patients with immunoglobulin-A nephropathy.

Atorvastatin- primary hypercholesterolemia and mixed dyslipdaemia, hypertriglyceridaemia, primary dysbetalipoproteinemia who donot respond to diet, homozygous familial hypercholesterolemia.

Drug Interactions.[15,16,17,18]

Table 3- drug-drug interactions of different statins

S.NO	Statin drug	Drug interactions	Type of interaction &MOA of interaction
1	Simvastatin	HIV protease inhibitors (saquinavirr, nelfinavir, lopinavir, ritonavir, tipranavir)	**Major-** increase blood levels of simvastatin; increase simvastatin AUC 3059% with saquinavir/ritonavir-400mg/400mg BID; increases the level or effect of simvastatin by affecting hepatic or intestinal enzymes by CYP3A4 metabolism and increases toxicity by OATP1B1 inhibitors, simvastatin increases the level or effect of nelfinavir by P-glycoprotein (MDR1) efflux transporter;
		Amiadarone	**Major-** increase in the blood levels of simvastatin occurs by decreasing the metabolism. Not to exceed simvastatin 20mg daily.
		Azole antifungals(ketoconazole, flucanazole, itraconazole)	**Major-** increase the lev4el or effect of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism; increase toxicity of simvastatin by OATP1B1 inhibitors and may increase risk of myopathy; increases the level of itraconazole by P-glycoprotein (MDR1) efflux transporter.
		Macrolide antibiotics (azithromycin, erythromycin, clarithromycin, Telithromycin, Troleandomycin, ciprofloxacin)	**Moderate-** simvastatin increase the level or effect of azithromycin by P-glycoprotein (MDR1) efflux transporter; **major-** erythromycin will increase the level or effect of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism; **Major-** clarithromycin will increase the level or effect of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism and OATP1B1 inhibitors.
		Calcium channel antagonists (verapamil, diltiazem, nifedipine, azelnidipine, benidipine)	**Major-** verapamil will increase the level or effect of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism. Do not exceed simvastatin 10mg daily when taken together. Both azelnidipine and benidipine have been shown to inhibit metabolism invitro in a concentration-dependent manner. **Moderate-** nifedipine will increase the level of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism.
		Warfarrin	**Minor-** simvastatin, warfarin competition by each drug for CYP3A4 mediated metabolism may result in increased INR (international normalized ratio). **Moderate-** phenytoin will decrease the level of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism. **Major-** increases the effects of one another by pharmacodynamics synergism. Also inhibits CYP2C8 and CYP2C9.
		phenytoin	**Major-** increases the level or effect of simvastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism. **Major-** it acts by inhibiting it acts by inhibiting CYP2C19.
		fibrates (fenofibrate, gemfibrozil)	**Major- -** simvastatin increase the level or effect of digoxin by P-glycoprotein (MDR1) efflux transporter.

		rifampicin clopidogrel digoxin	
2	Rosuvastatin	Fibrates (fenofibrate,gemfibrozil) Warfarin HIV protease inhibitor (saquinavir, nelfinavir, lopinavir, ritonavir, tipranavir) Azole anti-fungals (ketoconazole, fluconazole, itraconazole) Macrolide antibiotics (azithromycin, erythromycin, clarithromycin, telithromycin, troleandomycin, ciprofloxacin) rifampicin digoxin	**Major-** increases the effects of one another by pharmacodynamic synergism; increases toxicity by OATP1B1. **Moderate-** increases the anticoagulant effects of warfarin but doesnot alter warfarin levels, these two combination may lead to bleeding by unspecified interaction mechanism. **Major-** increase toxicity of rosuvastatin by OATP1B1 inhibitors0; nelfinavir increases toxicity by unknown mechanism; lopinavir and ritonavir increases levels of rosuvastatin by decreasing metabolism, limit rosuvastatin dose to 10mg per day; tipranavir same as simvastatin, dose should not exceed 10g per day. **Moderate-** increases toxicity of rosuvastatin by OATP1B1 inhibitors. **Minor-** itraconazole; fluconazole **Minor-** inhibition of GI absorption, increases toxicity of rosuvastatin by OATP1B1 inhibitors; clarithromycin same as erythromycin; **Minor-** increases toxicity of rosuvastatin by OATP1B1 inhibitors. **Minor-** increases toxicity of rosuvastatin by OATP1B1 inhibitors.
4	lovastatin	Phenytoin Rifampicin Warfarin Amiadarone Nefazodone Calcium channel antagonist (verapamil, diltiazem, nifedipine)	**Minor -** same as simvastatin. **Major-** decrease the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, decreases the level or effect by P-glycoprotein (MDR1) efflux transporter. **Moderate-** increase the effect of warfarin by unknown mechanism. **Major-** increase the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, increases the level or effect by P-glycoprotein (MDR1) efflux transporter, donot exceed 40mg of lovastatin. **Major-** increase the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, decreases the level or effect by P-glycoprotein (MDR1) efflux transporter. **Major-** verapamil increase the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, increases the level or effect by P-glycoprotein (MDR1) efflux transporter, do not exceed 20mg of lovastatin if used use lower doses and monitor for lovastatin toxicity i,e., myositis; diltiazem increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, do not exceed

		fibrates (fenofibrate, gemfibrozil) HIV protease inhibitor (saquinavir, nelfinavir, lopinavir, ritonavir, tipranavir) Azole anti-fungals (ketoconazole, fluconazole, itraconazole) Macrolide antibiotics (azithromycin, erythromycin, clarithromycin, telithromycin, troleandomycin, ciprofloxacin)	20mg avoid or use alternate drug; nifedipine increase the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, decreases the level or effect by P-glycoprotein (MDR1) efflux transporter, avoid or use alternate drug. **Major-** fenofibrate increases the effects of one another by pharmacodynamic synergism, avoid or use alternate drug, donot increase 20mg per day of lovastatin. **Major-** saquinavir will increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, & lovastatin increases levels of saquinavir increases by P-glycoprotein (MDR1) efflux transporter, avoid or use alternate drug; **l**opinavir increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism; ritonavir increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, increases the level or effect by P-glycoprotein (MDR1) efflux transporter, avoid or use alternate drug; tipranavir increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism. **Major-** ketoconazole, itraconazole increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism, increases the level or effect by P-glycoprotein (MDR1) efflux transporter, strong CYP3A4 inhibitors increase systemic statin inhibitor and risk of myopathy; flucanozole increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism. **Moderate-** lovastatin increases the level or effect of azithromycin by P-glycoprotein (MDR1) efflux transporter. **Major-** erythromycin, clarithromycin, telithromycin, troleandomycin will increases the level of lovastatin by effecting hepatic or intestinal enzymes CYP3A4 metabolism & and also lovastatin increases the level or effect of erythromycin by P-glycoprotein (MDR1) efflux transporter.

5	Pitavastatin	Macrolide antibiotics (erythromycin, clarithromycin, telithromycin, troleandomycin, ciprofloxacin) Rifampicin Fibrates (fenofibrate,gemfibrozil) Azole anti-fungals (ketoconazole) HIV protease inhibitor (saquinavir, nelfinavir, lopinavir, ritonavir, tipranavir)	**Major**- erythromycin, clarithromycin, telithromycin increases toxicity of pitavastatin by OATP1B1 inhibitors and erythromycin also increases the plasma levels by decreasing the metabolism. **Major-** increases toxicity of pitavastatin by OATP1B1 inhibitors and also increases the plasma levels of pitavastatin by decreasing the metabolism, donot exceed 2mg per day. **Major-** fenofibrate & gemfibrozil increases the effects of one another by pharmacodynamic synergism, and also gemfibrozil increases toxicity of pitavastatin by OATP1B1 inhibitors. **Minor-** ketaconazole increases toxicity of pitavastatin by OATP1B1 inhibitors. **Moderate-** Saquinavir, nelfinavir increases toxicity of pitavastatin by OATP1B1 inhibitors; **Major-** lopinavir, ritonavir increases the levels of pitavastatin by slowing the drug metabolism.
6	Fluvastatin	Digoxin Phenytion Rifampicin Warfarin Clopidogrel Amiadarone Fibrates (fenofibrate,gemfibrozil) Azole anti-fungals (ketoconazole, fluconazole, itraconazole) HIV protease inhibitor (saquinavir, nelfinavir, ritonavir) Macrolide antibiotics (erythromycin, clarithromycin, telithromycin)	**Minor-** digoxin increases toxicity of fluvastatin OATP1B1 inhibitors. **Minor-** fluvastatin increases the level of phenytoin by decreasing metabolism. **Moderate-** rifampin increases toxicity of fluvastatin by OATP1B1 inhibitors or decreases the level or effect of fluvastatin by affecting hepatic enzyme CYP2C9/10 metabolism. **Minor-** fluvastatin increases effects of warfarin by affecting CYP2C9/10 metabolism. **Minor-** increases levels of fluvastatin by decreasing metabolism. **Minor-** amiadarone will increase the level of fluvastatin by affecting hepatic enzyme CYP2C9/10 metabolism. **Major-** fenofibrate, gemfibrozil and fluvastatin either increases effects of one another by pharmacodynamics synergism, avoid or use alternate drug and also gemfibrozil increases toxicity of fluvasatain by OATP1B1 inhibitors. **Minor-** ketoconazole, flucanozole will increase the effects of fluvastatin by affecting hepatic enzyme CYP2C9/10 metabolism and also ketoconazole increases toxicity by OATP1B1 receptors. **Minor-** saqunavir, nelfinavir, ritonavir increases the toxicity of fluvastatin by OATP1B1. **Major-** erythromycin, clarithromycin, telithromycin increases toxicity of fluvastatin by OATP1B1 inhibitors.
7	Pravastatin	Rifampicin Digoxin Azole anti-fungals (ketoconazole) HIV protease inhibitor (saquinavir, nelfinavir, ritonavir) Macrolide antibiotics (erythromycin,	**Minor-** rifampicin increases toxicity of pravasatain by OATP1B1 inhibitors. **Minor-** increases toxicity of pravasatain by OATP1B1 inhibitors. **Minor-** ketoconazole increases toxicity of pravasatain by OATP1B1 inhibitors. **Minor-** saquinavir, nelfinavir, ritonavir increases toxicity of pravasatain by OATP1B1 inhibitors.

		clarithromycin, telithromycin)	**Moderate-** erythromycin increases toxicity of pravasatain by OATP1B1 inhibitors; clarithromycin increases levels of pravasatain by affecting hepatic or intestinal enzymes CYP3A4 metabolism and also increases toxicity by OATP1B1, donot exceed pravastatin dose 40mg per day when coadministered with clarithromycin. **Minor-** increases toxicity of pravasatain by OATP1B1 inhibitors.

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