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EMERGING DRUG INTERACTIONS WITH STATINS: MECHANISMS AND CLINICAL OUTCOMES

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Abstract

Statins are widely used lipid-lowering drugs to prevent heart diseases and are used in both primary and secondary prevention settings. Although stains appear relatively safe but mostly are associated with serious adverse effects like myalgia, myopathy and rhabdomyolysis. These adverse effects are often related to statin- drug interactions. These interactions are associated with the pharmacokinetic and pharmacodynamic properties of drug. The severity of these interactions depends upon the type of specific statin involved and interacting drug. However, factors like advanced age, polypharmacy, co-morbidities increase the risk of adverse effects. So various methodologies and strategies are employed to manage these adverse effects and to increase the therapeutic efficacy. Different strategies like avoidance of high-risk drug combination, dose adjustment, and the use of alternative stations or other safer combinations are employed. It is necessary to clinically educate patients about serious strain-drug interactions. Furthermore, statins may produce a synergistic effect in combination with chemotherapeutic agents. Further research direction also considered to alleviate the risk of adverse effects and improve therapeutic efficacy. This article discusses the mechanisms of statin drug interactions, their clinical outcomes and different strategies to overcome the adverse effects and minimize the risk factors.

Introduction of Statins

Statins, which are also named as 3-hydroxy-3-methylglutarylcoenzyme A (-HMGCoA) reductase inhibitors, are very important in pharmacology to reduce low-density lipoprotein cholesterol and for preventing atherosclerotic cardiovascular disease (CVD). Over the last few decades, their use has led to significant declines in cardiovascular disease and mortality worldwide. However, despite their proven effectiveness, there are clinically significant drug interactions (DDIs) related to statins that can affect patient safety and therapeutic outcomes. Due to the rapid introduction of new therapeutic agents and polypharmacy, especially in elderly patients, there is a need to understand emerging statin interactions, their mechanisms, and clinical outcomes (Mease et al., 2024; Zhou et al.,2024-).

Drug interactions occur when there is an alteration of the pharmacokinetics or pharmacodynamics of drugs. In the case of statins, pharmacokinetic interactions are more important than pharmacodynamics, as they affect plasma concentrations and metabolic clearance. Many statins, for example, simvastatin and atorvastatin, are predominantly metabolized by CYP3A4; the cytochrome P450 family. Inhibitors of this enzyme can increase statin levels, increasing the risk of adverse muscle events such as statin-associated muscle symptoms (SAMS) and rhabdomyolysis. Transporter proteins, such as organic -anion transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (-Pgp-), also regulate statin disposition and are important in clinical interactions (Zhou et al.,2024; Bellosta and Corsini, 2024).

The examination was done to know the interactions between Statin and Quinolone antibiotics that were prescribed in older adults with comorbid infections. Patients taking high-dose statins or concomitant CYP3A4 or transporter inhibitors have more interactions and in those with kidney dysfunction or older age (Zhou et al., 2024). It shows that interactions that were rare in the past have now been common, particularly when Statins are given with those drugs that share a metabolic pathway. Interactions with new therapeutic classes, i.e., antiplatelet agents, have also been seen. For example, Statins and ticagrelor (antiplatelet agents commonly used for the prevention of acute coronary syndrome) cause the risk of rhabdomyolysis. The mechanism was that it causes inhibition of CYP3A4 and drug transporters that cause statin accumulation and toxicity (Sim Mie, 2024).

The complex treatments are common for individuals who have multiple diseases like cancer, which highlights the interactions that were previously overlooked. Nearly 25% of examined cancer medications interacted with statins, the majority of which needed to be monitored or modified according to a comprehensive scoping assessment of statin interactions with oncology treatments. This explains how broadening treatment portfolios outside conventional cardiovascular areas can provide novel statin interaction risk profiles, a factor that has not received enough attention in previous research (Chou et al., 2025). Recent studies have looked at how clinical resource recommendations and regulatory labelling match underlying pharmacokinetic knowledge, going beyond particular interaction situations. There was a comparative study of the FDA in 2024, giving information and a tertiary clinical resource, which states that there is a high susceptibility of pharmacokinetic-based drug-drug interactions. The author argues that past regulatory decisions influence clinical decision-making and more research is needed on interaction studies (Mease et al., 2024).

Aging is something that affects interactions between medications. When older patients have terminal diseases, they usually take many medications at the same time, which increases the chance of bad interactions between these medications. Aging and taking medications at the same time make these patients more likely to have bad outcomes because of the way their bodies process medications as they get older and the fact that they are more likely to have other health problems. Therefore, things that are specific to each patient, such as the patient's age and how well their organs are. Genetic differences, like differences in the SLCO1B1 gene that affect how medications are moved in the body, make the situation even more complicated for the doctor and increase the chance of bad interactions, with statin medications (Alqasrawi et al., 2025).

Pharmacology of Statins

As we have discussed earlier, statins are used for lowering cholesterol, low-density lipoprotein (LDL), and the concentration of triglycerides. They are inhibitors of hydroxymethylglutaryl-CoA reductase enzymes. They not only have a low cholesterol level but have diverse effects that affect systemic metabolic pathways and interindividual therapeutic responses (Sizar et al., 2024). All statins lower circulating low-density lipoprotein cholesterol, but differences in their structure, metabolism and systemic distribution result in variation in their clinical effects and adverse effects (Sizar et al., 2024).

Classification on the basis of Hydrophilicity and lipophilicity

Statins are classified as hydrophilic and Lipophilic based on their solubility in water or lipid-containing media and hepatic uptake characteristics.

1. **Hydrophilic Statins**:

Hydrophilic statins include Rosuvastatin and Pravastatin. They are more hepatoselective and depend less on Cyp450 enzymes

2. **Lipophilic Statins:**

Lipophilic Statins include simvastatin, fluvastatin, lovastatin and atorvastatin. They can easily cross the membrane of a cell and distribute into hepatic tissues. Lipophilic Statins are predominantly used for cardiovascular diseases due to their greater efficacy of lowering low-density lipoprotein cholesterol (Climent et al., 2021). Below is the comparative table of Solubility, CYP Metabolism, Transporter dependence, Bioavailability, Half-life of Statins (Cordina et al., 2024; Muhammad et al., 2025).

Table 1: Comparison of properties of different statins

Statin	Solubility	CYP Metabolism	Transporter Dependence	Bioavailability	Half-life
Simvastatin	Lipophilic	CYP3A4	Moderate OATP	Low	Short
Atorvastatin	Lipophilic	CYP3A4	Moderate	Moderate	Long
Rosuvastatin	Hydrophilic	Minimal CYP	High OATP	Moderate	Long
Pravastatin	Hydrophilic	Non-CYP	High OATP	Moderate	Short
Fluvastatin	Lipophilic	CYP2C9	Moderate	Moderate	Short

Absorption

Absorption depends upon hydrophilicity and lipophilicity. Lipophilic drugs have greater absorption, such as atorvastatin, which is rapidly absorbed after oral administration, but its bioavailability is low (12%) due to first-pass metabolism. While hydrophilic Statins have greater bioavailability. Rosuvastatin has moderate bioavailability (20%) while pitavastatin has the highest bioavailability (60%) (Sizar et al., 2024).

Distribution

All Statins are extensively bound to plasma proteins except Pravastatin; therefore, the pharmacologically active drug is low. So, the highest concentration of circulating drug is Pravastatin (Schachter, 2024).

Metabolism

Statins are metabolized by the CYP450 enzyme system which consists of 30 isoenzymes. The most common are CYP3A4 which metabolize atorvastatin, lovastatin, and simvastatin and CYP2C9 which metabolize fluvastatin. CYP2C9 and CYP2C19 play a minor role in the metabolism of Rosuvastatin. Pravastatin, Pitavastatin and Rosuvastatin undergo metabolism by non-CYP450 pathways. The drugs that are metabolized by CYP450 enzymes cause toxicity due to drug interactions that cause inhibition of CYP450, and drugs accumulate in the body. OATP1B1, which is an anion-transporting polyprotein, helps in hepatic uptake of atorvastatin, rosuvastatin, simvastatin, pitavastatin and pravastatin from the body. On the other hand, OATPB3 is involved in transport of rosuvastatin, fluvastatin and pravastatin (Schachter, 2005; Sizar et al., 2024; Balasubramanian and Maideen, 2021).

Excretion

Statins, like atorvastatin and rosuvastatin and simvastatin, are broken down a lot by the body. So, the amount of statins that are excreted without being changed is small when they are eliminated through the kidneys. Rosuvastatin is different because it does not get broken down much and is mostly excreted in its form in urine and feces. Fluvastatin, lovastatin, pravastatin and simvastatin do not stay in the body for a long time. These statins should be taken in the evening or in an extended-release form, like fluvastatin or lovastatin, to work best. Atorvastatin and rosuvastatin, however, stay in the body for a time and can be taken at any time of day. HMG-CoA reductase inhibitors, which include statins, are also excreted into bile and feces (Sizar et al., 2024).

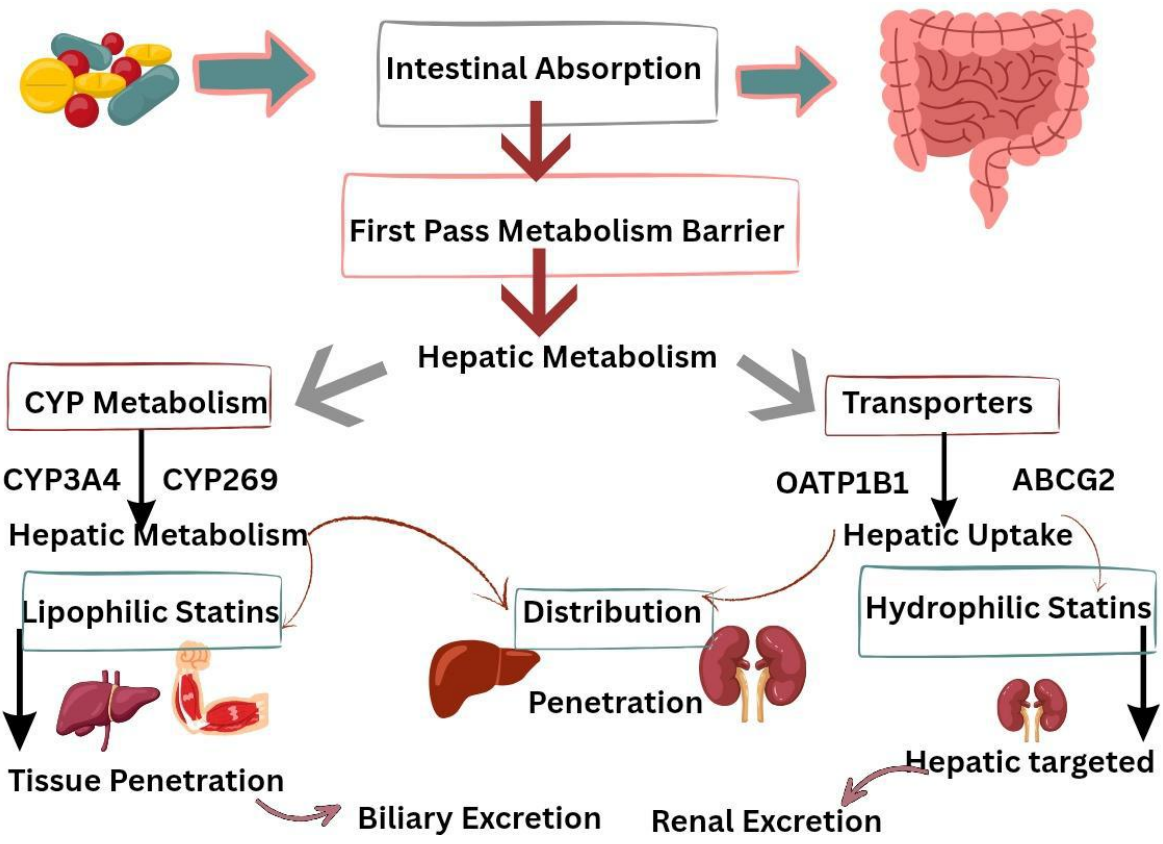

Figure 1: Pharmacokinetics of Statins

Transporter Proteins

Active transport plays a role in how statins work, especially for hydrophilic statins. Certain transporters in the body, like SLCO1B1 and ABCG2, help move statins into and out of the liver. This affects how statins work and how safe they are. Some people's genes for these transporters are different. These differences can have an impact on how well statins work for each person. For example, some changes in the SLCO1B1 gene can make statin levels in the body get too high. This can increase the risk of muscle problems. Changes in the ABCG2 gene have been linked to how the body works (Rajput et al., 2025). Transporter differences are now seen as crucial in making statin treatment personal. Medical specialists are trying to choose the statin or dose based on a patient's specific transporters. This combines what we know about genes and medicines to make treatment better and safer (González-Iglesias et al., 2024; Shi and Han, 2025).

Genetic and Interindividual Variability

Things that are passed down by our parents like the way our bodies break down medicines can affect how well statins work. The way some people's bodies break down statins can be different because of the genes they have. This is true for enzymes like CYP3A4, CYP2C9 and other things that help get rid of statins. These differences can change how quickly statins are removed from the body and how many of them are in the blood. Similarly, the way genes are turned on or off can also affect how the body breaks down statins. This can lead to reactions to medicine in different

people (Shi and Han., 2025). These new ideas have led to a way of giving statin therapy that is based on a person's genetic makeup. This means that doctors can make decisions about which medicine to give and how much to give. This can help the medicine work better and reduce side effects. This is especially important for people who have a lot of genes or who take a lot of medicines that can interact with each other. Statin therapy can be very different from person to person and genetic profiling can help doctors choose the statin for each patient (Rajput et al., 2025).

Mechanisms of Statins

Cholesterol functions in maintaining the integrity and fluidity of the cell membrane. It also interacts with phospholipid fatty acids and increases the membrane packing, so the fluidity and integrity of the membrane are changed (Sultan et al., 2019). The rate-determining step of cholesterol synthesis is inhibited by the inhibition of HMG CoA reductase, which results in up-regulation of LDL receptors and reduction of atherogenic LDL consequences. Statins are among the most effective agents used in the treatment of cardiovascular events (Jasinska et al., 2007). Prevention of cardiovascular disease has been transformed by statins, including thrombotic stroke (Betteridge et al., 2016). Studies suggest that the use of statins has caused various diseases like diabetes mellitus, cancer, cataracts, peripheral neuropathy, depression, Parkinson's disease, cognitive impairments, and many others. One study reported that when elderly individuals with high LDL cholesterol levels had a longer lifespan compared to those receiving statin treatment (Sultan et al., 2019).

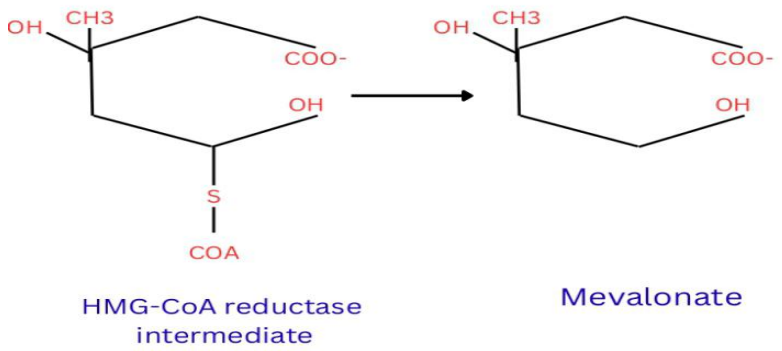

Figure 2: Conversion of HMG-CoA reductase intermediate to Mevalonate

Cellular Mechanism of Statins

Statins are among the most efficient agents for the prevention and treatment of cardiovascular diseases coupled with hyperlipidemia. Statins can be administered in different forms. For example, simvastatin is given in the inactive lactone form, while those given in the active β-hydroxy acid form are pravastatin, fluvastatin, and rosuvastatin (Souich et al., 2017; Afzal et al., 2025).

The major action of statins is the reduction of cholesterol levels in the blood. Cholesterol is produced from acetoacetyl coenzyme A through a pathway consisting of 28 steps. The second step of this pathway is blocked by statins, which is the conversion of 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) into l-mevalonate. This is also called the rate- determining step of cholesterol synthesis, and the enzyme that performs its catalysis is HMG-CoA reductase. Low-density lipoprotein

(LDL) receptors will be reduced by a reduced cholesterol level. The cell surface receptor display is not changed. Probably, the receptor cycle is elevated, by which the entry of LDL-bound cholesterol into the cell is increased, and levels of cholesterol in the blood are reduced as well. Some studies have also shown that the effects of statins are probably partially dependent on cholesterol. Apparently, the risk of myocardial infarction is reduced earlier and more strongly by statins than other cholesterol-lowering compounds at comparable cholesterol levels (Van der Most et al., 2009)

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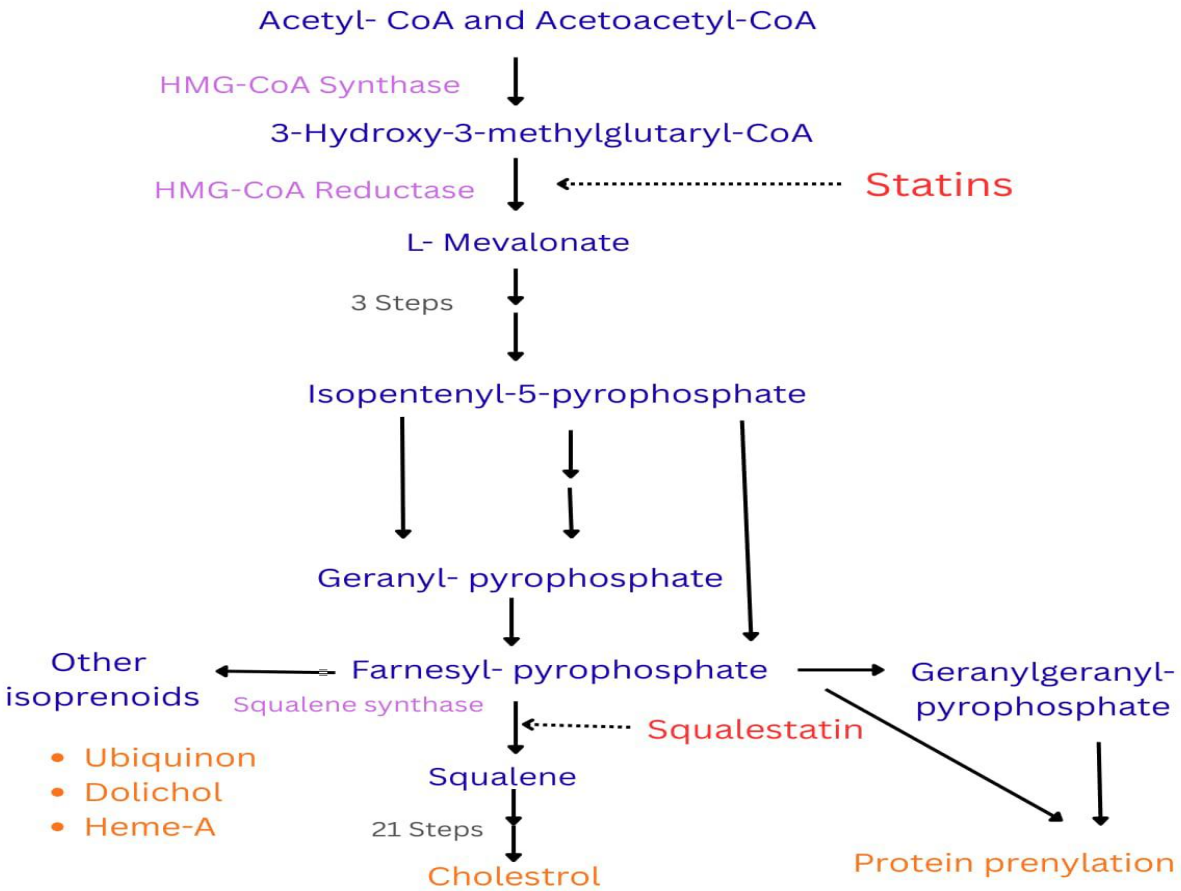

Figure 3: Synthesis of Cholesterol inhibited by Statins

Statins and Stroke

Hydroxymethylglutaryl coenzyme A reductase is found in the hepatic and non-hepatic tissues. Its function is catalysis of the early conversion of HMG-CoA to mevalonic acid due to its structure analogous to HMG-CoA. The cholesterol content is reduced in the liver, which results in downregulation of the loop leading to increased expression of low-density lipoprotein (LDL) receptors and reduction of total serum cholesterol levels. Statins share the same mechanism of their action, but they vary in different aspects like absorption, attachment, removal, and solubility. That's why they show variable efficacy regarding dose in reducing LDL-cholesterol, e.g., Pravastatin is very hydrophilic, so it can barely penetrate cells and is taken up by specific liver receptors. In comparison, simvastatin or lovastatin are lipophilic

and so can penetrate the blood–brain barrier (Endres, 2005).

Statins and Atherosclerotic Disease:

Lovastatin and simvastatin have been regarded as revolutionary treatments for atherosclerotic disease, and these are also the first HMG CoA reductase inhibitors to have acceptance from the regulatory agency for marketed use (Slater et al., 1998). Mechanisms of statins on atherosclerotic vascular disease are difficult to understand. In these different cells, like endothelial cells, leukocytes, macrophages, platelets, and smooth muscle cells, play a vital part. When statins are administered, they act to reduce the attachment of inflammatory cells, decrease stimulation of leukocytes and platelets, and promote vascular remodeling. Several mediators are affected by the statins, which are the cell signaling proteins and other products of the above-named cells. They decrease the ICAM-1, VCAM-1, selectins, ROS, MCP-1, TNF-alpha, IL-1, IL-6, IL -8, MMPs, and cathepsins levels, by which the amount of inhibitors of MMPs, eNOS, IL-10, TGF-beta, or superoxide dismutase is increased (Satny et al., 2021).

Diabetogenic Action of Statins

The mechanism for the development of diabetes by statins is still unclear. Also, the mechanism for the NOD generation is unclear. The inhibition of HMGCoAR activity appears to be a main factor. The effect of statins in producing diabetes involves many mechanisms that alter islet β-cell function, resulting in lower secretion of insulin. Statins partially and reversibly reduce cholesterol synthesis. The factors that contribute to the development of diabetes include reduced HMGCoAR activity coupled with lower LDL-C, slightly increased T2DM risk, and apparent gain in body weight. These findings show that the risk of developing diabetes is relevant to the degree by which activity of HMGCoAR is reduced and also to the statin potency (Carmena et al., 2019).

Myotoxic effects of Statins

Statin -induced myotoxicity results from multiple mechanisms within the muscle cells. The condition is dose-dependent. Within the sarcoplasm, inhibition of HMG-CoA reductase causes a reduction in geranylgeranyl pyrophosphate (GGPP). This decreases interaction with RhoA prenylation and activation, ultimately reducing AKT phosphorylation. As a result, the transcription factor FoxO3 translocates to the nucleus, promoting pathways involved in muscle protein degradation. In mitochondria**,** statins interact with complexes I and III of the oxidative phosphorylation chain, disturbing the normal function of mitochondria. This disruption decreases ATP production while increasing the generation of reactive oxygen species (ROS). Additionally, cytochrome c and calcium ions (Ca^{2+}) may leak into the cytosol. These changes stimulate AMP-activated protein kinase (AMPK), further enhancing FoxO3 nuclear translocation, proteolysis, and apoptosis.

Reduction in AKT activity also deteriorates the translocation of PGC-1α, leading to decreased expression of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as proteins involved in glucose and lactate transport (GLUT4 and MCT1/4). This leads to oxidative stress and impaired metabolism of muscle. Furthermore, inhibition of MCT4 and the chloride channel ClC-1 increases intracellular lactate levels and alters muscle stimulation by reducing chloride conductance. Elevated sarcoplasmic Ca^{2+}, ROS, and lactate levels, combined with reduced ATP availability and chloride conductance, produce clinical symptoms such as fatigue, muscle cramps, and pain. In severe cases, increased oxidative stress,

proteolysis, and apoptosis damage the sarcolemma, leading to elevated serum creatine kinase (CK) levels, which act as a biomarker of myotoxicity (Souich et al., 2017).

Statins and Asthma

In asthma, the effect of statins is transmitted through targeting various chemical messengers that are engaged in asthma phenotype production. It has been revealed through in vivo and in vitro studies that the proliferation of respiratory tract smooth muscle cells and mediators of inflammation are reduced by statins. Station reduces the chemokine release and mucus production from respiratory tract epithelial cells. It also attenuates subepithelial fibrosis and upregulates eosinophils. Statins reduce the increased responsiveness of the respiratory tract, inflammation, and transformation. Contradictory conclusions have been reported regarding the efficiency of statins in clinical examinations based on study design and treatment protocols. Therefore, further attempts are required to assess the function of statins in asthmatic patients (Sawalha et al., 2016).

Interactions of statins

Statins, when used in monotherapy, are generally well tolerated and have a lower incidence of adverse events. Nowadays, most patients use statins along with drugs for other medical conditions, and sometimes statins are generally prescribed or used with other agents like fibrates, ezetimibe, nicotinic acid, etc. So, the concomitant use of such drugs increases the risk and chances for possible pharmacodynamic and pharmacokinetic interaction. So, it is necessary to study these interactions and to know their possible clinical outcomes, to assure optimal performance, safety of drugs, and to avoid certain adverse drug effects (Bellosta & Corsini., 2008; Bellosta & Corsini., 2012). Different types of interactions are discussed as follows:

1. Pharmacokinetic interactions

These interactions alter statin concentration by affecting absorption, metabolism, and transport of statins in the body.

a. CYP3A4 inhibitors:

Antibiotics

Macrolide antibiotics like clarithromycin and erythromycin are strong inhibitors of the CYP3A4 enzyme. Azithromycin shows a lower incidence of myotoxic side effects and rhabdomyolysis on concomitant administration with statins compared to clarithromycin and erythromycin. These macrolides also block OATP1B1, which also accounts for the rise in plasma concentration and exposure of statins (Eljaaly & Alshehri, 2017; Ferri et al., 2024). Research studies show that combining statins and daptomycin does not significantly increase the risk for myotoxic adverse effects and elevation of CK level. In case there is a rise in CK levels, then daptomycin discontinuation will return CK levels to normal (Eljaaly & Alshehri, 2017).

Azoles

Itraconazole, a strong CYP3A4 blocker, increases simvastatin and lovastatin blood levels. It does not increase the level of pitavastatin, fluvastatin, pravastatin, and rosuvastatin, but increases the plasma level of atorvastatin to some extent. Ketoconazole is also a strong blocker of CYP3A4 and increases blood levels of simvastatin and lovastatin but has little effect on rosuvastatin and fluvastatin. Fluconazole is a strong CYP2C9 blocker and strongly increases the blood level of fluvastatin. It also increases blood levels of atorvastatin, simvastatin, and lovastatin. Posaconazole significantly increases the simvastatin level in the blood by inhibiting CYP3A4 enzymes (Eljaaly & Alshehri, 2017; Kivistö et al., 1998).

Immunosuppressants

Cyclosporine and tacrolimus both are metabolized by CYP3A4, also both act as substrates and blockers of P-gp, and inhibitors of OATP1B1. Because of these pharmacokinetic drug interactions, they can lead to higher risk of statin exposure, risk of muscle toxicity, and rhabdomyolysis. Atorvastatin, lovastatin, pitavastatin, and simvastatin combinations with cyclosporine are highly risky combinations (Kellick et al., 2014). Sirolimus and everolimus are both metabolized and transported by CYP3A4 and P-glycoprotein, respectively, so both present a risk for interaction with statins. Their choice for use with any statin, and for their dosing, needs the same guidelines and precautions as for calcineurin inhibitors (Wiggins Saseen et al., 2016).

Protease inhibitors

Coadministration of protease inhibitors like ritonavir and saquinavir with statins increases the exposure of statins and risk of myotoxic side effects. The risk is higher with simvastatin and atorvastatin as they are CYP3A4 substrates (Fichtenbaum et al., 2002; Ray, 2009).

Antiarrhythmic

Several CYP 450 enzymes like 3A4, 2C9, 2D6, and 1A2 are blocked by amiodarone. So concomitant administration of statins with amiodarone elevates the possibility of rhabdomyolysis and myopathy. This risk is higher with simvastatin and lovastatin (Mar et al., 2022). The concomitant administration causes a 4-fold rise in simvastatin and lovastatin plasma concentration, with a higher incidence in elderly people (Yan et al., 2018).

Calcium channel blockers

Increased exposure of simvastatin, atorvastatin, and lovastatin is observed on their simultaneous administration with verapamil and diltiazem. Verapamil and diltiazem both act as substrates and blockers of CYP3A4 and P-gp (Wiggins Saseen et al., 2016; Mar et al., 2022).

Gemfibrozil

Lipid-lowering agents such as gemfibrozil increase the incidence of myotoxic side effects, especially with cerivastatin. It's probably because gemfibrozil interferes with the metabolism of statins by inhibiting their glucuronidation and their elimination. Fenofibrates appear to be more suitable for use in combination with statins as they don't interfere with statins' metabolism and have the same action as gemfibrozil. (Feingold, 2024; Ferri et al., 2024; Ho & Walker, 2012).

b. OATP1B1 transporter inhibitor:

Macrolides

Discussed above in the antibiotics section.

Immunosuppressant

Already discussed above in the immunosuppressant section.

Carbamazepine

Discussed in CYP3A4 inducers.

c.CYP3A4 inducer:

Many drugs effect the efficacy of a statins by lowering their plasma concentration to a level lower than that is required to produce the therapeutic effect. One such example is carbamazepine having CYP3A4 inducing effect. The drugs increase the metabolism of statins by increasing CYP3A4 concentration (Ferri et al., 2024). Other example of such drugs is rifampin (Kyrklund et al., 2002). Rifampin shows a time-dependent interaction as it is a CP3A4 and 2C9 inducer, and OATP1B1/3 blocker. A single dose of rifampin may elevate statin level, but repeated administration reduces statin blood level due to enzyme induction (Eljaaly & Alshehri., 2017). St. John's Wort (*Hypericum perforatum)* has an inducing effect on CYP3A4. It lowers the plasma concentration and exposure of simvastatin but has

no effect on non CYP3A4 substrates like pravastatin (Sugimoto et al., 2001).

d. Absorption inhibitor:

Bile Acid Sequestrants (BASs)

BASs interfere with the absorption of statins by binding to bile acids in the gut. It can lead to GIT-related effects, including constipation, stomachache, abdominal distension (bloat), vomiting, heartburn, anorexia, and indigestion. Care should be taken, especially in the case of elderly patients and during drug administration (Ho & Walker, 2012; Lent & Jialal, 2025).

2. Pharmacodynamic Interactions:

These interactions do not significantly change statin concentration but increase risk of clinical outcomes and risk.

a. Increased muscle toxicity:

Colchicine

Colchicine can increase atorvastatin, simvastatin, and lovastatin exposure. It is because of its metabolism by CYP3A4. It also acts as a substrate for P-gp. The incidence of muscle toxicities rises with the coadministration of statins and colchicine. (Schwier et al., 2022)

Gemfibrozil

Already discussed above.

Nicotinic Acid (Niacin)

Statins, in addition to inhibiting HMG-COA reductase, also inhibit ubiquinone. It plays a vital role in aerobic respiration, which ultimately controls energy in nerves and muscles. So, niacin appears to be useful in alleviating stains induced neuropathy on coadministration. But the concomitant administration of niacin with statins is related to adverse effects like flushing, itching, and fatigue. (Lehrer & Rheinstein, 2020; Ho & Walker., 2012). Also, high doses can worsen glycemic control, so it should be used in low doses and with caution in type 2 diabetic patients (Grundy et al., 2002).

b. Increase bleeding risk:

Warfarin

Warfarin, a vitamin K antagonist, when co-administered with statins, doesn't increase statin exposure significantly. Statins reduce the dose of warfarin needed and significantly increase INR. This effect is particularly stronger with fluvastatin and rosuvastatin, and this interaction is due to protein binding and metabolism of warfarin by CYP2C9, affecting warfarin metabolite concentration and bleeding time (Engell et al., 2022; Wiggins Saseen et al., 2016).

c. Increase liver toxicity:

Alcohol

Statin and alcohol concomitant use can raise the level of liver enzymes (ALT, AST). The risk of alcoholic liver disease and cirrhosis is higher with simvastatin, lovastatin, and atorvastatin as they are substrates for the liver CYP3A4 enzyme (Chiu et al., 2021).

d. Complement lipid-lowering:

Ezetimibe

Ezetimibe is generally safe in all patients. It is also well tolerated in geriatric patients, so it is safe to use in combination therapy (Ho & Walker, 2012). Generally, it is combined with statins to lower LDL levels.

3. Food and Herbal interactions:

Grapefruit juice

Grapefruit juice contains bergamottin and 6′ ,7′ -dihydroxybergamottin(furanocoumarins). Grapefruit juice elevates the blood level of statins, thereby amplifying the risk of myotoxicity and rhabdomyolysis. They irreversibly block the CYP3A4, affecting the metabolism of CYP3A4 substrates such as simvastatin, lovastatin, and atorvastatin. Pravastatin, Rosuvastatin, and Fluvastatin show minimal interaction with grapefruit juice. To a small extent, it also inhibits Pgp and organic acid transport proteins (OATPS)

(Ateş & Şahin, 2023; Saathoff, 2018; Baraka et al., 2021).

Pomegranate juice

Polyphenols like ellagic acid and punicalagin have the possibility to increase the bioavailability of certain drugs, as they can inhibit CYP3A4 and 2C9 enzymes (Mansoor et al., 2023). The clinical evidence for this possibility is negligible (Rosenblat et al., 2013).

Alcohol

Already discussed above.

St. John's Wort:

Already discussed above.

Table 2: Potential pharmacokinetic and pharmacodynamic interactions of statins

Drug	Statins	Type of interactions	Recommendation	Reference
Antibiotics				
Clarithromycin	Atorvastatin	A CYP3A4 inhibitor blocks OATP1B1	Require caution, and dose reduction of statin	(Ferri et al., 2024)
	Simvastatin,	A CYP3A4 inhibitor blocks OATP1B1	Contraindicated combination	(Eljaaly & Alshehri., 2017)
	Pravastatin	A CYP3A4 inhibitor blocks OATP1B1	Require caution, and dose reduction of statin	(Zhuangqi & Shuxin., 2025)
Erythromycin	Simvastatin	A CYP3A4 inhibitor blocks OATP1B1	Contraindicated	(Zhuangqi & Shuxin., 2025; Ferri et al., 2024)
	Pravastatin	A CYP3A4 inhibitor blocks OATP1B1	Dose adjustment	(Eljaaly & Alshehri., 2017)
		CYP3A4 and	Simultaneous	(Zhuangqi & Shuxin., 2025;

Rifampin	Atorvastatin	CP2C9 Inducer OATP1B1 Blocker	administration recommended	Eljaaly & Alshehri., 2017)
Azoles				
Itraconazole	Simvastatin and Lovastatin	strong CYP3A4 blocker	Avoid coadministration	(Eljaaly & Alshehri., 2017; Kivistö et al., 1998)
Ketoconazole	Simvastatin and Lovastatin	strong blocker of CYP3A4	Avoid coadministration	(Eljaaly & Alshehri., 2017; Kivistö et al., 1998)
Fluconazole	Fluvastatin	CYP2C9 blocker	Limit dose Use alternative statins	(Eljaaly & Alshehri., 2017; Kivistö et al., 1998)
posaconazole	Simvastatin and Lovastatin	CYP3A4 blocker	Use with cautions	(Eljaaly & Alshehri., 2017; Kivistö et al., 1998)
Protease inhibitors				
Ritonavir, Saquinavir	Simvastatin Atorvastatin Pravastatin	Inhibit CYP3A4 Enzyme	Avoid combination Safe alternative	(Ray, 2009; Fichtenbaum et al., 2002)
Immune suppressants				

Cyclosporine, Tacrolimus, Sirolimus Everolimus	Simvastatin, Lovastatin	metabolized by CYP3A4, also both act as substrates amd blocker of P-gp, and inhibitors of OATP1B1	Avoid combination	(Wiggins Saseen et al., 2016; Kellick et al., 2014)
	Rosuvastatin, Pravastatin, Pitavastatin	Metabolized by CYP3A4, also both act as substrates and blockers of P-gp, and inhibitors of OATP1B1	Require dose limit	(Wiggins Saseen et al., 2016)
CNS drugs				
carbamazepine	Atorvastatin, simvastatin, pravastatin, lovastatin	CYP3A4-inducing effect OATP1B1blocker and P-gp inducer,	Avoid the combination if possible Switch to a safer alternative.	(Ferri et al., 2024)
	fluvastatin	CYP2C9 blocker	Take cautions	(Wiggins Saseen et al., 2016; Kyrklund et al., 2002)
Lipid-lowering agents				
Gemfibrozil	Lovastatin, pravastatin, and simvastatin	inhibits glucuronidation and the elimination of statins	Avoid combination	(Feingold., 2024; Ferri et al., 2024; Ho & Walker., 2012)
	Atorvastatin, pravastatin, rosuvastatin, fluvastatin	inhibiting their glucuronidation, and with their elimination	Combination acceptable if indicated	(Wiggins Saseen et al., 2016)
Ezetimibe	All statins	Minimal interaction	Safe combination	(Ho & Walker., 2012)

Nicotinic acid	Statins	Statins inhibit ubiquinone (coenzyme Q10)	Recommended for alleviating stain-induced neuropathy Caution in patients with type 2 diabetes	(Lehrer & Rheinsteine 2020; Ho & Walker., 2012; Grundy et al., 2002)
Bile acid sequestrant	Statins	Interferes with the absorption of statins by binding to bile acids in the gut.	Combination therapy is generally safe if timing is correct	(Ho & Walker., 2012; Lent & Jialal., 2025)
Antiarrhythmics				
Amiodarone	Simvastatin, Lovastatin	Block CYP 450 enzymes like 3A4, 2C9, 2D6,	Require dose adjustment	(Mar et al., 2022; Yan et al., 2018)
	rosuvastatin, pravastatin, fluvastatin, and pitavastatin		No dose adjustment required	(Wiggins Saseen et al., 2016)
	atorvastatin		No dose adjustment required	(Wiggins Saseen et al., 2016)
Calcium channel blocker				
Verapamil, Diltiazem	Simvastatin Atorvastatin lovastatin	substrate and inhibitor of CYP3A4 and P-gp	Combinations may be preferred when the benefit dominates potential risk	(Wiggins Saseen et al., 2016; Mar et al., 2022)
Anti-inflammatory				
Colchicine	Simvastatin Atorvastatin lovastatin	Metabolized by CYP3A4. Substrate of p-gp	Increased statin exposure/increased risk for myotoxicity	(Schwier et al., 2022; Wiggins Saseen et al., 2016)

Anticoagulants				
Warfarin	Fluvastatin Rosuvastatin	Blocked Metabolism by CYP2C9	Monitor the increased INR carefully	(Wiggins Saseen et al., 2016; Engell et al., 2022)
Fruit juices and drinks				
Grapefruit juice	Simvastatin, Lovastatin, and Atorvastatin	Irreversible blockage of CYP3A4, Inhibit p-gp and OATP	No concomitant administration	(Ateş & Şahin, 2023; Saathoff., 2018; Baraka et al., 2021)
Pomegranate juice	Simvastatin, Lovastatin, and Atorvastatin	CYP3A4 and 2C9	Avoid a large quantity of juice with CYP3A4 substrates	(Rosenblat et al., 2013; Mansoor et al., 2023)
Alcohol	Simvastatin, lovastatin, and atorvastatin	Alter liver enzyme function	Caution is required for liver disease.	(Chiu et al., 2021)
Herbs				
St. John's Wort	Simvastatin	Induces liver and intestinal CYP3A4 enzymes.	Avoid concomitant use. Requires close monitoring.	(Sugimoto et al., 2001)

Clinical outcomes and Risk factors

Statin monotherapy is significantly accepted with less chance of toxicity. Both myopathy and an asymptomatic elevation in hepatic transaminases are commonly occurring side effects that are linked with statin therapy. The possible statin and other drug interactions need careful monitoring because statins are recommended for extended periods, as many patients usually receive medication treatment for coexisting diseases throughout statin use (Bellosta & Corsini, 2012). The advantages of statins are widely recognized. However, muscle-related side effects, including myopathy and rhabdomyolysis, that are linked with statin use can be more dangerous. Sometimes, adverse effects are related to altered drug kinetics. Effective inhibitors of CYP 3A4 considerably raise the serum levels of potential metabolites of simvastatin, lovastatin, and atorvastatin (Hirota & Leiri, 2015). Statins have not been confirmed to increase the danger of carcinoma, cognitive decline, affective disorders, or renal issues.

Though statin-drug interactions are widely reported, particularly those that interact with the cytochrome

P450 enzyme group. There are different frequencies of myopathy recorded in studies ranging from 0.1-10%, but many of these studies use varying explanations, have different strategies of data acquisition, and have greater levels of biased documentation (Ramkumar et al., 2016). Drug relationships that increase the plasma concentrations of statins can raise the chance of dose-related side effects, including muscular discomfort, muscle disease, and severe muscle injury (Thai et al., 2016). The potency of some drugs may be increased or decreased by concomitant use of statins and other medications. Conditions such as muscular disorder, muscle breakdown, and renal failure are associated with statin toxicity. The use of statins in combination with clarithromycin, amiodarone, and colchicine may lead to rhabdomyolysis and myopathy. Therefore, cautiously observe the symptoms of myalgia and fatigue with concurrent treatment (Alyahawi et al., 2024).

The concomitant use of statin and fibrate drugs for mixed lipid abnormality is linked with an increased chance of muscular disorder up to 5%. There should be precautions for the use of Gemfibrozil with different statin drugs in which the interaction occurs via the CYP 3A4 enzyme and glucuronidation pathways. Grapefruit juice is an effective inhibitor of cytochrome P450 3A4 and can increase the risk of adverse effects with atorvastatin, lovastatin, and simvastatin. Patients should be counselled not to use grapefruit juice with these types. Anti- epileptic drugs such as phenytoin, carbamazepine, and phenobarbitone may decrease the statin drug concentration because these drugs are effective inducers of the cytochrome P450 enzyme. So, in these patients, dose modification or altered therapy of pravastatin is required (Ramkumar et al., 2016). Colchicine and statins are co- administered as prophylaxis and for the management of cardiac disorders, autoimmune disorders, and gouty arthritis.

According to literature, interaction may be linked with critical muscular disorder and severe muscle injury. Medication repositories and professional societies' protocols are deficient in detailed data related to possible causes and unique patient factors linked with drug- drug interactions. This may cause limited and contradictory advice on managing drug - drug interactions between statins and colchicine. Separately, statins and colchicine lead to muscle damage, which may proceed to muscle breakdown (Schwier et al., 2022). The combined proportional effects of antihypertensive drugs and statins on cardiac outcomes seem to be synergistic. The results do not rule out a potential interaction between treatments that could produce an effect slightly greater than multiplicative on cardiovascular events. However, it is improbable that the combined impact of treatments is weaker than a multiplicative effect. The recent data show that concomitant therapy with statins and antihypertensive drugs typically provides a combination of the minimum expected decrease in relative danger of each therapy (Sundstrom et al., 2018).

The joint use of atorvastatin with nicotinic acid, erythromycin, fibric acid derivatives, or azole antifungals may increase the danger of side effects such as muscular disorder or muscle breakdown. Therefore, it should be prevented wherever possible. The number of atorvastatin interactions ranges from about 44.28% of patients aged 60 or above to about 31.8% of patients aged between 50 and 59. The interactions of atorvastatin that come in category C (44.64%) need to be managed through therapy, and no step is required in category B (41.43%). But we should prevent the combination of category X (0.71%). In literature, the likely interactions are atorvastatin with

esomeprazole (16.07%), clopidogrel (12.64%), and sitagliptin (12.14%) (Dighriri et al., 2021).

Moreover, aged people showed significant clinical outcomes from drug interactions. These outcomes are due to age-associated bodily changes in drug pharmacology and drug efficacy response to medicines, individual differences, elderly conditions, nutritional health, co-morbidities, and multiple medications. The occurrence of likely drug-drug interactions varied between 1.5 and 47.4% and is linked with raised chances of inpatient care (Thai et al., 2016). The treatment of cardiac diseases like coronary artery disease and congestive heart failure, along with multi-morbidities, involves the use of various drugs that can raise the chance of statin- drug interactions in elderly people. Furthermore, the use of statin treatment for an extended period creates the notable possible statin-drug interactions that are susceptible to side effects like muscular symptoms, decreased mobility, and the likelihood of falling (Thai et al., 2016).

Table 3: Statin- drug interactions with clinical outcomes

Interacting drugs	Statins effected	Clinical outcomes	References
Clarithromycin	Simvastatin, Atorvastatin, lovastatin	Increased risk of myopathy and rhabdomyolysis	Hirota & Leiri, 2015
Amiodarone	Simvastatin, Atorvastatin	Muscle toxicity	Alyahawi et al., 2024
Gemfibrozil	Most statins	Increased risk of myopathy	Ramkumar et al., 2016
Colchicine	Several statins	Several muscular damage	Schwier et al., 2022
Clopidogrel	Atorvastatin	Increased adverse effects	Dighriri et al., 2021

Management Strategies for Drug Interactions with Statins

1. Avoidance of High-Risk Drug Combinations

Statins that are metabolized through the CYP3A4 pathway, including atorvastatin, lovastatin, and simvastatin, should generally not be used together with strong CYP3A4 inhibitors such as diltiazem, erythromycin, or azole antifungals because this interaction can increase the likelihood of statin toxicity. Coadministration of these statins with clarithromycin or erythromycin should be avoided (Eljaaly & Alshehri, 2017). Similarly, concomitant use of itraconazole or ketoconazole with simvastatin and lovastatin is contraindicated. Simvastatin and lovastatin are significantly metabolized by CYP3A4 and therefore should not be used with protease inhibitors such as darunavir, ritonavir, and lopinavir. Coadministration of lovastatin or simvastatin with cyclosporine or tacrolimus may increase the toxicity and should be avoided. Another important precaution is that gemfibrozil should be avoided with lovastatin, pravastatin, and simvastatin.

2. Use of Safer Alternative Statins

When drug-drug interactions cannot be avoided, clinicians may consider selecting statins that have a lower potential for CYP3A4-mediated interactions. When erythromycin therapy is required, rosuvastatin or fluvastatin may be preferred since they have a lower potential for interaction (Hylton Gravatt et al., 2017). Azithromycin is also considered a safer macrolide alternative when co-administered with statins. In addition, pitavastatin, fluvastatin, and pravastatin are not significantly affected by coadministration with itraconazole (Eljaaly & Alshehri, 2017). Pravastatin and rosuvastatin are preferred for administration with HIV protease inhibitors (Courlet et al., 2020). Furthermore, when statin-fibrate combination therapy is required, fenofibrate is preferred because it has a lower incidence of DDIs compared with statin-gemfibrozil combination therapy (Kellick et al., 2014). A non–CYP3A4-metabolized statin is also preferred when used in combination with diltiazem or verapamil (Wiggins et al., 2016).

3. Statin Dose Adjustment:

Dose adjustments may be required when statins are used with interacting medications. When pravastatin is prescribed alongside clarithromycin, the daily dose should generally be limited to a maximum of 40 mg (Eljaaly & Alshehri, 2017). Similarly, the recommended dose of atorvastatin should not exceed 10 mg/day when used with ritonavir-containing protease inhibitors (Courlet et al., 2020). If gemfibrozil must be used with atorvastatin, pitavastatin, or rosuvastatin, clinicians should prescribe the lowest effective statin dose to decrease the risk of myopathy. In addition, when cyclosporine or tacrolimus is used with statins, the daily dose of fluvastatin, pravastatin, and rosuvastatin should generally not exceed 40, 20, and 5 mg daily, respectively (Wiggins et al., 2016). Atorvastatin doses greater than 10 mg/day are not recommended with cyclosporine or tacrolimus without close monitoring of creatine kinase levels and signs of muscle toxicity. Doses of lovastatin or simvastatin greater than 20 mg/day with amlodipine are not recommended. Similarly, doses of simvastatin greater than 10 mg/day and lovastatin greater than 20 mg daily when used with diltiazem or verapamil are not advised (Wiggins et al., 2016).

4. Temporary Discontinuation

If coadministration cannot be avoided, it is recommended that the patient temporarily discontinue their statin during the course of macrolide therapy (Hylton Gravatt et al., 2017; Akram et al., 2026).

Management of Food-Drug Interactions

Consumption of grapefruit juice may block intestinal CYP3A4 enzymes and certain transport proteins, which can lead to higher circulating levels of statins in the body. Therefore, grapefruit juice should be limited when taking statins. Some recommendations suggest limiting intake to approximately 60 mL per day. Patients should limit or avoid grapefruit juice because separating intake from statin dosing does not completely prevent the interaction (Kellick et al., 2014).

Monitoring for Adverse Effects

Drug-drug interactions significantly contribute to the development of statin-associated myopathy. Severe statin-associated muscle injury, such as rhabdomyolysis, typically presents with intense muscle pain and a substantial increase in muscle enzyme levels, often exceeding ten times the upper limit of normal. The use of simvastatin at a dose of 80 mg per day is generally discouraged due to the increased likelihood of muscle-related adverse effects (Wiklund et al., 2013).

Clinical and Laboratory Surveillance

Appropriate clinical and laboratory monitoring is essential when patients receive statin therapy, particularly when interacting medications are used. Patients receiving statins should be observed for signs like muscle discomfort, weakness, or dark urine, as these symptoms may suggest muscle damage. Evaluation of liver function is recommended before initiating treatment with statins. Monitoring of renal function through measurements such as serum creatinine or creatinine clearance may also be necessary in certain patients. Lipid levels should be evaluated at baseline and reassessed 4-12 weeks after starting therapy or adjusting the dose, with periodic monitoring thereafter (Sizar et al., 2024).

Patient Education

Healthcare providers should counsel patients starting statin therapy about the appropriate dosage, potential side effects, and the importance of taking the medication as prescribed. Nursing staff should confirm adherence to therapy and ask about any new symptoms related to statin use. Patients should also be advised to report any unusual symptoms, particularly muscle pain or weakness. In addition, patients should inform their healthcare providers about all medications they are taking, including over-the-counter drugs and herbal supplements, to reduce the risk of harmful drug interactions (Sizar et al., 2024).

Future Directions for the Use of Statins

Statins are generally considered a base in the prevention of heart and vascular disease and have gained great recognition in cancer studies due to their extensive effects beyond cholesterol regulation, especially their roles in inhibiting different types of cancers, including breast and colorectal cancer. Marked variability remains in many of the clinically reported antitumor effects of statins, possibly due to diversity in statin type, dosage, duration of treatment, and pharmacogenomic features. While integrative therapies embracing statins with drug-based cancer therapy and immune-based therapy have displayed complementary effects in some studies, their practical application is yet to be recognized. However, the newest evidence indicates that statins have a putative role in decreasing breast and colorectal cancer-linked mortality rates. In the treatment of colorectal cancer, statins have demonstrated promising results, especially when used with anti-cancer agents (Dang et al., 2025). Dyslipidemia is a prevailing susceptibility for the development of coronary artery disease. Statin therapy is confirmed in several trials to lower the chances of acute cardiac and blood vessel disease and is the first-line treatment of atherothrombosis. Statins are currently prescribed as a primary treatment for dyslipidemia (Phan & Toth, 2013).

NASH is a pathogenic strain that is responsible for hepatic lobular inflammation. Once intra-lobular inflammation is induced in NASH, it is exacerbated by numerous maladaptive pathways that develop throughout the hepatic milieu, which culminate in liver fibrosis and hepatic melanoma. Redundant deposition of cholesterol in the liver tissue and blood vessels can trigger malfunctions such as steatosis of hepatocytes and atherothrombosis. Compromised hepatic lipid equilibrium and cholesterol clustering are deeply interlinked with the pathogenesis of NASH. As a result, downregulated hepatic cholesterol homeostasis leads to a 'nonspecific' pathogenesis of hepatocyte destruction and incomplete blockade of blood vessels. The hypocholesterolemia effect of statins shows the capability for offering therapeutic efficacy in NAFLD. Statins are gaining clinical traction for their pleiotropic effects, which surpass their cardinal role in regulating cholesterol. This phototherapeutic potential, termed ‘statin

pleiotropy', has opened the doors to a new scientific frontier, refining our insights into statins' broad-spectrum impact on CVD (Zhang et al., 2024).

Statins, most used for cardiovascular risk management, exhibit therapeutic aspects in MASLD by suppressing LDL and alleviating key coronary artery disorders involving atherosclerosis. The AASLD, which stands for the American Association for the Study of Liver Diseases, has directives that endorse statins for patients with MASLD and lipid metabolism disorders. Beyond the scope of their lipid-lowering action, statins also reduce inflammation and inhibit fibrogenesis. This may improve the worsening of liver fibrosis and suppress liver-associated diseases, such as end-stage liver disease and hepatic melanomas (Zhou et al., 2025).

Statins are commonly used for their lipid-lowering capabilities and have also been peer reviewed for their enhanced therapeutic effects, encompassing remarkable anti-inflammatory actions. Beyond their cholesterol-regulating effects, statins also influence inflammatory pathways by checking the levels of proinflammatory mediators, stunting the exacerbation of adhesion receptors, and optimizing the integrity of plaques. This action mediates a decrease in levels of inflammatory biomarkers, mimicking the effect observed with inflammation-reducing drugs (Mitsis et al., 2024).

Observational studies and "The Gold Standard" presented equivocal data on the effects of statins on depression. Therapeutic repurposing is the method of identifying newly recorded therapeutic effects of existing drugs. As the risk-benefit ratio of licensed agents is well calculated, repurposing of therapeutic agents presents a new, broad, and economically viable management strategy for working on new pharmacological cures for depression. One such category of drugs that has gained interest in this field is statins. Station inhibits HMG CoA reductase. Many Clinical experiments have provided solid proof that the usage of statins as adjuvants along with antidepressants is very effective in the treatment of depression. Multiple studies have postulated several mechanisms to describe the potential anti-depressive actions of statins. Furthermore, statins are indicated to inhibit thrombogenesis and boost cerebral perfusion, a process related to depression biology (Jiang et al., 2023).

Conclusion

Statin drug interactions are important to understand pharmacokinetic mechanisms. They are lipid-lowering agents whose pharmacokinetics depend on solubility, metabolism, transporters, and genetic variability. Statins are effective cholesterol-lowering agents that inhibit HMG-CoA reductase and reduce cardiovascular risk. Besides this, they exhibit multiple biological actions, although their use may also be associated with certain diseases like myotoxicity, asthma, etc. Interactions of statins range from pharmacokinetics, pharmacodynamics and interactions with food and herbs. Healthcare professionals must monitor these to ensure drug efficacy and lower risk for ADRs. Statins interact with different drugs and give clinical outcomes depending on the severity of their interactions. Effective management of statin therapy requires careful attention to potential drug-drug and food-drug interactions. Appropriate statin selection, dose adjustment, and regular monitoring help reduce the risk of adverse effects such as myopathy. Patient education and coordinated healthcare management are essential to ensure safe and effective treatment outcomes. Statins remain essential drugs for managing cardiovascular diseases and controlling cholesterol. Their pleiotropic effects suggest promising future roles in

cancer, liver diseases, and depression, though further clinical research is required to confirm their therapeutic potential.

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