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Review Article

Variations in Genes and Their Influence on Atorvastatin's Effectiveness: Tailoring Hyperlipidemia Therapy

Hufsa Arooj[1], Syeda Quratulain Ali[1], Faiza, Naseer*[2]

[1]Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[2]Department of Biosciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan.
*_Correspondence_: faiza.scps@stmu.edu.pk

Abstract

Hyperlipidemia, characterized by elevated levels of lipoproteins in the blood, is a significant public health concern due to its association with cardiovascular diseases like coronary artery disease (CAD) and stroke. Lipid-lowering agents mitigate the risks associated with hyperlipidemia, with statins, specifically 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, being the frontline treatment. Atorvastatin is one of the most widely prescribed drugs of this class. However, the safety and efficacy of Atorvastatin vary among individuals. Despite the widespread use of statins, adherence to the regimen remains a challenge, with up to 50% of patients discontinuing treatment within the first year. Statin intolerance, often due to musculoskeletal symptoms, is a significant reason for nonadherence. Genetic factors play a substantial role in statin disposition and adverse events, adding to the complexity of treatment response. This review article will explore the pharmacogenetics of statins with particular emphasis on Atorvastatin, i.e., genetic polymorphisms in *APOE, HMGCR, cytochrome P450 enzymes (CYP3A4, CYP3A5, and CYP2D6), CETP, LDLR, PCSK9, ABCB1, ABCG5/8, SLCO1B1*, and *KIF6*, and the influence on its hypolipidemic outcomes. Understanding the impact of genetic polymorphisms can aid in predicting individual responses to statin therapy, optimizing treatment outcomes, and preventing adverse effects. By tailoring hyperlipidemia treatment based on genetic profiles, personalized medicine can be achieved, bringing us closer to optimal management and control of hyperlipidemia-related health risks.

Keywords: Atorvastatin, genetic polymorphism, HMG CoA reductase, efficacy, adverse effects, statins, myopathies

1. Introduction

Hyperlipidemia, characterized by the elevation of lipoproteins in the blood, plays a vital role in the pathogenesis of cardiovascular diseases such as coronary artery disease (CAD)(Padhye and Yadav 2022; Alloubani, Nimer, and Samara 2021). Lipid-lowering agents significantly reduce the risk of cardiac morbidity and mortality. Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, are first-line treatments and are thought to be considered the most effective lipid-lowering drugs for the management of hyperlipidemia (Schaiff, Moe, and Krichbaum 2008). They act by inhibiting HMG-CoA reductase, leading to the upregulation of LDL receptors and increased uptake of Low-Density Lipoprotein (LDL) by hepatocytes, thus decreasing LDL levels in the blood. Stains are the most commonly prescribed medications (Liu et al. 2020), and an increased trend regarding their usage has been witnessed worldwide. Among US adults age 40 or above, statin use has increased to 78.9% from 21.8 million people in 2002-2003 to 39.2 million people in 2012-2013 (Salami et al. 2017).

Among statins, Atorvastatin was the most prescribed and purchased medicine in the

United States in 2006 (Di Stasi et al. 2010) and has been the most widely searched medication in the past 15 years (Lippi, Mattiuzzi, and Cervellin 2019). Despite the widespread use, the safety and efficacy of Atorvastatin vary among different individuals due to environmental behavior and genetic factors (Trompet et al. 2021). Various variations in genes associated with lipid metabolism, their uptake, and transport have been reported. For example, variants in the *SCLO1B1* gene that encode the organic anion transporter polypeptide protein 1B1 (OATP1B1) responsible for statin uptake in hepatocytes are associated with risk for statin-associated myopathy (Brunham et al. 2012b). Assessment of the single-nucleotide polymorphisms (SNPs) that affect the statin response may improve the treatment outcome and prevent their side effects (Ahangari et al. 2020). This article aims to provide a comprehensive review of the existing literature on the pharmacogenetics of statins, especially Atorvastatin, in hyperlipidemia patients.

2. Pathophysiology of Hyperlipidemia

The pathophysiology of hyperlipidemia is studied under two classes: primary and secondary hyperlipidemia. Primary hyperlipidemia results from genetic mutations, either monogenic or polygenic, within the receptor protein. Its pathophysiology involves the development of idiopathic hyperchylomicronemia owing to the defect in lipoprotein lipase activity (LPL) or the absence of surface Apoprotein CII31, leading to hypertriglyceridemia and hyperchylomicronemia (Onwe et al. 2015). Secondary hyperlipidemia is associated with underlying conditions, such as diabetes, myxedema, nephrotic syndrome, chronic alcoholism, and excessive use of drugs like corticosteroids and beta blockers. For example, diabetic patients show low lipoprotein lipase activity, leading to increased liver synthesis of very low-density lipoprotein (VLDL) cholesterol, causing hyperlipidemia. Hypothyroidism-induced low LPL and lipolytic activity reduces the hepatic transformation of cholesterol to bile acids. Similarly, hyperadrenocorticism increases VLDL synthesis, thus causing hypertriglyceridemia and hypercholesterolemia (HC) (Onwe et al. 2015). Hyperlipidemia is a common metabolic disorder involved in the development of atherosclerosis. These atherosclerotic lesions are thought to be caused by the retention and transport of plasma LDL from the endothelial cell layer to the extracellular matrix of sub-endothelial space, where LDL undergoes oxidation and attracts monocytes that are transformed into macrophages and further accelerate LDL oxidation. This process triggers an inflammatory response mediated by cytokines (Onwe et al. 2015). Also, hyperlipidemia can directly affect the heart's systolic function and electrophysiology, which may be caused by the slow accumulation of cardiac lipids, continuous systemic oxidative stress, and mitochondrial dysfunction (Yao, Li, and Zeng 2020).

3. Epidemiology of Hyperlipidemia

Hyperlipidemia involves increased cholesterol levels, including high-density lipoprotein (HDL) and low-density lipoprotein cholesterol (LDL-C). People with hyperlipidemia are more vulnerable to cardiovascular diseases (Karr 2017). It is one of the leading causes of death in the United States. More than 53% of adults in the US have elevated low-density lipoprotein (LDL) levels (Karr 2017). The global prevalence of hyperlipidemia is also high. In 2008, WHO reported a 39% occurrence of elevated total cholesterol (37% for males and 40% for females)

among adults worldwide. Recent statistics documented that 28.5 million adults aged 20 or above have raised serum total cholesterol, with a prevalence of 11.5% (Al-Zahrani et al. 2021). In the same report, WHO estimated that the prevalence of dyslipidemia in Southeast Asia was about 30.4% and 36.7% in the Western Pacific (Lin et al. 2018). On average, about 16% of normal and 68% of obese people develop hyperlipidemia in South Asia (Misra and Khurana 2011). In the second national diabetes survey of Pakistan (to observe the prevalence and pattern of hyperlipidemia in the Pakistani population), 10,384 participants were studied; 39.3% of subjects had hypercholesterolemia, 48.9% had hypertriglyceridemia, and 39.7% had high LDL-C levels, while 83.9% of men and 90% of women had low HDL levels. According to the report, High LDL and Low HDL levels were more prevalent in the age group 40-49, and the incidence of hypertriglyceridemia and HC was highest in people aged 50-59 years (Basit et al. 2020).

4. Treatment Options

The primary goal of treating hyperlipidemia is to correct the levels of lipids in the blood and prevent morbidity and mortality associated with hyperlipidemia. A combination of lifestyle modification and pharmacotherapy can manage dyslipidemia. Treatment options available to manage dyslipidemia are as follows:

4.1. Lifestyle Modification

The initial approach to managing hyperlipidemia is lifestyle modification, which is crucial in managing lipid levels. It includes adopting a heart-healthy diet low in trans fats, saturated fat, and cholesterol, smoking cessation, maintaining a healthy weight, and regular weekly exercise for at least 150 minutes (Saha, Banks, and Whayne 2021).

4.2. Pharmacotherapy

Statins, especially HMG-CoA Reductase Inhibitors, are the first-line treatment agents for hyperlipidemia. These agents prevent endogenous cholesterol synthesis by inhibiting the enzyme HMG-CoA Reductase, thereby interfering with the production of cholesterol precursor, mevalonic acid (Stancu and Sima 2001).

4.2.1. Bile-Acid Sequestrants (BAS)

In humans, bile acids are present as bile salts, produced from cholesterol in the liver. They are secreted from the cholecyst in the small intestine but are reabsorbed. BAS are large polymers that form complexes with these salts and prevent their reabsorption (Feng et al. 2021).

4.2.2. Nicotinic Acid (Niacin)

Niacin, also known as Vitamin B3, is a lipid-lowering agent effective in reducing the levels of low-density lipoprotein(LDL) cholesterol, triglycerides (TGAs), and lipoprotein(a) and increasing high-density lipoprotein(HDL) cholesterol.(Landray et al. 2014) These agents reduce the lipolysis in the adipose tissues, reducing the production of LDL lipoproteins in the liver. Nicotinic acid receptors activate the nicotinic acid receptor HCA2 (GPR109A). These receptors are G-protein coupled receptors. Activation of these receptors inhibits adenylyl cyclase. (Julius and Fischer 2013)

4.2.3. Probucol

Probucol has shown its effectiveness in regulating lipid levels in treating various forms of hypercholesterolemia, including non-familial hypercholesterolemia, homozygous familial hypercholesterolemia, and heterozygous familial hypercholesterolemia. Although the mechanism of action is not entirely known, this drug is believed to be a potent antioxidant of LDL-C (Buckley et al. 1989).

4.2.4. Fibrates

Fibrates reduce the levels of LDL-C and chylomicrons. However, these agents should be started after dietary and lifestyle modification (Brown 1987). Fibrates activate peroxisome proliferator-activated Receptor alpha (PPAR-alpha) to enhance the breakdown of TGA in the circulation, leading to decreased TGA levels (Bougarne et al. 2018).

Cholesterol absorption inhibitors (ezetimibe): ezetimibe inhibits the absorption of cholesterol by blocking the Niemann-Pick C1-Like 1(NPC1L1) protein in the small intestine(Davis and Veltri 2007). It is often used with statins (Chilbert and VanDuyn, 2022).

4.2.5. PCSK9 Inhibitors

Protein convertase subtilisin/kexin type 9 (PCSK9) proteins bind to LDL receptors on the cell surface, which clear cholesterol from circulation, leading to its degradation (Davis and Veltri 2007). Alirocumab and evolucumab are both monoclonal antibodies that target the PCSK9 and degrade it. As a result, less PCSK9 is available in circulation. Inclisran is a siRNA that effectively blocks the production of PCSK9 (Davis and Veltri 2007).

4.2.6. Omega-3 Fatty Acids

Omega-3 fatty acids reduce the gene expression of sterol regulatory binding protein enzymes, which control the production of cholesterol and TGAs.

4.2.7. Bempedoic Acid

Bempedoic acid inhibits the triphosphate-citrate lyase (ACL), an enzyme in cholesterol production. Its inhibition reduces cholesterol synthesis and expression of LDL receptors on cells, leading to the clearance of LDL levels from the blood.

5. Role of Statins in Managing Hyperlipidemia

Statins, a medication commonly prescribed for managing hyperlipidemia, have been shown to effectively lower lipid levels and reduce the risk of cardiovascular events (Lopez 2002). The 2013 ACC/AHA recommendations have demonstrated the efficacy of statin therapy in reducing the risk of cardiovascular events in primary and secondary prevention (Adhyaru and Jacobson 2018). Atorvastatin, a commonly prescribed statin, has proven beneficial in lowering LDL-C and is associated with reducing cardiovascular risk events (Adhyaru and Jacobson 2018).

A study was designed to evaluate the safety and efficacy of Atorvastatin compared with simvastatin and pravastatin in hyperlipidemia patients. Results showed that Atorvastatin significantly reduced LDL-C, compared with others, and increased HDL-C levels. The studies concluded that Atorvastatin was more effective than simvastatin and pravastatin (Jose et al. 2012). Similarly, large-scale trials, such as collaborative atorvastatin diabetes studies, also found Atorvastatin to be a beneficial drug in reducing cardiovascular risk in patients with diabetes (Colhoun et al. 2004).

6. Challenges with Statin Therapy

Despite the widespread use of statins, adherence to statin therapy is still a worldwide challenge. It has been reported that up to 25-50% of patients discontinue statin use within the first year after initiation of treatment (Ingersgaard et al. 2020). Non-adherence to statin therapy is associated with an increased risk of CVD, myocardial infarction, and death (Ryou et al. 2021), while a study reported a 15% lower chance of CVD in patients with high adherence to statin as compared to those with low adherence (Stroes et al. 2015). Statin intolerance is one of the significant reasons for its discontinuation. The appearance of statin-associated musculoskeletal symptoms was the main reason for statin non-adherence in 65% of former statin users (Stroes et al. 2015). Several

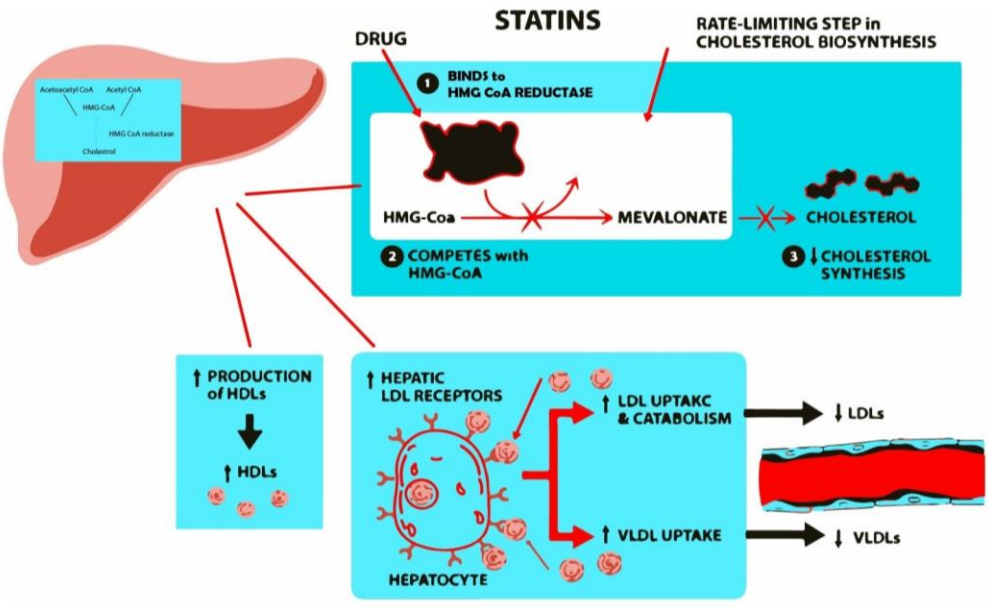

Figure 1: Mechanism of action of statins

pharmacogenetic variants, like SCLO1B1 and ABCG2, affect the statin disposition and adverse events during statin therapy (Cooper-DeHoff et al. 2022).

The response to statins in terms of lowering LDL-C levels and reducing cardiovascular events varies among individuals, and some of this variable response is attributed to genetic variants associated with differential LDL-C response to statin therapy (Postmus et al. 2014). For example, genetic polymorphism in transporter genes SCLO1B1, SCLO1B3, and ABCC2 can influence the pharmacokinetics and lipid-lowering response of Atorvastatin (Woo et al. 2017). Understanding the genetic variants associated with the safety and efficacy of statins can help personalize treatment and improve patient outcomes.

7. Genetic Polymorphisms Affecting Hypolipidemic Efficacy of Atorvastatin

7.1. *APOE*

Apolipoprotein E (*APOE*) plays a significant role in the metabolism and regulation of lipids. It's a component of several lipoproteins, including very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and chylomicron remnants, which are responsible for transporting TGAs and cholesterol in the bloodstream. APOE on lipoproteins serves as a ligand for the uptake of these molecules. APOE is encoded by the *APOE* gene located on the long arm of chromosome 19. *APOE* gene is polymorphic with three common alleles E2, E3, and E4, that code for three APOE isoforms E2, E3, and E4 (Pedro-Botet et al. 2001), resulting from two SNPs (526C>T and 388T>C) (Wang et al. 2021). E3 is a type allele that is most common in the general population with frequency rates of 85% in Asia, 82% in North America, and 77% in South America, while ε3 and ε4 are less commonly observed. These three alleles form six genotypes, i.e., E2/E2, E3/E3, and E4/E4, E2/E3, E2/E4, and E3/E4 (Bi et al. 2022).The molecular basis of *APOE* SNPs has been linked to the exchange of arginine and cysteine. These changes affect the metabolic rate and binding affinity of lipoproteins to lipoprotein receptors, thus resulting in different blood levels among individuals (Wang et al. 2021). For example, the APOE4 allele is associated with increased

plasma concentration of TGAs and LDL-C, while the APOE2 allele is associated with low plasma LDL-C levels (Horejsí and Ceska 2000). Thus, *APOE* genetic variants can affect the response of statin in lowering plasma lipid levels.

Various studies have shown that APOE E2 carriers offer a better response in LDL-C and total cholesterol reduction when treated with Atorvastatin, whereas the E4 allele is associated with inadequate response to Atorvastatin (Zhang, He et al. 2019, Wang et al. 2021, Bi et al. 2022). In a study, males with the E2 allele show a significant reduction in LDL-C levels with 10mg atorvastatin per day compared to those with E3 homozygotes and ε4 carriers. However, no such difference in treatment response was observed in women, with those carrying the E2 allele having a similar mean response as E3 homozygotes and E4 carriers. As a result, it was suggested that the variable response of Atorvastatin attributed to the APOE gene variant could be gender-specific (Pedro-Botet et al. 2001). However, some studies found no significant association between *APOE* genotypes and response to treatment with Atorvastatin (Christidis et al. 2006; Miltiadous et al. 2005).

7.2. *HMGCR*

HMG CoA reductase is an enzyme that plays a significant role in cholesterol biosynthesis and converts HMG CoA to mevalonic acid, the rate-limiting step in cholesterol synthesis. HMG CoA is the target of statins. HMG CoA reductase is encoded by the *HMGCR* gene located on human chromosome 5, specifically at the 5q13.3-14 band in humans (Lindgren et al. 1985). In a study involving a hundred CAD patients, researchers investigated the impact of SNP12 (rs17244841) and SNP29 (rs17238540) mutations in the HMGCR gene in response to statin therapy. Patients were treated with 20mg Lipitor (Atorvastatin) for one month. Biochemical measurements were taken before and after the treatment. *HMGCR* mutation was found in responders, suggesting that these mutations may enhance the lipid-lowering effect of Atorvastatin in these patients (Rizwan et al. 2021; Kirac et al. 2017). These SNPs are observed in equal frequencies and tightly linked to each other in the *HMGCR* gene. Genetic variants of *HMGCR* rs17671591 were evaluated in Chilean HC patients on Atorvastatin. The T allele of this SNP is associated with reduced LDL-C and enhanced HDL-C after treatment (Cuevas et al. 2016a).

Another study investigated the association between (TTA)n polymorphism in the *HMGCR* gene in the reduction of LDL-C, TGA levels, and total cholesterol treated with Atorvastatin. The study involved 64 patients who received Atorvastatin and were divided into three groups based on their genotype distribution: >10/>10 in 34%, >10/10 in 22%, and 10/10 in 44%. Results showed a reduction in LDL-C, total cholesterol, and TGA levels was observed after the treatment for all alleles, irrespective of the type of polymorphism (Noriega et al. 2009). Moreover, ethnic differences were noted in the prevalence of *HMGCR* gene variants and their effects on lipid response. For instance, the rs3846662 G allele was associated with increased LDL-C levels, particularly among Whites and Japanese populations, while black individuals exhibited a higher frequency of the G allele and a lesser response to a given statin dose in comparison with Whites(Krauss et al. 2008, Hiura et al. 2010, Simon et al. 2006). Despite these findings, discrepancies in the association between HMGCR SNPs and statin response have also been reported. One study reported that HMGCR SNP29 GG was associated with a more significant reduction in LDL-C levels after atorvastatin therapy (Poduri et al. 2010). On the other hand, a study reported

contradictory results for the same SNP (Chasman et al. 2004).

7.3. Cytochrome P450

Cytochrome P450, a group of structurally and functionally related genes, plays a vital role in metabolizing numerous exogenous and endogenous substances. It includes 57 active genes and 58 pseudogenes. Based on their primary protein structure, CYP450 isoenzymes are classified into 18 families and 44 subfamilies (Peng et al. 2018). Various CYP isoenzymes are involved in the metabolism of different statins. While CYP3A4 primarily metabolizes Atorvastatin and simvastatin, fluvastatin is metabolized by CYP2C9. The polymorphism of CYP isoenzymes contributes to the varying response to statins (Morofuji et al. 2022). In a study, the A-290G variant in the *CYP3A4* promoter (also called CYP3A4*1B or CYP3A4-V) was found in association with poor response to Atorvastatin (higher LDL-C levels after treatment). In contrast, the M445T missense variant (also known as CYP3A4*3) showed better efficacy i.e. a more significant reduction in LDL-C levels (Kajinami, Brousseau, et al. 2004a). However, the later findings found no considerable non-association (Poduri et al. 2010) or increased reduction in serum total cholesterol (TC) and LDL-C levels in patients carrying the mutant allele (A-290G variant) as compared to those carrying a homozygous wild allele (Rosales et al. 2012). Similarly, CYP3A4*1G (an allele in Asia with a high frequency of 0.249 among the Japanese and 0.221 in the Chinese population) was found to an increased hypolipidemic effect of Atorvastatin, in contrast to simvastatin (Gao, Zhang, and Fu 2008). Another study assessed the impact of CYP3A4*22 on the lipid-lowering response of Atorvastatin and simvastatin; however, it didn't find any significant association between them (Ragia et al. 2015). *CYP3A5* also plays a part in the metabolism of certain statins. CYP3A5*1 is the wild-type allele. Individuals carrying at least one copy of this allele express CYP3A5 protein in the liver, while individuals who are homozygous for the CYP3A5*3 allele, resulting from a single point mutation (6986A>G) within intron 3 of the CYP3A5 gene, are non-expressers of CYP3A5 enzyme. A study observed that simvastatin, lovastatin, and Atorvastatin were significantly less effective in expressers than non-expressers, while no effect was noticed for statins independent of CYP3A5 enzyme influence. These findings suggest the role of *CYP3A5* polymorphism in individual differences in response to statins (Kivistö et al. 2004). However, a definitive answer remained elusive due to subsequent research. For instance, (Wei and Zhang 2015) discovered no apparent connection, while contradictory outcomes emerged in later studies. Notably, reduced atorvastatin response linked with the CYP3A13 allele was observed in non-African individuals(Willrich et al. 2008).

Cholesterol 7-α hydroxylase, encoded by the *CYP7A1* gene, is an enzyme involved in the first and rate-limiting step of the biotransformation of cholesterol into bile acids. Thus, variation in the *CYP7A1* gene can affect the statin response. Numerous studies show that the promoter variant in *CYP3A7* (A-204C) is associated with poor response to Atorvastatin (Kajinami et al. 2005; Poduri et al. 2010; Wei et al. 2011; Kadam et al. 2016). These studies also report that the *CYP3A7* A-240C interaction with other genetic variants like *ABCG8* 119A, *ABCG8* H19, and *APOE* can influence atorvastatin response. Further, SNP rs8192870, located in the first intron of *CYP3A7*, has been shown to affect the LDL-lowering response of Atorvastatin (Jiang et al. 2012). *CYP2D6*, located on human chromosome 22, is a highly polymorphic gene that encodes an enzyme that metabolizes around 20-25% of the drugs. Various studies

conclude that *CYP2D6* influences the lipid-lowering effect of simvastatin, but at present, there is an inadequate number of studies to establish a firm relationship between *CYP2D6* polymorphism and atorvastatin efficacy. A study published in 2018 found that rs1065852 in *CYP2D6* influences the effect of Atorvastatin, and the GG genotype is associated with a better response to Atorvastatin (Peng et al. 2018).

7.4. *CETP*

Cholesteryl ester transfer protein (*CETP*) plays an essential role in lipoprotein metabolism. It mediates the exchange of cholesteryl esters and triglycerides between plasma lipoproteins, resulting in net exchange of Cholesteryl ester from HDL to apo-lipoprotein B-containing lipoproteins and uptake of cholesterol by hepatocytes (van Venrooij et al. 2003). The *CETP* gene is located on chromosome 16q12-16q21; polymorphism within the *CETP* gene can affect CETP enzyme levels, lipid metabolism, and statin response (Gu et al. 2014). The most studied *CETP* polymorphism is a silent base change, affecting the 277th nucleotide in the first gene that modifies the restriction site for the enzyme TaqI (van Venrooij et al. 2003). There are three genotypes for TaqI RFLP: B1B1, B2B2, and B3B3. Individuals who are homozygous for the B1 allele (presence of restriction site) have lower HDL-C levels as compared to carriers of the B2 allele (associated with lack of restriction site) (Mohrschladt et al. 2005).

Polymorphism in *CETP* TaqI has a significant association with the lipid-lowering effect of Atorvastatin (Yue et al. 2016). In a study, B1B1 carriers respond better to statin therapy, with a more significant increase in HDL levels and reduction in triglycerides than the B2B2 carriers after atorvastatin treatment (van Venrooij et al. 2003). In another study, B1 carriers had a 4% increase in HDL levels compared to individuals carrying the B2 allele, whereas post-atorvastatin therapy showed a 4% decrease in HDL levels. Furthermore, Individuals homozygous for the B1 allele experienced less reduction in TG levels, although the difference was not statistically significant (Kolovou et al. 2010). In another study, patients with a variant allele carrying genotype of *CETP* TaqI showed a more tremendous increase in HDL concentration after atorvastatin therapy (Poduri et al. 2010). Similarly, another study found that HDL-C levels were higher in patients with the B1B2 genotype than those with B1B1, and plasma TG levels were significantly decreased in the B2B2 genotype and were lower than in those with the B1 allele (Li et al. 2014). Research conducted in the Jordanian population demonstrated contradictory results and didn't find any association between the *CETP* Taq1b and LDL reduction after atorvastatin therapy.

Another polymorphism, A-629C, located in the promoter region of the *CETP* gene, affects the varying response of statins. Numerous studies suggest that the AA variant is associated with higher HDL-C levels, but patients with the CC genotype respond better to atorvastatin therapy with a reduction in LDL-C and lipoprotein A-I (LpA-I) levels (Gao et al. 2013, Gu et al. 2014, van Venrooij et al. 2003). *CETP* I405V (rs5882) polymorphism, located in exon 14, is caused by an A to G substitution that changes the amino acid from isoleucine to valine at codon 405. In a study, patients carrying a variant allele of I405V showed a lower reduction in TC levels (Poduri et al. 2010).

7.5. *LDLR*

Low-density Lipoprotein Receptor (LDLR) is a protein present on the surface of various cells, including hepatocytes, adipocytes, and cells in

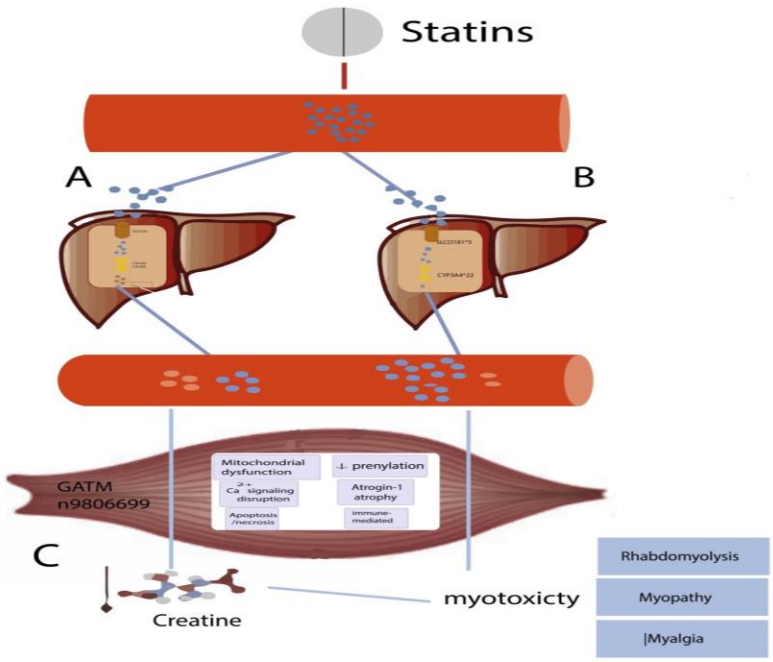

Figure 2: Mechanism of statin-induced myopathy.

other tissues that are involved in cholesterol and lipid metabolism in the body. This receptor has a role in the uptake of cholesterol, such as LDL-C and VLDL-C from blood into cells, thereby regulating cholesterol levels in the blood. *LDLR* gene encodes the LDL receptor located in the short arm of chromosome 19 (19p13.1-13.3) (Galicia-Garcia et al. 2020).

Defects in the LDL receptor pathway caused by a mutation in the *LDLR* gene can result in familial hypercholesterolemia (FH). A study evaluated the effects of Atorvastatin on LDLR genetic mutation in patients with heterozygous FH. Studies showed that patients having the V mutation (G1775A mutation) experienced a more significant decrease in LDL-C than class II mutations (G1646A and C858A mutations) (Miltiadous et al. 2005). In another study, an 8-year-old male patient with FH, homozygous for c.1055G>A mutation in *LDLR* gene, causing p.Cys352Tyr (known as the Mexico 2 mutation), initial treatment with Atorvastatin was not satisfactory. The genetic analysis of 5 polymorphisms, namely rs1003723C>T, rs5930A>G, rs688C>T, rs5929T>C, and rs5927A>G, suggested a common ancestor for the mutation and linkage to TGTCG haplotype (Magaña Torres et al. 2014). Another study showed that *LDLR* AvaII was associated with initial levels the of LDL in hypercholesterolemic patients at the time of diagnosis. However, LDLR AvaII did not significantly reduce LDL levels after the patients received Atorvastatin (Zihlif et al. 2022). Another study investigated the impact of the genetic variant rs14158G>A in the LDLR gene located in 3′-UTR (3′-Untranslated Region). It was observed that there was no significant association between the rs14158 SNP in response to atorvastatin therapy. The rs14158 G allele was also more prevalent in hypercholesterolemic patients (Zambrano et al. 2015). A study conducted in Chilean Amerindian subjects showed no association of

1959C>T SNP (rs5925) in the *LDLR* gene in response to atorvastatin treatment in hypercholesterolemic patients (Lagos et al. 2015).

7.6. *PCSK9*

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a protein encoded by the *PCSK9* gene in humans on chromosome 1. This protein is involved in the metabolism of cholesterol in the blood by binding the LDL receptors on hepatocytes, leading to its degradation, resulting in fewer LDL receptors to clear the LDL-C from the blood and high cholesterol levels in the blood.

A study investigated the impact of the rs17111557 genetic variant (C>T) located in the 3'UTR (3'-untranslated Region) of the *PCSK9* gene, influencing lipid profile and response to Atorvastatin in Brazilian Subjects. The study's findings showed that subjects carrying the T allele had lower HDL-C levels than the C allele, and no association was seen between the *PCSK9* genetic variant and atorvastatin response (Zambrano et al. 2015). Another study conducted on Brazilian subjects for three different genetic variants, E670G, I474V, and R46L, showed no association with the cholesterol-lowering effect of Atorvastatin. It was also seen that E670G was associated with high LDL-C, while I474V was not related to cholesterol levels (Anderson et al. 2014). *PSCK9* gene E670G polymorphism has different genotypes. A study conducted in the Chinese population indicated that the GG genotype had a higher level of LDL-C and reduced response to Atorvastatin than the AG and AA genotypes (Zhang et al. 2017). Another study conducted on Han and Uighur, ischemic stroke patients, showed no association of SNP rs505151 with blood lipid levels after treatment with Atorvastatin (Yue et al. 2016). A study conducted on the Chilean population indicated that the presence of *PCSK9* rs7552841 did not lead to significant changes in lipid levels when patients were treated with Atorvastatin (Cuevas et al. 2016a). A study analyzed SNP rs6235 and rs11206510 related to lipid metabolism, and the patients received equipotent doses of statins with about 90% on simvastatin or Atorvastatin. The result showed no significant association between the *PCSK9* genetic variant and statin efficacy (Vrablík et al. 2012).

7.7. *ABCB1*

ABC transporters constitute a large family of membrane proteins that play a crucial role in transporting molecules across cell membranes. Out of these 48 transporters, approximately half are involved in transporting lipids and related compounds (Tarling, de Aguiar Vallim, and Edwards, 2013). *ABCB1* gene, also known as the multi-drug resistant gene (*MDR1*), encodes glycoprotein P that contributes to eliminating statin and their metabolites via bile. Polymorphism in genes encoding these transporters can affect the statins' response and safety (Rebecchi et al. 2009).

A study investigated the effect of C3435T polymorphism, located at codon 1145 in exon 26, in *the MRDI* gene and found that the CC genotype is associated with slight LDL reduction and an increase in HDL as compared to variant allele carriers in women (Kajinami, Brousseau, et al. 2004b). However, a smaller subsequent study didn't find a significant association between atorvastatin response and C3435T polymorphism (Rodrigues et al. 2005). Another study replicated that the CC genotype is associated with lower atorvastatin efficacy (reduced LDL reduction) (Hoenig et al. 2011). However, the findings of later studies are inconsistent, as some studies indicated that the TT genotype is associated with poor response to Atorvastatin (Munshi 2012) (Sałacka et al. 2014), while a recent survey in the Uygur population found that the TT genotype more

Table 1. Summary of HMGCR SNPs associated with response to Atorvastatin

Genetic Variation	Population Size	Effect	Reference(s)
rs33761740	365	Linked to total cholesterol (TC) levels	(Akadam-Teker et al. 2013)
rs10474433	1984	Strongly associated with LDL-C response to Atorvastatin	(Thompson et al. 2009)
rs17671591	1984	Strongly associated with LDL-C response to Atorvastatin	(Thompson et al. 2009)
rs6453131	1984	Strongly associated with LDL-C response to Atorvastatin	(Thompson et al. 2009)
rs3846662	35	GG genotype linked to higher LDL-C levels	(Chung et al. 2012)
rs12654264	895	No significant influence on lipid-lowering therapy with statins	(Vrablík et al. 2012)
(rs17238540	372	Not associated with baseline lipid values or statin-induced LDL-C lowering response	(Chen et al. 2005)
rs17238540	1601	Associated with less favorable response to statin therapy in terms of TC and TG reduction	(Donnelly et al. 2008)
Rs12916 C/T	265	Synergistic effect with other loci on statin response	(Poduri et al. 2010)
rs17244841, rs17238540	100	Mutations enhance lipid-lowering effect of Atorvastatin	(Rizwan et al. 2021, Kirac et al. 2017)
rs17671591	101	T allele associated with reduced LDL cholesterol, enhanced HDL cholesterol, and greater LDL-C reductions following atorvastatin treatment	(Cuevas et al. 2016b)
(TTA)n	64	Reduction in LDL cholesterol, triglyceride levels, and total cholesterol after atorvastatin treatment, regardless of genotype distribution	(Noriega et al. 2009)
rs3846662	994	G allele associated with increased LDL-C levels, ethnic differences in prevalence and response	(Krauss et al. 2008, Hiura et al. 2010, Simon et al. 2006)
SNP29 GG	265	Associated with a greater reduction in LDL-C levels	(Poduri et al. 2010)
SNP29 GG	1536	Contrarily, associated with an increase in LDL-C levels	(Chasman et al. 2004)

effectively lowered TG levels than other polymorphisms(Wang et al. 2023).

G2677T/A/C is a synonymous polymorphism with the *ABCB1* gene located at exon 26, leading to three different amino acids (Ser, Thr, and Pro). A study found that individuals carrying 2677A responded more to Atorvastatin (Rebecchi et al. 2009). Another polymorphism -41A/G located in the promoter region has shown an association with a greater increase in HDL concentration following atorvastatin therapy. (Poduri et al. 2010)

ABCG5/8 are transporter proteins located in the plasma and intracellular membranes of hepatocytes and enterocytes. These transporters limit the intestinal absorption and

biliary excretion of sterols. Variation in the genes encoding for ABCG5/8 can affect individual response to statin drugs. It has been shown that rs11887534 DH19 variant of *ABCG8*, also known as c.55G >C that causes substitution of aspartic acid by histidine, is associated with greater LDL-C lowering response (Kajinami, Brousseau, Nartsupha, et al. 2004) and decrease in HDL response to Atorvastatin (Sałacka et al. 2021). On the contrary, other studies didn't find its association with inter-individual variation in response to statin drugs (Srivastava et al. 2010, Abed et al. 2021).

ABCA1 plays a vital role in HDL metabolism and mediates the transport of cholesterol and phospholipid molecules across the cell membrane, where it is removed by lipid-poor HDL apolipoprotein. Studies conducted on *ABCA1* gene variation showed that rs12003906 polymorphism is associated with reduced lipid-lowering response to Atorvastatin, while other SNPS R219K and C-105T didn't indicate any association. Multidrug resistance protein 2 (MRP2), encoded by the gene *ABCC2*, is another transporter protein associated with statin response. It is expressed in proximal renal tubular cells, enterocytes, and hepatocytes,, acting as an efflux pump. c.1249G>A SNP in *ABCC2* is associated with reduced lipid response to Atorvastatin (Woo et al. 2017). A study found that the variant allele of SNP 24C>T is associated with a smaller TG and TG/HDL ratio reduction by Atorvastatin; however, this effect was only observed in Chilean males and not in females (Prado et al. 2018).

7.8. *SLCO1B1*

Organic anion-transporting polypeptides (OATPs) are influx transporters with a critical role in statin uptake by liver cells, contributing significantly to statin pharmacokinetics (PK) and response. Among them, OATP1B1 and OATP2B1 are encoded by *SLCO1B1* and *SLCO2B1*, respectively, and are of particular importance (Guan et al. 2019). OATP1B1 is expressed in the sinusoidal membrane of hepatocytes and transports many therapeutic drugs, including Atorvastatin (Dagli-Hernandez et al. 2022).

*SLCO1B1**5 and *15 Variants, known as low-function variants, lead to reduced uptake of pravastatin, atorvastatin, and cerivastatin (Kameyama et al. 2005). Notably, homozygous carriers of SLCO1B1*15 exhibit altered plasma levels of Atorvastatin, pitavastatin, and rosuvastatin (Dagli-Hernandez et al. 2022). However, the effect of SLCO1B1*5 and *15 on statin response remains limited, with LDL-C reduction observed to be less than 5% (Kitzmiller et al. 2016). In another study, investigations on the transporting activities of different allelic variants of SLCO1B1, including *5, *15, and *15 + C1007G, showed significantly decreased activities for Atorvastatin. However, no significant alterations were observed in the transporting activities of SLCO1B1*1b, *1a + C1007G, and *1b + C1007G for Atorvastatin (Kameyama et al. 2005).

Conversely, a significant association observed between SLCO1B1*5 alleles and increased levels of Atorvastatin and its metabolite, 2-hydroxy Atorvastatin, was supported by various studies conducted on different ethnic groups (Turner et al. 2020; DeGorter et al. 2013, Nozawa et al. 2002).

In contrast to the low-function variants, *SLCO1B1*1B* was found to have no significant impact on transporter function (Kameyama et al. 2005). *SLCO1B1*1B* does not affect the LDL-C response to Atorvastatin or simvastatin in HC patients (Fu et al. 2013, Giannakopoulou et al. 2014). On the other hand, carriers of *SLCO1B1*1B* have been reported to exhibit lower atorvastatin plasma concentrations in one study (DeGorter et al. 2013). Rodrigues and colleagues showed that the *SLCO1B1* c.388A>G

Table 2. Summary of CYP450 gene polymorphism associated with atorvastatin response.

Genetic variation	Population size	Effect	References
CYP3A4 A-290G	340	Poor response to Atorvastatin	(Kajinami, Brousseau, et al. 2004a)
CYP31A4 A-290G	265	No association	(Poduri et al. 2010)
CYP3A14 A-290G variant	142	Increased reduction in TLC and LDL levels	(Rosales et al. 2012)
CYP3A14*G	217	Increased Lipid-lowering effect	(Gao, Zhang, and Fu 2008)
CYP3A4*22	416	No association	(Ragia et al. 2015)
CYP3A5*3A	139	No association	(Willrich et al. 2008)
CYP3A5*3	179	No association	(Wei and Zhang 2015)
CYP3A7 (A-204C)	177-324	Reduced response	(Kajinami et al. 2005, Poduri et al. 2010, Wei et al. 2011, Kadam et al. 2016)
CYP2D6 rs1065852	192	GC allele is associated with better response	(Peng et al. 2018)

variant has been associated with increased atorvastatin response (Rodrigues et al. 2011).

7.9. KIF6

Kinesin-like protein 6 (KIF6) is a member of the kinesin family and has a role in the intracellular transport of protein complexes, membrane organelles, and mRNA along microtubules in various tissues, including vascular systems. It is encoded by the *KIF6* gene on chromosome 6. Several studies suggest that one genetic variant, rs20455 (Trp719Arg), is associated with a response to statin therapy and coronary heart disease. One study, the Atorvastatin and Atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE IT-TIMI22), suggested that in people with the 719Arg allele, statins are more effective in preventing heart problems than in non-carriers (Li et al. 2011, Li et al. 2010, Iakoubova et al. 2008). Another study suggested that *KIF6* Trp719Arg genotype carriers did not affect the risk of cardiovascular disease or the effectiveness of Atorvastatin (Hoffmann et al. 2011).

8. Genetic Polymorphisms Affecting Adverse Effects of Atorvastatin

8.1. SLCO1B1

*SLCO1B1**5 (rs4149056) has increased the risk of statin-induced myopathy (SIM). Several meta-analyses consistently report a significant association between SLCO1B1*5 and an elevated risk of SIM (Hou et al. 2015; Lee and Chun 2018). This genetic variant has been linked to overall statin-induced adverse reactions, including SIM, in specific populations (Jiang et al. 2016). Notably, a recent genome-wide association study reported that SLCO1B1*5 allele carriers were significantly associated with increased muscular symptoms ($p = 0.016$) and atorvastatin intolerance ($p = 0.014$) (Turner et al. 2020). These findings

highlight the importance of *SLCO1B1*5* in predicting adverse drug reactions (ADRs) related to statin therapy.

However, the relationship between *SLCO1B1* polymorphisms and SIM in atorvastatin users is still debatable, as not all studies have consistently observed a significant association. Some investigations have reported no important link between *SLCO1B1*5* and SIM in atorvastatin-treated patients (Brunham et al. 2012a, Carr et al. 2013, Hou et al. 2015, Liu et al. 2017, Ramakumari et al. 2018). Additionally, a PK study exploring atorvastatin-related myopathy cases found no association between elevated area under the curves of atorvastatin lactone and p-hydroxy atorvastatin lactone with *SLCO1B1* polymorphisms or creatine kinase (CK) levels (Hermann et al. 2006).

8.2. CYP 450

A study found that the CYP2D6*4 variant is associated with Atorvastatin-induced muscle events (Frudakis et al. 2007). Current evidence does not link *CYP3A4* variants to atorvastatin-induced myopathy, despite its role in atorvastatin metabolism. Individuals homozygous for the *CYP3A5*3* variant may show higher creatine kinase levels than this heterozygote for *CYP3A5*3*, but this variant isn't associated with muscular side effects. (Wilke, Moore, and Burmester 2005)

8.3. ABC Transporter

A study found that the T allele associated with the C3435T polymorphism in *the MRD1* gene was more common in patients with myalgia, while the C allele was less frequent in those with muscular symptoms (Hoenig et al. 2011). In another study, the prevalence of the 2677G allele was greater in patients with atorvastatin-induced liver injury (AILI) compared to those without AILI. However, no significant differences in the frequencies of 2677A and 2677T were observed in AILI and non-AILI patients, indicating that the G allele might be a risk factor for AILI (Fukunaga et al. 2016). A later study confirmed that G allele carriers with G2677T/A are at more risk of developing Atorvastatin-induced liver injury. Further, it concluded that 3434CT heterozygotes were more easily exposed to the risk of AILI, and the haplotype G-C (G2677T/A and C3435T) is associated with an increased risk of AILI (Qu et al. 2020).

Moreover, mutation (A allele) of rs237588 in *ABCB1* is associated with an increased risk of atorvastatin-induced myopathy (Zhang, Lv, et al. 2019).*ABCG2*, also known as breast cancer resistance protein, is another efflux transporter expressed in the liver, intestine, and kidney. Its polymorphism can affect the plasma concentration of Atorvastatin, thus affecting the efficacy and toxicity of statin therapy (Keskitalo et al., 2009). A case study found that patients with the 421AA or CA genotype had a 2.9 times greater risk of developing atorvastatin dose-dependent ADRs than those with the CC genotype (Mirošević Skvrce et al. 2015).

9. Recommendations

A firm connection should be established among *APOE, HMGCA, cytochrome P450 enzymes (CYP3A4, CYP3A5, CYP2D6), CETP, LDLR, PCSK9, ABCB1, ABCG5/8, SLCO1B1,* and *KIF6* polymorphism and their impact on atorvastatin efficacy, which warrants in-depth research into the topic. In case a consistent correlation is confirmed between the statins and this genetic polymorphism in large cohorts of people, healthcare providers should adapt their practices accordingly. Genetic screening for relevant polymorphisms of relevant genes before prescribing Atorvastatin can help predict individual responses to the therapy and guide personalized treatment decisions. Additionally, variation in atorvastatin response to SNPs among diverse racial groups demands global-scale strategies, like developing

thorough pharmacogenetic guidelines for statins, which can aid the prescribers in treatment or dose calibration based on a patient's genetic profile. Notably, the healthcare agents identify the patients predisposed to SIM and proceed cautiously or move on to other lipid-lowering strategies.

The aberrations that reduce drug efficacy, like with the APOE E4 allele, alternative anti-hyperlipidemia routes should be explored. In addition to the genes mentioned in the study, more studies, including the entire genomic sequence, should be done to identify new SNPs and their impact on the hypolipidemic actions of statins.

Furthermore, the gender-specific response to Atorvastatin opens up another avenue for research and investigation that often gets neglected due to various socioeconomic reasons. Adjustments to the treatment plan may be necessary based on the patient's genetic profile and lipid response to Atorvastatin.

Further recommendations include regular monitoring of lipid levels, critical biomarkers, and an emphasis on lifestyle modification. Lastly, increasing public awareness about hyperlipidemia, its association with cardiovascular diseases, and the role of genetic factors in statin therapy can promote better understanding among patients. This can foster greater acceptance of genetic testing and personalized treatment strategies.

10. Conclusions

In conclusion, the delicate interplay of pharmacogenetics and statins, particularly Atorvastatin, presents a promising avenue for treating hyperlipidemia and enhancing patient outcomes. The role of polymorphic nature of genes such as *APOE*, *HMGCA*, cytochrome P450 enzymes (*CYP3A4*, *CYP3A5*, *CYP2D6)*, *CETP*, *LDLR*, *PCSK9*, *ABCB1*, *ABCG5/8*, *SLCO1B1*, and *KIF6* polymorphism in influencing individual responses to Atorvastatin has opened the door for tailored management plans for hyperlipidemia. The *APOE* E2 allele's impact on atorvastatin response differed between men and women, emphasizing the importance of gender-specific factors in pharmacogenetics studies; further research is needed to understand these complexities. Furthermore, varying atorvastatin outcomes in racially diverse cohorts have underscored the need to calibrate global treatment strategies. With patients' informed consent as an ethical cornerstone, integrating genetic screening for relevant polymorphisms before prescribing Atorvastatin can be instrumental in identifying patients who stand to benefit from the therapy and devising alternative lipid-lowering strategies for those with specific genetic variations. To fully harness the potential of pharmacogenetics, additional research is warranted, including comprehensive studies covering the entire genomic sequence to identify new SNPs and their impact on statin efficacy. Moreover, regular monitoring of lipid levels and other biomarkers, coupled with adjustments to the treatment plan based on a patient's genetic profile and lipid response, is essential for personalized and effective hyperlipidemia management. Embracing these advancements will undoubtedly lead to improved patient outcomes, enhanced treatment adherence, and a step closer to achieving the goal of personalized, precision medicine for hyperlipidemia and cardiovascular disease management.

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Conflicts of interest

The authors of the study have no conflict of interest with this study.

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NA

Consent to Participate

NA

Availability of Data

The data used in this manuscript is available from the corresponding author.

Author Contributions

FN conceptualized the study, HA and SQA did the literature search and analyzed the results, and FN and HA wrote the initial manuscript. All the authors contributed to the final manuscript.

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