p-ISSN : 2788-5569 | e-ISSN : 2788-5445
DOI(Journal): 10.31703/gpsr
DOI(Volume): 10.31703/gpsr/.2024(IX)
DOI(Issue): 10.31703/gpsr.2024(IX.I)

www.gicdrjournal.com
Global Pharmaceutical Sciences Review
GPSR

GPSR

GLOBAL PHARMACEUTICAL SCIENCES REVIEW

HEC-RECOGNIZED CATEGORY-Y

VOL. IX, ISSUE I, WINTER (MARCH-2024)

HumanityPublications
sharing research
www.humapub.com
US | UK | Pakistan

Double-blind Peer-review Research Journal
www.gpsrjournal.com

Humanity Publications
(HumaPub)
www.humapub.com
Doi: https://dx.doi.org/10.31703

Global Pharmaceutical Sciences Review
GPSR

Article Title

Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment

Global Pharmaceutical Sciences Review
p-ISSN: 2788-5569 e-ISSN: 2788-5445
DOI(journal): 10.31703/gpsr
Volume: IX (2024)
DOI (volume): 10.31703/gpsr.2024(IX)
Issue: (Winter-March 2024)
DOI(Issue): 10.31703/gpsr.2024(IX-I)
Home Page
www.gpsrjournal.com
Volume: IX (2024)
https://www.gpsrjournal.com/Current-issues
Issue: I-Winter (March-2024)
https://www.gpsrjournal.com/Current-issues/9/1/2024
Scope
https://www.gpsrjournal.com/about-us/scope
Submission
https://humaglobe.com/index.php/gpsr/submissions
Google Scholar

Visit Us

Abstract

Hyperlipidemia is a main risk factor for coronary heart disease, which is commonly treated with statins, especially atorvastatin. However, the efficacy and harmful effects vary from person to person. Nearly 50% discontinue treatment within one year, mainly because of intolerance to statins associated with musculoskeletal symptoms. The presence of genetic polymorphisms in various genes greatly affects atorvastatin metabolism, response, and adverse events. This review covers pharmacogenetics in genes such as APOE, HMGCR, CYP3A4, CYP3A5, CYP2D6, CETP, LDLR, PCSK9, ABCB1, ABCG5/8, SLCO1B1, and KIF6 affecting atorvastatin lipid-lowering therapeutic action. The knowledge of these genetic factors is crucial in adjusting therapy to reduce adverse reactions and in paving the way for personalized therapeutics in the management of hyperlipidemia.

Keywords: Genetic Polymorphism, Statin, Atorvastatin, Hyperlipidemia, LDL, HDL.

Authors:

Huma Sajjad: ASHP IPPRP Resident Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.

Syed Muhammad Talha: (Corresponding author)
ASHP IPPRP Resident Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.
(Email: syedmuhammadtalhahez@gmail.com)

Syeda Qurat ul Ain Ali: Staff Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.

Hufsa Arooj: Clinical Trial Pharmacist, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan.

Pages: 29-50
DOI: 10.31703/gpsr.2024(IX-I).03
DOI link: https://dx.doi.org/10.31703/gpsr.2024(IX-I).03
Article link: http://www.gpsrjournal.com/article/genetic-polymorphism-and-its-impact-on-atorvastatin-efficacy-personalizing-hyperlipidemia-treatment
Full-text Link: https://gpsrjournal.com/fulltext/genetic-polymorphism-and-its-impact-on-atorvastatin-efficacy-personalizing-hyperlipidemia-treatment
Pdf link: https://www.gpsrjournal.com/jadmin/Auther/31rvIolA2.pdf

Humanity Publications (HumaPub)
www.humapub.com
Doi:https://dx.doi.org/10.31703

Citing this Article

03	Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment						
	Author	Huma Sajjad Syed Muhammad Talha Syeda Qurat ul Ain Ali Hufsa Arooj		DOI	10.31703/gpsr.2024(IX-I).03		
Pages	29-50	Year	2024	Volume	IX	Issue	I
Referencing & Citing Styles	APA	Sajjad, H., Talha, S. M., Ali, S. Q. u. A., & Arooj, H. (2024). Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment. *Global Pharmaceutical Sciences Review*, *IX*(I), 29-50. https://doi.org/10.31703/gpsr.2024(IX-III).03					
	CHICAGO	Sajjad, Huma, Syed Muhammad Talha, Syeda Qurat ul Ain Ali, and Hufsa Arooj. 2024. "Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment." *Global Pharmaceutical Sciences Review* IX (I):29-50. doi: 10.31703/gpsr.2024(IX-III).03.					
	HARVARD	SAJJAD, H., TALHA, S. M., ALI, S. Q. U. A. & AROOJ, H. 2024. Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment. *Global Pharmaceutical Sciences Review,* IX**,** 29-50.					
	MHRA	Sajjad, Huma, Syed Muhammad Talha, Syeda Qurat ul Ain Ali, and Hufsa Arooj. 2024. 'Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment', *Global Pharmaceutical Sciences Review*, IX: 29-50.					
	MLA	Sajjad, Huma, et al. "Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment." *Global Pharmaceutical Sciences Review* IX.I (2024): 29-50. Print.					
	OXFORD	Sajjad, Huma, et al. (2024), 'Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment', *Global Pharmaceutical Sciences Review,* IX (I), 29-50.					
	TURABIAN	Sajjad, Huma, Syed Muhammad Talha, Syeda Qurat ul Ain Ali, and Hufsa Arooj. "Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment." *Global Pharmaceutical Sciences Review* IX, no. I (2024): 29-50. https://dx.doi.org/10.31703/gpsr.2024(IX-III).03.					

e-ISSN: 2788-5445 Volume: IX (2024) Issue: I-Winter (March-2024) p-ISSN: 2788-5569

Global Pharmaceutical Sciences Review
www.gpsrjournal.com
DOI: http://dx.doi.org/10.31703/gpsr

Pages: 29-50 URL: https://doi.org/10.31703/giidr.2024(IX-I).03 Doi: 10.31703/gpsr.2024(IX-I).03

Cite Us

Title

Genetic Polymorphism and Its Impact on Atorvastatin Efficacy: Personalizing Hyperlipidemia Treatment

Abstract

Hyperlipidemia is a main risk factor for coronary heart disease, which is commonly treated with statins, especially atorvastatin. However, the efficacy and harmful effects vary from person to person. Nearly 50% discontinue treatment within one year, mainly because of intolerance to statins associated with musculoskeletal symptoms. The presence of genetic polymorphisms in various genes greatly affects atorvastatin metabolism, response, and adverse events. This review covers pharmacogenetics in genes such as APOE, HMGCR, CYP3A4, CYP3A5, CYP2D6, CETP, LDLR, PCSK9, ABCB1, ABCG5/8, SLCO1B1, and KIF6 affecting atorvastatin lipid-lowering therapeutic action. The knowledge of these genetic factors is crucial in adjusting therapy to reduce adverse reactions and in paving the way for personalized therapeutics in the management of hyperlipidemia.

Contents

- Introduction
- Etiology of Hyperlipidemia
- Treatment Options
- Nicotinic Acid (Niacin)
- Probucol
- Fibrates
- APOE gene
- HMGCR gene
- Cytochrome P450
- CETP gene
- ABCB1 Genes
- Recommendations
- Conclusion
- References

Keywords:

Genetic Polymorphism, Statin, Atorvastatin, Hyperlipidemia, LDL, HDL

Authors:

Huma Sajjad: ASHP IPPRP Resident Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.

Syed Muhammad Talha: (Coprrespondant author)
ASHP IPPRP Resident Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.
(Email: syedmuhammadtalhahez@gmail.com)

Syeda Qurat ul Ain Ali: Staff Pharmacist, Shifa International Hospital (SIH), Islamabad, Pakistan.

Hufsa Arooj: Clinical Trial Pharmacist, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan.

Introduction

Hyperlipidemia, characterized by the elevation of lipoproteins in the blood and a thickened stream, enhances the risk of cardiovascular diseases such as coronary artery disease (CAD)(Padhye & Yadav, 2022; Alloubani, Nimer, & Samara, 2021). Reduction of lipid-lowering agents significantly decreases the morbidity and mortality associated with cardiovascular diseases. Statins--3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors--are first-line agents thought to be the most efficient lipid-lowering drugs indicated to treat hyperlipidemias (Schaiff, Moe, & Krichbaum, 2008). They work by inhibiting HMG-CoA reductase. The process causes LDL receptor expression to rise, thus increasing

the capacity of liver cells to take up Low-Density Lipoprotein (LDL), which lowers LDL concentrations within the bloodstream. The medical community most frequently selects stains as their primary choice for patient treatment (Liu et al., 2020), and an increased trend regarding their usage has been witnessed worldwide. Among adults aged 40 or above, statin consumption has increased up to 78.9% from 21.8 million people in 2002-2003 to 39.2 million people in 2012-2013 in the USA (Salami et al., 2017).

In the US in 2006, atorvastatin was the most widely used of all statins (Stasi et al., 2010) and remained the most widely searched medication, as observed over the next 15 years (Lippi, Mattiuzzi, & Cervellin, 2019). Regardless of being widely used, atorvastatin's safety and efficacy differ from person to person because of factors both genetic and environmental (Trompet et al., 2021). Different genetic variations connected to lipid metabolism, along with their uptake and transport functions, have been observed. The SCLO1B1 gene variants, which code for the organic anion transporter polypeptide protein 1B1 (OATP1B1), control statin absorption in liver cells and are associated with risk for statin-associated Muscle disease (Brunham et al., 2012b). Evaluating single-nucleotide polymorphisms (SNPs) that affect statin therapy response leads to better treatment results and reduces the possibility of adverse effects (Ahangari et al., 2020). The paper aims to deliver an exhaustive summary about statin pharmacogenetics with special focus on atorvastatin treatment in patients with hyperlipidemia.

Etiology of Hyperlipidemia

The etiology of hyperlipidemia is divided into two classes: primary and secondary hyperlipidemia. Primary hyperlipidemia results from the genetic mutations, either monogenic or polygenic, in the receptor protein. The pathophysiological process of this disease begins when idiopathic hyperchylomicronemia develops because of lipoprotein lipase activity (LPL) failure or surface Apo protein CII31 deficiency, which results in 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 synthesis of VLDL cholesterol by the liver, causing hyperlipidemia. Hypothyroidism causes low LPL and lipolytic activity, which reduces the liver transformation of cholesterol to bile acids. Similarly, hyperadrenocorticism increases synthesis of VLDL, thus causing hypertriglyceridemia & hypercholesterolemia (HC) (Onwe et al., 2015).

Hyperlipidemia is a common metabolic disorder involved in the formation of atherosclerosis. The Atherosclerotic lesions form because plasma LDL particles move through endothelial cells into the sub-endothelial extracellular matrix, where they oxidize and stimulate monocyte migration, which transforms these cells into macrophages that promote additional LDL oxidation. This whole process triggers an inflammatory response mediated by cytokines (Onwe et al., 2015). Hyperlipidemia produces a direct influence upon heart systolic performance alongside its electrophysiological properties through progressive cardiac lipid build-up and ongoing oxidative stress throughout the system and mitochondrial damage (Yao, Li, & Zeng, 2020).

Epidemiology of Hyperlipidemia

Hyperlipidemia involves an increased amount of cholesterol in the blood, including high-density lipoprotein (HDL) cholesterol and low-density lipoprotein cholesterol (LDL-C). People with hyperlipidemia are more vulnerable to cardiovascular diseases (Karr, 2017). It ranks as one of the main causes of mortality in the United States.. More than 53% of adults in the US have high low-density lipoprotein (LDL) levels (Karr, 2017). The global prevalence of hyperlipidemia is also high. In 2008, the World Health Organization (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 & Khurana, 2011). The Second National Diabetes Survey in Pakistan included 10,384 participants who underwent a study to measure hyperlipidemia patterns across the Pakistani population. The study discovered that 39.3% of study participants exhibited HC, while 48.9% showed hypertriglyceridemia and 39.7% showed elevated LDL-C levels. According to the survey results, 83.9% of men and 90% of women showed decreased levels of HDL. According to the report, increased LDL levels and decreased 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).

Treatment Options

The main treatment objective for hyperlipidemia involves normalizing blood lipid levels and avoiding illnesses that result from this condition. The treatment of dyslipidemia requires both lifestyle changes and medication therapy. The following treatment options exist for managing dyslipidemia:

Lifestyle Modification

Hyperlipidemia management begins with lifestyle modifications that serve as fundamental elements for controlling lipid levels. A heart-healthy diet that minimizes trans fats, along with saturated fat and cholesterol, serves as the foundation for this approach, and patients should stop smoking while working to achieve a healthy weight and perform 150 minutes of exercise per week (Saha, Banks, & Whayne, 2021).

Pharmacotherapy

HMG-CoA Reductase Inhibitors function as the primary drugs that doctors use to treat hyperlipidemia through their statin classification. These drugs block the HMG-CoA reductase enzyme to stop the production of mevalonic acid, which serves as a precursor for cholesterol synthesis (Stancu & Sima, 2001).

Bile-Acid Sequestrants (BAS)

Bile acid compounds are found within the body as bile salts, which are made in liver cells from cholesterol. Cholecysts in the tiny intestines release this, but they are reabsorbed. BAS are large polymers that form complexes with these salts and prevent their reabsorption (Feng et al., 2021)

Nicotinic Acid (Niacin)

The medicinal compound Niacin, which goes by Vitamin B3, functions as a lipid-lowering agents that lower LDL cholesterol and TGAs and lipoprotein (a) while raising HDL cholesterol levels (Landray et al., 2014). These agents prevent lipolysis in the adipose tissues and hence reduce the production of LDL lipoproteins in the liver. The nicotinic acid receptors HCA2, which scientists also call GPR109A, become activated when nicotinic acid binds to them. These receptors are G-protein-linked receptors. Activation of these receptors inhibits adenylyl cyclase (Julius & Fischer, 2013).

Probucol

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

Fibrates

Fibrates lower both LDL-C levels and chylomicrons in the body. These agents need to be introduced following the implementation of dietary and lifestyle changes(Brown 1987). The activation of PPAR-alpha by fibrates improves TGA breakdown in circulation, which results in reduced TGA concentrations (Bougarne et al., 2018).

Cholesterol Absorption Inhibitors (Ezetimibe): Ezetimibe stops the absorption of cholesterol by inhibiting Niemann-Pick C1-Like 1(NPC1L1) protein in the small intestine (Davis & Veltri, 2007). It is often used in combination with statins (Chilbert & VanDuyn, 2022).

PCSK9 Inhibitors

The PCSK9 proteins connect with LDL receptors on cell surfaces that eliminate cholesterol from circulation by causing its breakdown (Davis and Veltri 2007 (Davis & Veltri, 2007). Alirocumab and evolucumab are MABs that target the PCSK9 and degrade it, resulting in less PCSK9 being available in circulation. Inclisran is a siRNA that effectively blocks the production of PCSK9 (Davis & Veltri, 2007).

Omega-3 Fatty Acids

Omega-3 fatty acids inhibit the gene expression of sterol regulatory binding protein enzymes that manage cholesterol and TGA production.

Bempedoic Acid

Bempedoic acid is a compound that blocks the triphosphate-citrate lyase (ACL) enzymes, avoiding the synthesis of cholesterol in the body.. The inhibition process decreases cholesterol generation while activating LDL receptors that remove LDL from the bloodstream.

Role of Statins with Focus on Atorvastatin

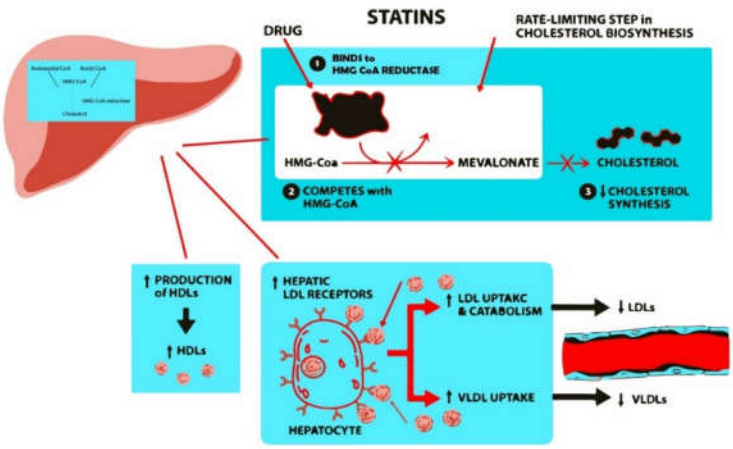
The medication class Statin, which doctors frequently use for hyperlipidemia treatment, demonstrates effective lipid reduction and cardiovascular event prevention benefits

(Lopez, 2002). The 2013 ACC/AHA clinical evidence established statin therapy as a proven method to decrease cardiovascular event risks among both initial and subsequent patients (Adhyaru & Jacobson, 2018). Atorvastatin serves as a widely prescribed statin medication that effectively decreases LDL-C levels and subsequently lowers cardiovascular risk events (Adhyaru & Jacobson, 2018).

A research project was carried out to determine how safe and effective atorvastatin is compared to simvastatin and pravastatin in hyperlipidemic patients. The study demonstrated that atorvastatin lowered LDL-C more effectively than the two other drugs while raising HDL-C levels. The research found that atorvastatin demonstrated superior effects compared to 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 decreasing cardiovascular risk in the population with diabetes (Colhoun et al., 2004).

Figure 1

Statin mechanism of action



Challenges with Statin Therapy

Statins remain popular among patients, yet the worldwide challenge to maintain proper adherence to this therapy continues to exist. Research shows that between 25 and 50 percent of patients stop taking statin medication during their initial year of treatment (Ingersgaard et al., 2020). When patients fail to follow statin treatment protocols, they face elevated chances of developing cardiovascular disease, together with heart attacks and fatal outcomes (Ryou et al., 2021), while a study reported 15% less risk of CVD in patients with high adherence to statin as compared to those with low adherence (Stroes et al., 2015). Intolerance to statins is one of the significant reasons for their discontinuation. Appearance of statin-associated musculoskeletal symptoms was the main reason for statin non-adherence in 65% of former statin users (Stroes et al., 2015). There are several pharmacogenetic variants, like SCLO1B1 and ABCG2, that affect the statin disposition and adverse events during statin therapy (Cooper-DeHoff et al., 2022).

The way different people respond to statins in their ability to decrease LDL-C levels and decrease cardiac events depends on their genetic makeup because certain genetic variants affect how statins lower LDL-C (Postmus et al. 2014). The pharmacokinetics and lipid-decreasing effects of atorvastatin are affected by genetic polymorphisms in the transporter genes SCLO1B1, SCLO1B3, and ABCC2 (Woo et al. 2017). Understanding the genetic variants associated with safety, the efficacy of

statins can help personalize treatment and improve patient outcomes.

Genetic Polymorphisms Influence on Hypolipidemic Effects of Atorvastatin:

APOE gene

The Apo lipoprotein E (APOE) functions as a crucial element in both lipid metabolism and regulatory processes. Triglycerides and cholesterol levels are carried through the circulatory system by APOE, an essential component of several lipoproteins.. The lipoproteins containing APOE utilize this protein to bind with receptors, which enable their uptake process. The APOE protein exists as a product of the APOE gene, which resides on the long arm of chromosome 19. The APOE gene contains 3 polymorphic alleles E2, E3, and E4, which produce three distinct APOE isoforms: E2, E3, and E4 (Pedro-Botet et al., 2001), concluding by 2 SNPS (526C>T and 388T>C) (Wang et al., 2021). The E3 variant functions as the normal allele because it occurs at the highest rates across Asia and North America and South America with percentages reaching 85% 82% and 77% respectively The three alleles produce six different genetic combinations known as E2/E2 E3/E3 E4/E4 E2/E3 E2/E4 and E3/E4 (Bi et al. 2022).

The molecular foundation of APOE SNPs has been linked to the swapping of arginine and cysteine. These changes influence the metabolic rate and binding affinity of lipoproteins to lipoprotein receptors, thus resulting in different blood levels among different individuals (Wang et al., 2021). E.g., the APOE4 allele is linked with increased plasma concentration of TGAs and LDL-C, while the APOE2 allele is linked with low plasma LDL-C levels (Horejs & Ceska, 2000). Thus, APOE genetic variants can affect the response to statins in lowering plasma lipid levels.

Research demonstrates that individuals with APOE E2 alleles experience superior LDL-C and total cholesterol decreases during atorvastatin treatment, while E4 allele carriers experience suboptimal atorvastatin responses (Zhang, He, et al. 2019, Wang et al. 2021, Bi et al. 2022). Study shows that males with the E2 allele show a significant reduction in LDLC levels with 10mg atorvastatin per day as compared to those with E3 homozygotes and ε4 carriers. E2 variant transporters had a mean response that was comparable to that of E3 homozygotes and E4 transporters, but no variation in response to therapy was seen in women.. 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). The research found no significant link between atorvastatin treatment response and APOE genotypes according to Christidis et al (Christidis et al. 2006, Miltiadous et al. 2005).

HMGCR gene

The enzyme known as HMG CoA reductase functions as a key biosynthetic enzyme that converts HMG CoA into mevalonic acid while serving as the rate-defining step for cholesterol synthesis. Statins specifically target HMG CoA, which functions as their molecular target. The HMG CoA reductase enzyme exists because of genetic instructions that come from the HMGCR gene, which exists at human chromosome 5 at the 5q13.3-14 band position (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 given 20mg Lipitor (atorvastatin) for one month, and biochemical measurements were taken before and after the treatment. The presence of HMGCR mutations in responder patients indicates that these genetic changes could boost the lipid-reducing capabilities of atorvastatin (Rizwan et al. 2021, Kirac et al., 2017). Both of these SNPs are observed in equal frequencies and are closely linked to each other in the HMGCR gene.

The genetic variant of HMGCR rs17671591 was evaluated in Chilean HC patients on atorvastatin. Following treatment, having the T variant for this single-nucleotide polymorphism is associated with lower LDL-C and higher HDL-C (Cuevas et al. 2016a).

Another study investigated the association between the (TTA)n polymorphism in the HMGCR gene and the reduction of LDL-C, TGA levels, and total cholesterol treated with atorvastatin. 64 atorvastatin-treated patients participated in the research. They were split into three categories according to their genetic makeup: 34% had a genetic makeup of >10/>10, 22% had a genetic makeup of >10/10, and 44% had a genetic makeup of 10/10. Irrespective of the type of variation, the results showed that all alleles encountered a reduction in LDL cholesterol, overall cholesterol, and the TGA levels after therapy (Noriega et al. 2009).

The frequency of HMGCR gene variants and their impact on lipid levels demonstrated variations across different ethnic groups. The G allele at rs3846662 showed increased LDL-C levels primarily in White populations, along with Japanese groups, but black people had more G

alleles while showing reduced statin dose response compared to Whites (Krauss et al. 2008, Hiura et al. 2010, Simon et al. 2006).

Research findings demonstrate conflicting evidence regarding the link between HMGCR SNPs and statin therapy effectiveness. One study found that the presence of the HMGCR SNP29 GG genotype was linked with a greater decrease in LDL-C following atorvastatin treatment (Chasman et al. 2004).

Cytochrome P450

The Cytochrome P450 family consists of multiple related genes that help break down various external and internal compounds. The group contains 57 functional genes and 58 inactive pseudogenes. The classification system for CYP450 isoenzymes divides them into 18 families and 44 subfamilies according to their primary protein sequence (Peng et al. 2018). Various CYP isoenzymes metabolize different statins. While atorvastatin and simvastatin are primarily metabolized by CYP3A4, fluvastatin is metabolized by CYP2C9. The polymorphism of CYP isoenzymes contributes to the varying response to statins (Morofuji et al. 2022).

Research demonstrated that people with the A-290G variant in the CYP3A4 promoter (also known as CYP3A4*1B or CYP3A4-V) showed poor atorvastatin response because their LDL-C levels remained high after treatment. The M445T missense variant (also referred to as CYP3A4*3) demonstrated superior efficacy because it lowered LDL-C levels more effectively (Kajinami, Brousseau, et al. 2004a). However, the latter findings failed to establish any link between the two (Poduri et al. 2010) or an increased reduction in serum total cholesterol (TC) and LDL-C levels in patients having the mutant allele (A-290G variant) as compared to those carrying the homozygous wild allele (Rosales et al. 2012). Likewise, CYP3A4*1G, an Asian allele with a prevalence of 0.249 in the Japanese and 0.221 in the Chinese, has been linked to atorvastatin's more powerful hypolipidemic effect as opposed to simvastatin (Gao, Zhang, & Fu, 2008). Another study checked the effects of CYP3A4*22 on the lowering effects of atorvastatin and simvastatin; however, it didn't find any significant association among them (Ragia et al. 2015).

For specific statins, the enzyme CYP3A5 carries out metabolic tasks. The wild-type allele exists as CYP3A5*1. People who have one or two copies of this allele will produce CYP3A5 protein in their livers, but people who have two copies The CYP3A5 enzyme cannot be produced by the 6986A>G change in the CYP3A5 gene's intron 3 cannot produce the CYP3A5 enzyme. Research findings demonstrated that simvastatin, lovastatin, and atorvastatin showed reduced effectiveness in patients with CYP3A5 enzyme expression compared to patients without such expression, although statins unaffected by CYP3A5 enzyme showed no such differences. The study results indicate that the genetic variation in CYP3A5 impacts how people react to statin medications (Kivist□ et al. 2004). However, a definitive answer remained elusive due to subsequent research. For instance, Wei and Zhang (2015) discovered no clear connection, while contradictory outcomes emerged in later studies. Notably, reduced atorvastatin response linked with the CYP3A1%3 allele was observed in non-African people (Willrich et al. 2008).

The CYP7A1 gene produces the enzyme cholesterol 7-α hydroxylase, which manages the primary and most critical transformation of cholesterol into bile acids. The response to statin treatment depends on variations that occur within the CYP7A1 gene. Multiple research investigations have demonstrated that the promoter variant in CYP3A7 (A-204C) produces a suboptimal atorvastatin response (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, present at the first intron of CYP3A7, has been shown to influence the LDL-lowering response of atorvastatin (Jiang et al. 2012).

CYP2D6, located on human chromosome 22, is a highly polymorphic enzyme *gene that encodes enzymes which?* metabolize 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 individuals with the GG genotype experience superior atorvastatin effects (Peng et al., 2018).

CETP gene

CETP functions as a critical component of lipoprotein breakdown. The protein drives the transfer of CETO along with triglycerides in plasma lipo-proteins, which produces net cholesteryl ester motion away from HDL > Apo lipo-protein B containing lipo-proteins and

cholesterol intake by hepatocytes (Venrooij et al., 2003). The Cholesteryl Ester Transfer Protein gene exists at chromosome 16q12-16q21, where its polymorphisms influence enzyme levels and lipid processing and statin response (Gu et al. 2014). The most studied CETP polymorphism is a silent base alteration that impacts the 277th nucleotide in the first gene that contains the restriction site for the enzyme TaqI (Venrooij et al., 2003). The TaqI RFLP exists in three genetic variants: B1B1, B2B2, and B3B3. The HDL-C levels in people who are homozygous for the B1 allele (restriction site present) are lower compared to those who possess the B2 allele (restriction site absent) (Mohrschladt et al., 2005).

Polymorphism in CETP TaqI plays a notable role in how atorvastatin lowers lipid levels (Yue et al. 2016). According to research, B1B1 carriers typically react better to statin medications than B2B2 carriers, with HDL levels significantly rising and triglycerides falling after atorvastatin treatment (Venrooij et al., 2003).). In another study, B1 carriers saw a 4% boost in HDL levels compared to those with the B2 allele, while post-atorvastatin therapy led to a 4% drop in HDL levels for the latter group. Furthermore, triglyceride levels decreased less in those homozygous for the B1 allele, though this difference was not statistically significant (Kolovou et al., 2010). According to a different study, after taking atorvastatin, patients with the alternative allele of Cholesteryl Ester Transfer Protein TaqI saw a more noticeable rise in HDL concentration (Poduri et al., 2010). Similarly, a different study indicated that High Density Lipoprotein-C levels were elevated in patients with the B1-B2 genotype compared to those with B1-B1, while plasma triglyceride levels significantly decreased in the B2-B2 genotype, being lower than in individuals with the B1 allele (Li et al. 2014). However, research conducted on a Jordanian population yielded contradictory results, showing no association between CETP Taq1b and LDL reduction after atorvastatin therapy.

Another polymorphism, A629C, found in the promoter area of the Cholesteryl Ester Transfer Protein gene, influences the varying responses to statins. Many studies suggest that the AA variant is linked to higher High density Lipoprotein-C levels, but patients with the CC genotype tend to respond better to atorvastatin therapy, reduction in the levels of lipoprotein A-I (LpA-I) and LDL-C(Gao et al. 2013, Gu et al. 2014, van Venrooij et al. 2003). CETP I405V (rs5882) polymorphism, located in exon 14, results from an A to G substitution that changes the amino acid from isoleucine to valine at codon 405. In one study, patients carrying the variant allele of I405V exhibited a smaller decrease in total cholesterol (Poduri et al. 2010).

LDLR-gene

LDLR is a protein present on the surface of various cells, including hepatocytes, adipocytes, and cells in other tissues, involved in cholesterol and lipid breakdown in the body. This receptor has taken part in taking up cholesterol, such as LDL-C and VLDL-C, from the blood into cells, thereby regulating cholesterol levels in the blood. The Low-Density Lipoprotein receptor gene encodes the Low-Density Lipoprotein receptor located on 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. In a study, the outcome of atorvastatin on LDLR genetic mutation in patients with heterozygotic familial hypercholesterolemia was evaluated. Study showed that patients having the V mutation (G1775A mutation) experienced a greater reduction in Low Density Lipoprotein-C than class 2 mutations (G1646-A and C858-A mutations)(Miltiadous et al. 2005). In another study, an 8-year-old kid with familial hypercholesterolemia, homozygous for c-1055G>A alteration in the Low Density Lipoprotein R gene, causing p.Cys352Tyr (known as Mexico 2 mutation), initial treatment with atorvastatin was not satisfactory. The genetic analysis of five polymorphisms, namely rs-1003723C>T, rs-5930A>G, rs-688C>T, rs-5929T>C, and rs-5927A>G, indicated a shared ancestor for the change and its association with the TGTCG-haplotype (Torres et al., 2014).

According to another study, LDLR AvaII was linked to the initial LDL levels in high-cholesterol individuals at the moment of diagnosis. However, following atorvastatin administration, LDLR AvaII had no discernible impact on lowering LDL levels (Zihlif et al., 2022). The effects of the genetic variant rs14158G>A in the LDLR gene, which is located in the 3'-UTR (3'-Untranslated Region), were examined in a separate investigation. It was found that the rs14158 SNP did not significantly correlate with response to atorvastatin treatment. The outcome of atorvastatin treatment was not found to be significantly correlated with the rs14158 SNP (Zambrano et al., 2015). A study conducted in Chilean Amerindian subjects showed no association of 1959C>T SNP (rs5925) in the LDLR gene as a result of atorvastatin therapy in healthy people (Lagos et al., 2015).

PCSK9 Gene

PCSK-9 is a protein that is encoded by the PCSK9 gene on human chromosome 1. By binding to the receptors for LDL on hepatocytes and causing their degradation, this protein contributes to the metabolism of blood cholesterol by lowering the number of Low-Density Lipoprotein receptors that can remove LDL-C from the blood and raising the blood cholesterol levels.

A study examined how the rs17111557 genetic variant (C>T) in the 3'UTR of the PCSK9 gene affected the lipid profile and atorvastatin response of Brazilian people. The study's conclusions demonstrated that individuals with the T-allele had lower High-Density Lipoprotein-C levels than those with the C-allele, and there was no correlation 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 linked to high Low-Density Lipoprotein-C, while I474V was not related to cholesterol levels (Anderson et al. 2014). There are various genotypes for the PSCK9 gene E670G polymorphism. A study in the Chinese population found that the G-G genotype had a raised level of LDL-C and a lower response to atorvastatin than the AG and AA genotypes (Zhang et al., 2017). SNP rs505151 did not correlate with blood lipid levels following atorvastatin therapy, according to a different study done on Han and Uyghur ischemic stroke patients (Yue et al. 2016). According to a study conducted on the Chilean population, atorvastatin treatment did not significantly alter lipid levels in patients with PCSK9 rs7552841 (Cuevas et al. 2016a). In a study that examined the lipid metabolism-related SNPs rs6235 and rs11206510, patients were given statins at equipotent doses, with simvastatin or atorvastatin accounting for roughly 90% of the total.. The result showed no significant association between the PCSK9 genetic variant and statin efficacy (Vrabl□k et al. 2012).

ABCB1 Genes

A wide family of membrane proteins known as ABC transporters is essential for moving different kinds of molecules across cell membranes. About half of these 48 transporters are engaged in the movement of lipids and related material (Tarling, de Aguiar Vallim, & Edwards, 2013). The ABCB-1 gene, referred to as MDR-1, encodes glycoprotein P, which aids in the bile-based removal of statins and their metabolites. Gene polymorphisms encoding these transporters may impact the safety and response of statins (Rebecchi et al., 2009).

In contrast to variant-allele-carriers in women, a study demonstrating the response of the C3435T variation, located at codon 1145 in exon 26 in the MRDI gene, found that the CC genotype is linked to a slight decrease in LDL and an increase in HDL (Kajinami et al., 2004b). Although a smaller subsequent study didn't find a significant association between the atorvastatin effect and the C3435-T polymorphism (Rodrigues et al., 2005). Another study replicated the result that the CC genotype is associated with lower atorvastatin efficacy (reduced LDL reduction) (Hoenig et al. 2011). Although results of later studies are not consistent, as some studies indicated that the T-T genotype is linked with poor results to atorvastatin (Munshi 2012) (Sa acka et al. 2014), while a recent study in Uyghur people found that the T-T genotype more efficiently decreases triglyceride levels than the remaining polymorphisms (Wang et al. 2023).

Three distinct amino acid sequences (Ser, Thr, and Pro) are produced by the ABCB1 gene's synonymous polymorphism G2677T/A/C, which is found at exon 26. According to a study, people with 2677A responded more favorably to the atorvastatin (Rebecchi et al. 2009). Following atorvastatin therapy, a higher increase in HDL concentration has been associated with another polymorphism in the promoter region, -41A/G (Poduri et al. 2010).

The intracellular and plasma membranes of liver cells and enterocytes contain the ABCG5/8 transporter proteins. These transporters are responsible for limiting the intestinal absorption and biliary excretion of sterols. Individual responses to statin medications may be impacted by variations in the genes encoding ABCG5/8. It was demonstrated that a higher Low-Density Lipoprotein-C lowering response is linked to the rs11887534 DH19 variant of ABCG8, also referred to as c.55G >C, which results in the substitution of histidine for aspartic acid (Kajinami et al., 2003) and a decrease in HDL response to atorvastatin (Sa acka et al., 2021). On the contrary, other studies didn t find its association with inter-individual variation in the result of statin drugs (Srivastava et al. 2010, Abed et al. 2021).

A key player in HDL metabolism, ABCA1 facilitates the passage of phospholipid and cholesterol across cell membranes. They are eliminated by lipid-poor High Density Lipoproteins Apolipoprotein. While other SNPS R219K and C-105T did not exhibit any association, studies on the ABCA1 gene variation revealed that the rs12003906 polymorphism is linked to a decreased lipid-lowering

response to atorvastatin. Another transporter protein linked to statin therapy is MRP-2, which is encoded by the gene ABCC-2. It functions as an efflux pump and is expressed in hepatocytes, enterocytes, and proximal renal tubular cells. c.1249G>A ABCC2 SNP has been connected with a diminished lipid response to atorvastatin (Woo et al. 2017). Research finds that the variant allele of SNP 24C>T is linked with a smaller decrease of T-G and T-G/HDL ratio by atorvastatin; however, this effect was only observed in Chilean males and not in females (Prado et al. 2018).

SLCO1B1 Gene

Statin pharmacokinetics (PK) and response are greatly influenced by Organic Anion Transporting Polypeptides (OATPs), which are influx transport proteins that are essential for statin uptake by liver cells. Of these, OATP1B-1 and OATP2B-1, which are encoded by SLCO1B1 and SLCO2B1, are particularly significant (Guan et al., 2019). OATP1B1 is found in sinus-like membranes of liver cells and transports a variety of pharmaceutical drugs, including atorvastatin (Dagli-Hernandez et al., 2022).

Low-function variants of SLCO1B1*5 and *15 cause decreased absorption of atorvastatin, cerivastatin, and pravastatin in in vitro experiments (Kameyama et al., 2005). Interestingly, atorvastatin, pitavastatin, and rosuvastatin plasma levels vary in homozygous carriers of SLCO1B1*15 (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 of SLCO1B1*1b, *1a+C1007G, and *1b+C1007G for atorvastatin (Kameyama et al. 2005).

On the other hand, numerous studies carried out on various ethnic groups supported the significant correlation found between SLCO1B1*5 alleles and high concentrations of 2-hydroxy, the cholesterol-lowering drug, an intermediate product of the cholesterol-lowering drug (Turner et al., 2020; DeGorter et al., 2013; Nozawa et al., 2002).

In contrast to the low-function variants, SLCO1B1*1B has been found to have no significant impact on transporter function (Kameyama et al. 2005). Research has indicated that SLCO1B1*1B does not affect HC patients' LDL-C response to atorvastatin or simvastatin (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).

Variant SLCO1B1 c.388A>G: An elevated atorvastatin response has been linked to the SLCO1B1 c.388A>G variant (Rodrigues et al., 2011).

KIF6 Gene

In many tissues, including the vascular system, KIF6, a member of the kinesin family, contributes to the migration of membrane organelles, complexes of proteins, and mRNA within cells along microtubules. It is encoded by the KIF6 gene on chromosome 6.

According to a number of studies, heart disease and the result of statin treatment are linked to a particular genetic variant called rs20455 (Trp719Arg). Statins are more effective at preventing heart problems in people with the 719 Arg-allele than in non-carriers, according to one study, the PROVE IT-TIMI22 (Li et al., 2011, Li et al., 2010, Iakoubova et al., 2008). According to a different study, the effectiveness of atorvastatin and cardiovascular disease risk were unaffected by KIF6 Trp719Arg genotype carriers (Hoffmann et al., 2011).

Genetic Polymorphisms Affecting the Adverse Effects of Atorvastatin

SLCO1B1

SLCO1B1*5 (rs4149056) has been tied to a greater likelihood of statin-induced myopathy (SIM). A substantial correlation between SLCO1B1*5 and an increased risk of SIM has been consistently reported by a number of meta-analyses (Hou et al. 2015, Lee and Chun 2018). In some populations, this genetic variation has been connected to all statin-produced ADRS, involving SIM (Jiang et al. 2016). Notably, SLCO1B1*5 allele carriers were found to be significantly linked to raised symptoms of muscles (p-0.016) and atorvastatin bigotry p-0.014 in a recent genome study (Turner et al. 2020).

These results show how important SLCO1B1*5 is for predicting bad drug reactions (ADRs) that happen when people take statins.

But there is still some disagreement about the link between SLCO1B1 polymorphisms and SIM in people who take atorvastatin, because not all studies have consistently found a strong link. Some studies have found no strong link between SLCO1B1*5 plus SIM in people taking lipid-lowering drugs (Brunham et al. 2012a, Carr et

al. 2013, Hou et al. 2015, Liu et al. 2017, Ramakumari et al. 2018). Significant areas under the curve of atorvastatin lactone and p-hydroxy atorvastatin lactone were not associated with SLCO1B1 variations or creatine kinase levels, according to a PK study that examined cases of atorvastatin-related myopathy. In many tissues, including the vascular system, kinesin-like protein 6 (KIF6), a member of the kinesin family, contributes to the intracellular migration of membrane organelles, protein complexes, and mRNA along microtubules. It is encoded by the KIF6 gene on chromosome 6 (Hermann et al., 2006).

CYP 450

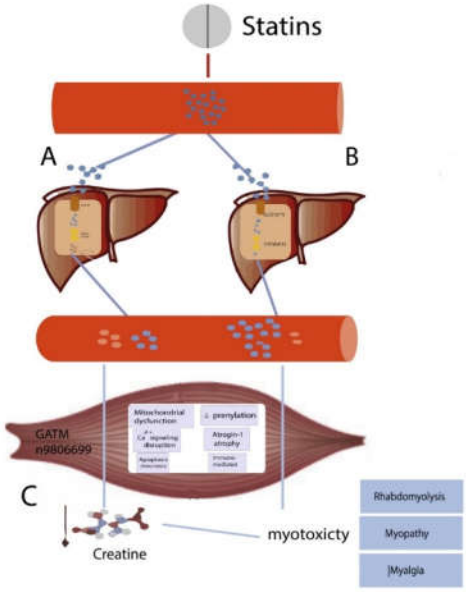
According to a study, the CYP2D6*4 variant is linked to muscle problems caused by atorvastatin (Frudakis et al., 2007). Current evidence does not link CYP3A4 variants to atorvastatin-induced myopathy, in spite of its role in atorvastatin metabolism. Although people who are homozygous for the CYP3A5*3 variant may have higher levels of creatine kinase than those who are heterozygote, this variant is not linked to the development of muscular negative consequences (Wilke, Moore, & Burmester, 2005)

ABC Transporter Gene

According to a study, those suffering from myalgia were more likely to carry the T-allele linked to the C3435T polymorphism in the MRD1 gene, whereas patients with muscular symptoms were less likely to carry the C-allele (Hoenig et al., 2011). In a different study, people with AILI had more of the 2677G allele than people without AILI. There were no big differences in the frequencies of 2677A and 2677T between atorvastatin-induced liver injury and non-atorvastatin-induced liver injury patients, though. This suggests that the G-allele might be a risk factor for atorvastatin-induced liver injury (Fukunaga et al. 2016). Later research showed that people with the G2677T/A allele are more likely to get liver damage from atorvastatin. Additionally, it found that 3434CT heterozygotes were more likely to be at risk for AILI and that the haplotype G-C (G2677T/A and C3435T) is linked to a greater risk of AILI (Qu et al. 2020). Furthermore, a higher risk of atorvastatin-induced myopathy is linked to a mutation (A allele) of rs237588 in ABCB1 (Zhang, Lv, et al. 2019). Yet another efflux-transporter that is expressed in the renal, liver, and intestine is ABCG2. Another name for this protein is cancer of the breast resistance to it.. The effectiveness and toxicity of statin therapy may be impacted by its polymorphism, which can alter the plasma concentration of atorvastatin (Keskitalo et al. 2009). A case study found that individuals who carried the 421AA or CA genotype had a 2.9-fold higher risk of atorvastatin dose-related unwanted drug reactions (ADRs) compared to those with the CC genotype (Miro□evi□ Skvrce et al., 2015).

Figure 2

Mechanism of action for statin-induced myopathy



Recommendations

An extensive investigation into the relationship between APOE, HMGCA, cytochrome P450 (CYP3A4, CYP3A5, CYP2D6), CETP, LDLR, PCSK9, ABCB1, ABCG5/8, SLCO1B1, and KIF6 polymorphism and atorvastatin efficacy is necessary. If a consistent correlation is confirmed between statins and this genetic polymorphism in large cohorts of people, the healthcare providers should adapt their practices accordingly. Genetic screening for relevant polymorphisms of relevant genes prior to prescribing atorvastatin can help predict not only individual responses to the therapy but also guide personalized treatment decisions. Additionally, variation in atorvastatin response to SNPs among diverse racial groups demands global-scale strategies, such as developing thorough pharmacogenetics guidelines for statins, which, depending on a patient's genetic profile, can help prescribers with treatment or dose calibration. Notably, the healthcare agents identify the patients predisposed to SIM and proceed with caution 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. Apart from the genetic factors listed in the research, more studies, including the entire genomic sequence, should be done to identify new SNPs and their impact on the hypolipidemic actions of atorvastatin. Furthermore, gender-specific result of atorvastatin opens up another avenue for research and investigation that often gets neglected due to various socio-economic reasons. Depending on the patient's lipid response to atorvastatin and genetic profile, changes to the treatment plan might be required. 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 treatment can promote better understanding among patients. This can foster greater acceptance of genetic testing and personalized treatment strategies.

Conclusion

In conclusion, the delicate interplay of pharmacogenetics and statins, particularly atorvastatin, presents a promising avenue for hyperlipidemia treatment and enhancement of results in patients. The role of polymorphic nature of genes such as *APOE, HMGCA,* cytochrome *P450*, *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 for calibration of global treatment strategies. With the informed consent of patients 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 in devising alternative lipid-lowering strategies for those with specific genetic variations More research is necessary to fully realize the possibilities of pharmacogenetics, including thorough analyses that look at the entire genome to find novel SNPs and how they affect the effectiveness of statins. Additionally, routinely checking lipid levels and other biomarkers and modifying the treatment plan according to a patient's genetic profile and lipid response are essential for personalized and effective hyperlipidemia management. Embracing these advancements will undoubtedly lead to improved patient outcomes, enhanced treatment adherence, and one more step toward accomplishing the objective of customized, precision medicine for hyperlipidemia and cardiovascular disease management.

References

Abed, E., Jarrar, Y., Alhawari, H., Abdullah, S., & Zihlif, M. (2020). How the cytochrome 7a1 (CYP7A1) and ATP-binding cassette G8 (ABCG8) genetic variants affect atorvastatin response among type 2 diabetic patients attending the University of Jordan Hospital. *International Journal of Clinical Pharmacology and Therapeutics*, *59*(02), 99–108. https://doi.org/10.5414/cp203779
Google Scholar Worldcat Fulltext

Adhyaru, B. B., & Jacobson, T. A. (2018). Safety and efficacy of statin therapy. *Nature Reviews Cardiology*, *15*(12), 757–769. https://doi.org/10.1038/s41569-018-0098-5
Google Scholar Worldcat Fulltext

Ahangari, N., Doosti, M., Ghayour Mobarhan, M., Sahebkar, A., Ferns, G. A., & Pasdar, A. (2020). Personalised medicine in hypercholesterolaemia: the role of pharmacogenetics in statin therapy. *Annals of medicine*, *52*(8), 462–470. https://doi.org/10.1080/07853890.2020.1800074
Google Scholar Worldcat Fulltext

Akadam-Teker, B., Kurnaz, O., Coskunpinar, E., Daglar-Aday, A., Kucukhuseyin, O., Cakmak, H. A., Teker, E., Bugra, Z., Ozturk, O., & Yilmaz-Aydogan, H. (2013). The effects of age and gender on the relationship between HMGCR promoter-911 SNP (rs33761740) and serum lipids in patients with coronary heart disease. *Gene*, *528*(2), 93–98. https://doi.org/10.1016/j.gene.2013.07.056
Google Scholar Worldcat Fulltext

Alloubani, A., Nimer, R., & Samara, R. (2021). Relationship between Hyperlipidemia, Cardiovascular Disease and Stroke: A Systematic Review. *Current cardiology reviews*, *17*(6), e051121189015. https://doi.org/10.2174/1573403X16999201210200342
Google Scholar Worldcat Fulltext

Al-Zahrani, J., Shubair, M. M., Al-Ghamdi, S., Alrasheed, A. A., Alduraywish, A. A., Alreshidi, F. S., Alshahrani, S. M., Alsalamah, M., Al-Khateeb, B. F., Ashathri, A. I., El-Metwally, A., & Aldossari, K. K. (2021). The prevalence of hypercholesterolemia and associated risk factors in Al-Kharj population, Saudi Arabia: a cross-sectional survey. *BMC cardiovascular disorders*, *21*(1), 22. https://doi.org/10.1186/s12872-020-01825-2
Google Scholar Worldcat Fulltext

Anderson, J. M., Cerda, A., Hirata, M. H., Rodrigues, A. C., Dorea, E. L., Bernik, M. M., Bertolami, M. C., Faludi, A. A., & Hirata, R. D. (2014). Influence of PCSK9 polymorphisms on plasma lipids and response to atorvastatin treatment in Brazilian subjects. *Journal of Clinical Lipidology*, *8*(3), 256–264. https://doi.org/10.1016/j.jacl.2014.02.008
Google Scholar Worldcat Fulltext

Basit, A., Sabir, S., Riaz, M., Fawwad, A., Abro, M. U. R., Ahmed, K. I., Ahmed, K., Bilal, A., Butt, A., Devrajani, B. R., Hayder, I., Humayun, Y., Irshad, R., Khan, R. A., Khan, A., Khowaja, A. A., Khowaja, R., Masroor, Q., Mehmood, M., . . . Zafar, J. (2020). NDSP 05: Prevalence and pattern of dyslipidemia in urban and rural areas of Pakistan; a sub-analysis from the second National Diabetes Survey of Pakistan (NDSP) 2016–2017. *Journal of Diabetes & Metabolic Disorders*, *19*(2), 1215–1225. https://doi.org/10.1007/s40200-020-00631-z
Google Scholar Worldcat Fulltext

Bi, Q., Zhou, X., Lu, Y., Fu, W., Wang, Y., Wang, F., & Wang, J. (2022). Polymorphisms of the apolipoprotein E gene affect response to atorvastatin therapy in acute ischemic stroke. *Frontiers in Cardiovascular Medicine*, *9*. https://doi.org/10.3389/fcvm.2022.1024014
Google Scholar Worldcat Fulltext

Bougarne, N., Weyers, B., Desmet, S. J., Deckers, J., Ray, D. W., Staels, B., & De Bosscher, K. (2018). Molecular actions of PPARA in lipid metabolism and inflammation. *Endocrine Reviews*, *39*(5), 760–802. https://doi.org/10.1210/er.2018-00064
Google Scholar Worldcat Fulltext

Brown, W. (1987). Potential use of fenofibrate and other fibric acid derivatives in the clinic. *The American Journal of Medicine*, *83*(5), 85–89. https://doi.org/10.1016/0002-9343(87)90876-x
Google Scholar Worldcat Fulltext

Brunham, L. R., Lansberg, P. J., Zhang, L., Miao, F., Carter, C., Hovingh, G. K., Visscher, H., Jukema, J. W., Stalenhoef, A. F., Ross, C. J. D., Carleton, B. C., Kastelein, J. J. P., & Hayden, M. R. (2011). Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *The Pharmacogenomics Journal*, *12*(3), 233–237. https://doi.org/10.1038/tpj.2010.92
Google Scholar Worldcat Fulltext

Buckley, M. M., Goa, K. L., Price, A. H., & Brogden, R. N. (1989). Probucol. *Drugs*, *37*(6), 761–800. https://doi.org/10.2165/00003495-198937060-00002
Google Scholar Worldcat Fulltext

Carr, D. F., O Meara, H., Jorgensen, A. L., Campbell, J., Hobbs, M., McCann, G., Van Staa, T., & Pirmohamed, M. (2013). SLCO1B1 Genetic variant Associated with Statin-Induced Myopathy: A Proof-of-Concept Study using the Clinical Practice Research Datalink. *Clinical Pharmacology & Therapeutics*, *94*(6), 695–701. https://doi.org/10.1038/clpt.2013.161
Google Scholar Worldcat Fulltext

Chasman, D. I. (2004). Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA*, *291*(23), 2821. https://doi.org/10.1001/jama.291.23.2821
Google Scholar Worldcat Fulltext

Chilbert, M. R., VanDuyn, D., Salah, S., Clark, C. M., & Ma, Q. (2022). Combination therapy of ezetimibe and rosuvastatin for dyslipidemia: Current insights. *Drug Design Development and Therapy*, *Volume 16*, 2177–2186. https://doi.org/10.2147/dddt.s332352
Google Scholar Worldcat Fulltext

Christidis, D. S., Liberopoulos, E. N., Kakafika, A. I., Miltiadous, G. A., Cariolou, M., Ganotakis, E. S., Mikhailidis, D. P., & Elisaf, M. S. (2006). The effect of apolipoprotein E polymorphism on the response to Lipid-Lowering treatment with atorvastatin or fenofibrate. *Journal of Cardiovascular Pharmacology and Therapeutics*, *11*(3), 211–221. https://doi.org/10.1177/1074248406293732
Google Scholar Worldcat Fulltext

Chung, J. Y., Cho, S. K., Oh, E. S., Lee, D. H., Lim, L. A., Jang, S. B., Lee, Y. J., Park, K., & Park, M. S. (2011). Effect of HMGCR variant alleles on Low-Density lipoprotein cholesterol—lowering response to atorvastatin in healthy Korean subjects. *The Journal of Clinical Pharmacology*, *52*(3), 339–346. https://doi.org/10.1177/0091270011398239
Google Scholar Worldcat Fulltext

Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. W., Livingstone, S. J., Thomason, M. J., Mackness, M. I., Charlton-Menys, V., & Fuller, J. H. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *The Lancet*, *364*(9435), 685–696. https://doi.org/10.1016/s0140-6736(04)16895-5
Google Scholar Worldcat Fulltext

Cooper-DeHoff, R. M., Niemi, M., Ramsey, L. B., Luzum, J. A., Tarkiainen, E. K., Straka, R. J., Gong, L., Tuteja, S., Wilke, R. A., Wadelius, M., Larson, E. A., Roden, D. M., Klein, T. E., Yee, S. W., Krauss, R. M., Turner, R. M., Palaniappan, L., Gaedigk, A., Giacomini, K. M.,... Voora, D. (2022). The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clinical Pharmacology & Therapeutics*, *111*(5), 1007–1021. https://doi.org/10.1002/cpt.2557
Google Scholar Worldcat Fulltext

Cuevas, A., Fern□ndez, C., Ferrada, L., Zambrano, T., Rosales, A., Saavedra, N., & Salazar, L. A. (2015). HMGCR rs17671591 SNP Determines Lower Plasma LDL-C after Atorvastatin Therapy in Chilean Individuals. *Basic & Clinical Pharmacology & Toxicology*, *118*(4), 292–297. https://doi.org/10.1111/bcpt.12493
Google Scholar Worldcat Fulltext

Dagli-Hernandez, C., Zhou, Y., Lauschke, V. M., Genvigir, F. D. V., Hirata, T. D. C., Hirata, M. H., & Hirata, R. D. C. (2021). Pharmacogenomics of statins: lipid response and other outcomes in Brazilian cohorts. *Pharmacological Reports*, *74*(1), 47–66. https://doi.org/10.1007/s43440-021-00319-y
Google Scholar Worldcat Fulltext

Davis, H. R., & Veltri, E. P. (2007). ZETIA: inhibition of Niemann-Pick C1-like 1 (NPC1L1) to reduce intestinal cholesterol absorption and treat hyperlipidemia. *Journal of Atherosclerosis and Thrombosis*, *14*(3), 99–108. https://doi.org/10.5551/jat.14.99
Google Scholar Worldcat Fulltext

DeGorter, M. K., Tirona, R. G., Schwarz, U. I., Choi, Y., Dresser, G. K., Suskin, N., Myers, K., Zou, G., Iwuchukwu, O., Wei, W., Wilke, R. A., Hegele, R. A., & Kim, R. B. (2013). Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. *Circulation Cardiovascular Genetics*, *6*(4), 400–408. https://doi.org/10.1161/circgenetics.113.000099
Google Scholar Worldcat Fulltext

Di Stasi, S. L., MacLeod, T. D., Winters, J. D., & Binder-Macleod, S. A. (2010). Effects of statins on skeletal muscle: A perspective for physical therapists. *Physical Therapy*, *90*(10), 1530–1542. https://doi.org/10.2522/ptj.20090251
Google Scholar Worldcat Fulltext

Feng, Y., Li, Q., Ou, G., Yang, M., & Du, L. (2021). Bile acid sequestrants: a review of mechanism and design. *Journal of Pharmacy and Pharmacology*, *73*(7), 855–861. https://doi.org/10.1093/jpp/rgab002
Google Scholar Worldcat Fulltext

Frudakis, T. N., Thomas, M. J., Ginjupalli, S. N., Handelin, B., Gabriel, R., & Gomez, H. J. (2007). CYP2D6*4 polymorphism is associated with statin-induced muscle effects. *Pharmacogenetics and Genomics*, *17*(9), 695–707. https://doi.org/10.1097/fpc.0b013e328012d0a9
Google Scholar Worldcat Fulltext

Fu, Q., Li, Y., Gao, Y., Yang, S., Lu, P., Jia, M., & Zhang, L. (2012). Lack of association between SLCO1B1 polymorphism and the lipid-lowering effects of atorvastatin and simvastatin in Chinese individuals. *European Journal of Clinical Pharmacology*, *69*(6), 1269–1274. https://doi.org/10.1007/s00228-012-1453-9
Google Scholar Worldcat Fulltext

Fukunaga, K., Nakagawa, H., Ishikawa, T., Kubo, M., & Mushiroda, T. (2016). ABCB1 polymorphism is associated with atorvastatin-induced liver injury in the Japanese

population. *BMC Genomic Data*, *17*(1). https://doi.org/10.1186/s12863-016-0390-5
Google Scholar Worldcat Fulltext

Galicia-Garcia, U., Benito-Vicente, A., Uribe, K. B., Jebari, S., Larrea-Sebal, A., Alonso-Estrada, R., Aguilo-Arce, J., Ostolaza, H., Palacios, L., & Martin, C. (2020). Mutation type classification and pathogenicity assignment of sixteen missense variants located in the EGF-precursor homology domain of the LDLR. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-58734-9
Google Scholar Worldcat Fulltext

Gao, J., Cong, H., Mao, Y., Liu, Y., Zhang, N., Chen, Q., Liu, T., & Cui, R. (2013). [Influence of CETP gene -629C/A polymorphism on the efficacy of atorvastatin treatment and clinical outcome]. *PubMed*, *30*(5), 553–558. https://doi.org/10.3760/cma.j.issn.1003-9406.2013.05.010
Google Scholar Worldcat Fulltext

Gao, Y., Zhang, L., & Fu, Q. (2008). CYP3A4*1G polymorphism is associated with lipid-lowering efficacy of atorvastatin but not of simvastatin. *European Journal of Clinical Pharmacology*, *64*(9), 877–882. https://doi.org/10.1007/s00228-008-0502-x
Google Scholar Worldcat Fulltext

Giannakopoulou, E., Ragia, G., Kolovou, V., Tavridou, A., Tselepis, A. D., Elisaf, M., Kolovou, G., & Manolopoulos, V. G. (2014). No impact of SLCO1B1 521T>C, 388A>G, and 411G>A polymorphisms on response to statin therapy in the Greek population. *Molecular Biology Reports*, *41*(7), 4631–4638. https://doi.org/10.1007/s11033-014-3334-z
Google Scholar Worldcat Fulltext

Gu, G., Xu, X., Yang, Q., & Zeng, R. (2014). Effect of CETP Polymorphism on Atorvastatin Lipid-Regulating Effect and Clinical Prognosis of Patients with Coronary Heart Disease. *Medical Science Monitor*, *20*, 2824–2829. https://doi.org/10.12659/msm.892711

Guan, Z., Wu, K., Li, R., Yin, Y., Li, X., Zhang, S., & Li, Y. (2019). Pharmacogenetics of statins treatment: Efficacy and safety. *Journal of Clinical Pharmacy and Therapeutics*, *44*(6), 858–867. https://doi.org/10.1111/jcpt.13025
Google Scholar Worldcat Fulltext

Hermann, M., Bogsrud, M., Molden, E., Asberg, A., Mohebi, B., Ose, L., & Retterstol, K. (2006). Exposure of atorvastatin is unchanged, but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. *Clinical Pharmacology & Therapeutics*, *79*(6), 532–539. https://doi.org/10.1016/j.clpt.2006.02.014
Google Scholar Worldcat Fulltext

Hiura, Y., Tabara, Y., Kokubo, Y., Okamura, T., Goto, Y., Nonogi, H., Miki, T., Tomoike, H., & Iwai, N. (2010). Association of the functional variant in the 3-Hydroxy-3-Methylglutaryl-Coenzyme A reductase gene with Low-Density Lipoprotein-Cholesterol in Japanese. *Circulation Journal*, *74*(3), 518–522. https://doi.org/10.1253/circj.cj-09-0790
Google Scholar Worldcat Fulltext

Hoenig, M. R., Walker, P. J., Gurnsey, C., Beadle, K., & Johnson, L. (2011). The C3435T polymorphism in ABCB1 influences atorvastatin efficacy and muscle symptoms in a high-risk vascular cohort. *Journal of Clinical Lipidology*, *5*(2), 91–96. https://doi.org/10.1016/j.jacl.2011.01.001
Google Scholar Worldcat Fulltext

Hoffmann, M. M., M□rz, W., Genser, B., Drechsler, C., & Wanner, C. (2011). Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: The 4D study. *Atherosclerosis*, *219*(2), 659–662. https://doi.org/10.1016/j.atherosclerosis.2011.07.126
Google Scholar Worldcat Fulltext

Horejs□, B., & Ceska, R. (2000). *Apolipoproteins and atherosclerosis: Apolipoprotein E and apolipoprotein(a) as candidate genes of premature development of atherosclerosis. Physiological Research, 49*(Suppl 1), S63–S69.

Hou, Q., Li, S., Li, L., Li, Y., Sun, X., & Tian, H. (2015). Association between SLCO1B1 gene T521C polymorphism and Statin-Related Myopathy Risk. *Medicine*, *94*(37), e1268. https://doi.org/10.1097/md.0000000000001268
Google Scholar Worldcat Fulltext

Iakoubova, O. A., Sabatine, M. S., Rowland, C. M., Tong, C. H., Catanese, J. J., Ranade, K., Simonsen, K. L., Kirchgessner, T. G., Cannon, C. P., Devlin, J. J., & Braunwald, E. (2008). Polymorphism in the KIF6 gene and benefit from statins after acute coronary syndromes. *Journal of the American College of Cardiology*, *51*(4), 449–455. https://doi.org/10.1016/j.jacc.2007.10.017
Google Scholar Worldcat Fulltext

Ingersgaard, M. V., Andersen, T. H., Norgaard, O., Grabowski, D., & Olesen, K. (2020). Reasons for Nonadherence to Statins – A Systematic Review of Reviews *Patient Preference and Adherence*, *Volume 14*, 675–691. https://doi.org/10.2147/ppa.s245365
Google Scholar Worldcat Fulltext

Jiang, J., Tang, Q., Feng, J., Dai, R., Wang, Y., Yang, Y., Tang, X., Deng, C., Zeng, H., Zhao, Y., & Zhang, F. (2016). Association between SLCO1B1 521T>C and 388A>G polymorphisms and risk of statin-induced adverse drug reactions: A meta-analysis. *SpringerPlus*, *5*(1). https://doi.org/10.1186/s40064-016-2912-z
Google Scholar Worldcat Fulltext

Jiang, X., Zhang, Q., Chen, P., Li, S., Zhang, N., Chen, X., Wang, G., Wang, H., Zhuang, M., & Lu, M. (2012). CYP7A1 polymorphism influences the LDL cholesterol-lowering response to atorvastatin. *Journal of Clinical Pharmacy and Therapeutics*, *37*(6), 719–723. https://doi.org/10.1111/j.1365-2710.2012.01372.x
Google Scholar Worldcat Fulltext

Jose, M., Anandkumar, S., Narmadha, M., & Sandeep, M. (2012). A comparative effect of atorvastatin with other statins in patients with hyperlipidemia. *Indian Journal of Pharmacology*, *44*(2), 261. https://doi.org/10.4103/0253-7613.93864
Google Scholar Worldcat Fulltext

Julius, U., & Fischer, S. (2013). Nicotinic acid as a lipid-modifying drug – A review. *Atherosclerosis Supplements*, *14*(1), 7–13. https://doi.org/10.1016/j.atherosclerosissup.2012.10.036
Google Scholar Worldcat Fulltext

Kadam, P., Ashavaid, T. F., Ponde, C. K., & Rajani, R. M. (2016). Genetic determinants of lipid-lowering response to atorvastatin therapy in an Indian population. *Journal of Clinical Pharmacy and Therapeutics*, *41*(3), 329–333. https://doi.org/10.1111/jcpt.12369
Google Scholar Worldcat Fulltext

Kajinami, K., Brousseau, M. E., Nartsupha, C., Ordovas, J. M., & Schaefer, E. J. (2004). ATP-binding cassette transporter G5 and G8 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin. *Journal of Lipid Research*, *45*(4), 653–656. https://doi.org/10.1194/jlr.m300278-jlr200
Google Scholar Worldcat Fulltext

Kajinami, K., Brousseau, M. E., Ordovas, J. M., & Schaefer, E. J. (2003). CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hypercholesterolemia. *The American Journal of Cardiology*, *93*(1), 104–107. https://doi.org/10.1016/j.amjcard.2003.08.078
Google Scholar Worldcat Fulltext

Kajinami, K., Brousseau, M. E., Ordovas, J. M., & Schaefer, E. J. (2005). A promoter polymorphism in cholesterol 7α-hydroxylase interacts with apolipoprotein E genotype in the LDL-lowering response to atorvastatin. *Atherosclerosis*, *180*(2), 407–415. https://doi.org/10.1016/j.atherosclerosis.2004.12.019
Google Scholar Worldcat Fulltext

Kajinami, K., Brousseau, M. E., Ordovas, J. M., & Schaefer, E. J. (2004). Polymorphisms in the multidrug resistance-1 (MDR1) gene influence the response to atorvastatin treatment in a gender-specific manner. *The American Journal of Cardiology*, *93*(8), 1046–1050. https://doi.org/10.1016/j.amjcard.2004.01.014
Google Scholar Worldcat Fulltext

Kameyama, Y., Yamashita, K., Kobayashi, K., Hosokawa, M., & Chiba, K. (2005). Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15, and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. *Pharmacogenetics and Genomics*, *15*(7), 513–522. https://doi.org/10.1097/01.fpc.0000170913.73780.5f
Google Scholar Worldcat Fulltext

Karr, S. 2017. "Epidemiology and management of hyperlipidemia." *Am J Manag Care* no. 23 (9 Suppl): S139-s148.
Google Scholar Worldcat Fulltext

Keskitalo, J. E., Zolk, O., Fromm, M. F., Kurkinen, K. J., Neuvonen, P. J., & Niemi, M. (2009). ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. *Clinical Pharmacology & Therapeutics*, *86*(2), 197–203. https://doi.org/10.1038/clpt.2009.79
Google Scholar Worldcat Fulltext

Kirac, D., Bayam, E., Dagdelen, M., Gezmis, H., Sarikaya, S., Pala, S., Altunok, E. C., & Genc, E. (2017). HMGCR and ApoE mutations may cause different responses to lipid-lowering statin therapy. *Cellular and Molecular Biology*, *63*(10), 43–48. https://doi.org/10.14715/cmb/2017.63.10.6
Google Scholar Worldcat Fulltext

Kitzmiller, J., Mikulik, E., Dauki, A., Mukherjee, C., & Luzum, J. (2016). Pharmacogenomics of statins: understanding susceptibility to adverse effects. *Pharmacogenomics and Personalized Medicine*, *Volume 9*, 97–106. https://doi.org/10.2147/pgpm.s86013
Google Scholar Worldcat Fulltext

Kivist□, K. T., Niemi, M., Schaeffeler, E., Pitk□l□, K., Tilvis, R., Fromm, M. F., Schwab, M., Eichelbaum, M., & Strandberg, T. (2004). Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics*, *14*(8), 523–525. https://doi.org/10.1097/01.fpc.0000114762.78957.a5
Google Scholar Worldcat Fulltext

Kolovou, G., Mihas, C., Anagnostopoulou, K., Kolovou, V., Giannakopoulou, V., Kostakou, P., Stamatelatou, M., Mavrogeni, S., Degiannis, D., & Mikhailidis, D. P. (2010). Cholesteryl ester transfer protein gene and the effectiveness of lipid-lowering of atorvastatin. *The Open Cardiovascular Medicine Journal*, *4*(1), 297–301. https://doi.org/10.2174/1874192401004010297
Google Scholar Worldcat Fulltext

Krauss, R. M., Mangravite, L. M., Smith, J. D., Medina, M. W., Wang, D., Guo, X., Rieder, M. J., Simon, J. A., Hulley, S. B., Waters, D., Saad, M., Williams, P. T., Taylor, K. D., Yang, H., Nickerson, D. A., & Rotter, J. I. (2008). Variation

in the 3-Hydroxyl-3-Methylglutaryl coenzyme a reductase gene is associated with racial differences in Low-Density lipoprotein cholesterol response to simvastatin treatment. *Circulation*, *117*(12), 1537–1544. https://doi.org/10.1161/circulationaha.107.708388
Google Scholar Worldcat Fulltext

Lagos, J., Zambrano, T., Rosales, A., & Salazar, L. (2015). APOE polymorphisms contribute to reduced atorvastatin response in Chilean Amerindian subjects. *International Journal of Molecular Sciences*, *16*(4), 7890–7899. https://doi.org/10.3390/ijms16047890
Google Scholar Worldcat Fulltext

Landray, M. J., R. Haynes, J. C. Hopewell, S. Parish, T. Aung, J. Tomson, K. Wallendszus, M. Craig, L. Jiang, R. Collins, and J. Armitage. 2014. "Effects of extended-release niacin with laropiprant in high-risk patients." *N Engl J Med* no. 371 (3):203-12. https://doi.org/10.1056/nejmoa1300955
Google Scholar Worldcat Fulltext

Lee, Y. S., & Chun, P. (2018). Effect of SLCO1B1 T521C on statin-induced myotoxicity: a systematic review and meta-analysis. *Korean Journal of Clinical Pharmacy*, *28*(4), 320–332. https://doi.org/10.24304/kjcp.2018.28.4.320
Google Scholar Worldcat Fulltext

Li, J., Zhang, L., Xie, N., Deng, B., Lv, L., & Zheng, L. (2014). Relationship between the cholesterol ester transfer protein TaqIB polymorphism and the lipid-lowering effect of atorvastatin in patients with coronary atherosclerotic heart disease. *Genetics and Molecular Research*, *13*(1), 2140–2148. https://doi.org/10.4238/2014.march.24.21
Google Scholar Worldcat Fulltext

Li, Y., Iakoubova, O. A., Shiffman, D., Devlin, J. J., Forrester, J. S., & Superko, H. R. (2010). KIF6 polymorphism as a predictor of risk of coronary events and of clinical event reduction by statin therapy. *The American Journal of Cardiology*, *106*(7), 994–998. https://doi.org/10.1016/j.amjcard.2010.05.033
Google Scholar Worldcat Fulltext

Li, Y., Sabatine, M. S., Tong, C. H., Ford, I., Kirchgessner, T. G., Packard, C. J., Robertson, M., Rowland, C. M., Bare, L. A., Shepherd, J., Devlin, J. J., & Iakoubova, O. A. (2010). Genetic variants in the KIF6 region and coronary event reduction from statin therapy. *Human Genetics*, *129*(1), 17–23. https://doi.org/10.1007/s00439-010-0892-6
Google Scholar Worldcat Fulltext

Lin, C., Chang, Y., Chien, S., Lin, Y., & Yeh, H. (2018). Epidemiology of dyslipidemia in the Asia Pacific region. *International Journal of Gerontology*, *12*(1), 2–6. https://doi.org/10.1016/j.ijge.2018.02.010
Google Scholar Worldcat Fulltext

Lindgren, V., Luskey, K. L., Russell, D. W., & Francke, U. (1985). Human genes involved in cholesterol metabolism: chromosomal mapping of the loci for the low density lipoprotein receptor and 3-hydroxy-3-methylglutaryl-coenzyme A reductase with cDNA probes. *Proceedings of the National Academy of Sciences*, *82*(24), 8567–8571. https://doi.org/10.1073/pnas.82.24.8567
Google Scholar Worldcat Fulltext

Lippi, G., Mattiuzzi, C., & Cervellin, G. (2019). Statins' popularity: A global picture. *British Journal of Clinical Pharmacology*, *85*(7), 1614–1615. https://doi.org/10.1111/bcp.13944
Google Scholar Worldcat Fulltext

Liu, J., Liu, X., Chen, S., Zhang, Y., Cai, L., Yang, M., Lai, W., Ren, B., & Zhong, S. (2017). SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case–control study. *European Journal of Clinical Pharmacology*, *73*(11), 1409–1416. https://doi.org/10.1007/s00228-017-2318-z
Google Scholar Worldcat Fulltext

Liu, Y., Lv, X., Xie, N., Fang, Z., Ren, W., Gong, Y., Jin, Y., & Zhang, J. (2020). Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012–2018). *BMC Cardiovascular Disorders*, *20*(1). https://doi.org/10.1186/s12872-020-01482-5
Google Scholar Worldcat Fulltext

Lopez, L. M. (2002). Managing hyperlipidemia: Current and future roles of HMG-CoA reductase inhibitors. *American Journal of Health-System Pharmacy*, *59*(12), 1173–1179. https://doi.org/10.1093/ajhp/59.12.1173
Google Scholar Worldcat Fulltext

Miltiadous, G., Xenophontos, S., Bairaktari, E., Ganotakis, M., Cariolou, M., & Elisaf, M. (2005). Genetic and environmental factors affecting the response to statin therapy in patients with molecularly defined familial hypercholesterolaemia. *Pharmacogenetics and Genomics*, *15*(4), 219–225. https://doi.org/10.1097/01213011-200504000-00005
Google Scholar Worldcat Fulltext

Misra, A., & Khurana, L. (2010). Obesity-related non-communicable diseases: South Asians vs White Caucasians. *International Journal of Obesity*, *35*(2), 167–187. https://doi.org/10.1038/ijo.2010.135
Google Scholar Worldcat Fulltext

Mohrschladt, M. F., Van Der Sman-De Beer, F., Hofman, M. K., Van Der Krabben, M., Westendorp, R. G., & Smelt, A. H. (2005). TaqIB polymorphism in the CETP gene: the influence on incidence of cardiovascular disease in statin-treated patients with familial hypercholesterolemia.

European Journal of Human Genetics, *13*(7), 877–882. https://doi.org/10.1038/sj.ejhg.5201426
Google Scholar Worldcat Fulltext

Morofuji, Y., Nakagawa, S., Ujifuku, K., Fujimoto, T., Otsuka, K., Niwa, M., & Tsutsumi, K. (2022). Beyond Lipid-Lowering: Effects of statins on cardiovascular and cerebrovascular diseases and cancer. *Pharmaceuticals*, *15*(2), 151. https://doi.org/10.3390/ph15020151
Google Scholar Worldcat Fulltext

Munshi, A. (2012). Genetic variation in MDR1, LPL, and eNOS genes and the response to atorvastatin treatment in ischemic stroke. *Human Genetics*, *131*(11), 1775–1781. https://doi.org/10.1007/s00439-012-1202-2
Google Scholar Worldcat Fulltext

Noriega, V., Pennanen, C., S□nchez, M. P., Chiong, M., Llancaqueo, M., Lavandero, S., & Prieto, J. C. (2008). (TTA)n Polymorphism in 3-Hydroxy-3-Methylglutaryl-Coenzyme A and Response to Atorvastatin in Coronary Artery Disease Patients. *Basic & Clinical Pharmacology & Toxicology*, *104*(3), 211–215. https://doi.org/10.1111/j.1742-7843.2008.00341.x
Google Scholar Worldcat Fulltext

Nozawa, T., Nakajima, M., Tamai, I., Noda, K., Nezu, J., Sai, Y., Tsuji, A., & Yokoi, T. (2002). Genetic polymorphisms of human organic anion transporters OATP-C (SLC21A6) and OATP-B (SLC21A9): allele frequencies in the Japanese population and functional analysis. *Journal of Pharmacology and Experimental Therapeutics*, *302*(2), 804–813. https://doi.org/10.1124/jpet.302.2.804
Google Scholar Worldcat Fulltext

Onwe, P., Folawiyo, M., Anyigor-Ogah, C. S., Umahi, G., Okorocha, A. E., & Afoke, A. (2015). *Hyperlipidemia: Etiology and possible control. IOSR Journal of Dental and Medical Sciences,* *14*(10), 93–100. https://doi.org/10.9790/0853-14106931oo
Google Scholar Worldcat Fulltext

Padhye, M., & Yadav, N. (2022). Plethora of adverse drug reactions in the geriatric population receiving statin therapy for dyslipidaemia. *Journal of Family Medicine and Primary Care*, *11*(7), 3726–3729. https://doi.org/10.4103/jfmpc.jfmpc_2205_21
Google Scholar Worldcat Fulltext

Pedro-Botet, J., Schaefer, E. J., Bakker-Arkema, R. G., Black, D. M., Stein, E. M., Corella, D., & Ordovas, J. M. (2001). Apolipoprotein E genotype affects plasma lipid response to atorvastatin in a gender specific manner. *Atherosclerosis*, *158*(1), 183–193. https://doi.org/10.1016/s0021-9150(01)00410-5
Google Scholar Worldcat Fulltext

Peng, C., Ding, Y., Yi, X., Shen, Y., Dong, Z., Cao, L., Li, Q., Ren, H., He, L., Zhou, D., & Chen, X. (2018). Polymorphisms in CYP450 genes and the therapeutic effect of atorvastatin on ischemic stroke: a retrospective cohort study in the Chinese population. *Clinical Therapeutics*, *40*(3), 469-477.e2. https://doi.org/10.1016/j.clinthera.2018.02.002
Google Scholar Worldcat Fulltext

Poduri, A., Khullar, M., Bahl, A., Sehrawat, B., Sharma, Y., & Talwar, K. K. (2010). Common variants of HMGCR, CETP, APOAI, ABCB1, CYP3A4, andCYP7A1Genes as predictors of Lipid-Lowering response to atorvastatin therapy. *DNA And Cell Biology*, *29*(10), 629–637. https://doi.org/10.1089/dna.2009.1008
Google Scholar Worldcat Fulltext

Postmus, I., Trompet, S., Deshmukh, H. A., Barnes, M. R., Li, X., Warren, H. R., Chasman, D. I., Zhou, K., Arsenault, B. J., Donnelly, L. A., Wiggins, K. L., Avery, C. L., Griffin, P., Feng, Q., Taylor, K. D., Li, G., Evans, D. S., Smith, A. V., De Keyser, C. E., . . . Spencer, C. C. A. (2014). Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nature Communications*, *5*(1). https://doi.org/10.1038/ncomms6068
Google Scholar Worldcat Fulltext

Prado, Y., Arencibia, A., Zambrano, T., & Salazar, L. A. (2017). Gender-Specific Association Between ABCC2-24C>T SNP and Reduction in Triglycerides in Chilean Patients Treated With Atorvastatin. *Basic & Clinical Pharmacology & Toxicology*, *122*(5), 517–522. https://doi.org/10.1111/bcpt.12943
Google Scholar Worldcat Fulltext

Qu, K., Zhang, C., Dong, L., Wang, S., Zhang, Z., & Zhang, L. (2019). Association of ABCB1 polymorphisms with lipid homeostasis and liver injury response to atorvastatin in the Chinese population. *Canadian Journal of Physiology and Pharmacology*, *98*(1), 15–22. https://doi.org/10.1139/cjpp-2019-0339
Google Scholar Worldcat Fulltext

Ragia, G., Kolovou, V., Tavridou, A., Elens, L., Tselepis, A. D., Elisaf, M., Van Schaik, R. H., Kolovou, G., & Manolopoulos, V. G. (2014). No effect of CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) on lipid-lowering response to statins in Greek patients with primary hypercholesterolemia. *Drug Metabolism and Personalized Therapy*, *30*(1), 43–48. https://doi.org/10.1515/dmdi-2014-0021
Google Scholar Worldcat Fulltext

Ramakumari, N., Indumathi, B., Katkam, S. K., & Kutala, V. K. (2018). Impact of pharmacogenetics on statin-induced myopathy in South-Indian subjects. *Indian Heart Journal*, *70*, S120–S125. https://doi.org/10.1016/j.ihj.2018.07.009
Google Scholar Worldcat Fulltext

Rebecchi, I. M. M., Rodrigues, A. C., Arazi, S. S., Genvigir, F. D. V., Willrich, M. a. V., Hirata, M. H., Soares, S. A., Bertolami, M. C., Faludi, A. A., Bernik, M. M. S., Dorea, E. L., Dagli, M. L. Z., Avanzo, J. L., & Hirata, R. D. C. (2008). ABCB1 and ABCC1 expression in peripheral mononuclear cells is influenced by gene polymorphisms and atorvastatin treatment. *Biochemical Pharmacology*, *77*(1), 66–75. https://doi.org/10.1016/j.bcp.2008.09.019
Google Scholar Worldcat Fulltext

Rizwan, M., Aslam, N., Ashfaq, U. A., Hayat, M., & Hussain, S. M. (2021). SNP of HMGCR and Apo E genes and their impact in response to statin therapy in hypercholesterolemic and hypertriglyceridemic patients in Pakistan. *Pakistan journal of pharmaceutical sciences*, *34*(4(Supplementary)), 1577–1583.
Google Scholar Worldcat Fulltext

Rodrigues, A. C., Perin, P. M. S., Purim, S. G., Silbiger, V. N., Genvigir, F. D. V., Willrich, M. a. V., Arazi, S. S., Luchessi, A. D., Hirata, M. H., Bernik, M. M. S., Dorea, E. L., Santos, C., Faludi, A. A., Bertolami, M. C., Salas, A., Freire, A., Lareu, M. V., Phillips, C., Porras-Hurtado, L., . . . Hirata, R. D. C. (2011). Pharmacogenetics of OATP Transporters reveals that SLCO1B1 C.388A□G variant is determinant of increased atorvastatin response. *International Journal of Molecular Sciences*, *12*(9), 5815–5827. https://doi.org/10.3390/ijms12095815
Google Scholar Worldcat Fulltext

Rodrigues, A., Rebecchi, I., Bertolami, M., Faludi, A., Hirata, M., & Hirata, R. (2005). High baseline serum total and LDL cholesterol levels are associated with MDR1 haplotypes in Brazilian hypercholesterolemic individuals of European descent. *Brazilian Journal of Medical and Biological Research*, *38*(9), 1389–1397. https://doi.org/10.1590/s0100-879x2005000900014
Google Scholar Worldcat Fulltext

Rosales, A., Alvear, M., Cuevas, A., Saavedra, N., Zambrano, T., & Salazar, L. A. (2011). Identification of pharmacogenetic predictors of lipid-lowering response to atorvastatin in Chilean subjects with hypercholesterolemia. *Clinica Chimica Acta*, *413*(3–4), 495–501. https://doi.org/10.1016/j.cca.2011.11.003
Google Scholar Worldcat Fulltext

Ryou, I. S., Chang, J., Son, J. S., Ko, A., Choi, S., Kim, K., Kim, S. M., & Park, S. M. (2021). Association between CVDs and initiation and adherence to statin treatment in patients with newly diagnosed hypercholesterolaemia: a retrospective cohort study. *BMJ Open*, *11*(4), e045375. https://doi.org/10.1136/bmjopen-2020-045375
Google Scholar Worldcat Fulltext

Saha, S. P., Banks, M. A., & Whayne, T. F. (2020). Managing Cardiovascular Risk Factors without Medications: What is the Evidence? *Cardiovascular & Hematological Agents in Medicinal Chemistry*, *19*(1), 8–16. https://doi.org/10.2174/1871525718666200518093418
Google Scholar Worldcat Fulltext

Sa acka, A., Bi□czak-Kuleta, A., Kaczmarczyk, M., Hornowska, I., Safranow, K., & Clark, J. S. C. (2014). Possible association of ABCB1:c.3435T>C polymorphism with high-density-lipoprotein-cholesterol response to statin treatment - a pilot study. *Biomolecules and Biomedicine*, *14*(3), 144–149. https://doi.org/10.17305/bjbms.2014.3.43
Google Scholar Worldcat Fulltext

Sa acka, A., Boro□, A., Gor□cy, I., Hornowska, I., Safranow, K., & Ciechanowicz, A. (2021). An association of ABCG8: rs11887534 polymorphism and HDL-cholesterol response to statin treatment in the Polish population. *Pharmacological Reports*, *73*(6), 1781–1786. https://doi.org/10.1007/s43440-021-00302-7
Google Scholar Worldcat Fulltext

Salami, J. A., Warraich, H., Valero-Elizondo, J., Spatz, E. S., Desai, N. R., Rana, J.S., Virani, S. S., Blankstein, R., Khera, A., Blaha, M. J., Blumenthal, R. S., Lloyd-Jones, D., & Nasir, K. (2016). National trends in statin use and expenditures in the US adult population from 2002 to 2013. *JAMA Cardiology*, *2*(1), 56. https://doi.org/10.1001/jamacardio.2016.4700
Google Scholar Worldcat Fulltext

Schaiff, R. A., Moe, R. M., & Krichbaum, D. W. (2008). *An overview of cholesterol management. American Health & Drug Benefits, 1*(9), 39–48.
Google Scholar Worldcat Fulltext

Simon, J. A., Lin, F., Hulley, S. B., Blanche, P. J., Waters, D., Shiboski, S., Rotter, J. I., Nickerson, D. A., Yang, H., Saad, M., & Krauss, R. M. (2006). Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: the Cholesterol and Pharmacogenetics (CAP) study. *The American Journal of Cardiology*, *97*(6), 843–850. https://doi.org/10.1016/j.amjcard.2005.09.134
Google Scholar Worldcat Fulltext

Skvrce, N. M., □arini□, V. M., □imi□, I., Ganoci, L., Katanec, D. M., & Bo□ina, N. (2015). ABCG2 Gene Polymorphisms as risk factors for atorvastatin Adverse reactions: A Case–Control Study. *Pharmacogenomics*, *16*(8), 803–815. https://doi.org/10.2217/pgs.15.47
Google Scholar Worldcat Fulltext

Srivastava, A., Garg, N., Srivastava, A., Srivastava, K., & Mittal, B. (2010). Effect of genetic variant (rs11887534) in the ABCG8 gene in coronary artery disease and response to atorvastatin therapy. *DOAJ (DOAJ: Directory of Open Access Journals)*, *28*(5), 307–313. https://doi.org/10.3233/dma-2010-0710
Google Scholar Worldcat Fulltext

Stancu, C., & Sima, A. (2001). Statins: mechanism of action and effects. *Journal of Cellular and Molecular Medicine*, *5*(4), 378–387. https://doi.org/10.1111/j.1582-4934.2001.tb00172.x
Google Scholar Worldcat Fulltext

Stroes, E. S., Thompson, P. D., Corsini, A., Vladutiu, G. D., Raal, F. J., Ray, K. K., Roden, M., Stein, E., Tokg□zo□lu, L., Nordestgaard, B. G., Bruckert, E., De Backer, G., Krauss, R. M., Laufs, U., Santos, R. D., Hegele, R. A., Hovingh, G. K., Leiter, L. A., Mach, F., . . . Wiklund, O. (2015). Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *European Heart Journal*, *36*(17), 1012–1022. https://doi.org/10.1093/eurheartj/ehv043
Google Scholar Worldcat Fulltext

Tarling, E. J., De Aguiar Vallim, T. Q., & Edwards, P. A. (2013). Role of ABC transporters in lipid transport and human disease. *Trends in Endocrinology and Metabolism*, *24*(7), 342–350. https://doi.org/10.1016/j.tem.2013.01.006
Google Scholar Worldcat Fulltext

Thompson, J. F., Hyde, C. L., Wood, L. S., Paciga, S. A., Hinds, D. A., Cox, D. R., Hovingh, G. K., & Kastelein, J. J. (2009). Comprehensive Whole-Genome and Candidate gene analysis for response to statin therapy in the treating New Targets (TNT) cohort. *Circulation Cardiovascular Genetics*, *2*(2), 173–181. https://doi.org/10.1161/circgenetics.108.818062
Google Scholar Worldcat Fulltext

Torres, M. T. M., Mora-Hern□ndez, S., C□rdenas, N. a. V., & Jaimes, A. G. (2014). Homozygous familial hypercholesterolemia: The c.1055G>A mutation in the LDLR gene and clinical heterogeneity. *Journal of Clinical Lipidology*, *8*(5), 525–527. https://doi.org/10.1016/j.jacl.2014.05.002
Google Scholar Worldcat Fulltext

Trompet, S., Postmus, I., Warren, H. R., Noordam, R., Smit, R. A. J., Theusch, E., Li, X., Arsenault, B., Chasman, D. I., Hitman, G. A., Munroe, P. B., Rotter, J. I., Psaty, B. M., Caulfield, M. J., Krauss, R. M., Cupples, A. L., & Jukema, W. J. (2022). The Pharmacogenetics of Statin Therapy on Clinical Events: No Evidence that Genetic Variation Affects Statin Response on Myocardial Infarction. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.679857
Google Scholar Worldcat Fulltext

Turner, R. M., Fontana, V., Zhang, J. E., Carr, D., Yin, P., FitzGerald, R., Morris, A. P., & Pirmohamed, M. (2020). A genome-wide association study of circulating levels of atorvastatin and its major metabolites. *Clinical Pharmacology & Therapeutics*, *108*(2), 287–297. https://doi.org/10.1002/cpt.1820
Google Scholar Worldcat Fulltext

Van Venrooij, F. V., Stolk, R. P., Banga, J., Sijmonsma, T. P., Van Tol, A., Erkelens, D. W., & Dallinga-Thie, G. M. (2003). Common cholesteryl ester transfer protein gene polymorphisms and the effect of atorvastatin therapy in type 2 diabetes. *Diabetes Care*, *26*(4), 1216–1223. https://doi.org/10.2337/diacare.26.4.1216
Google Scholar Worldcat Fulltext

Vrabl□k, M., Hub□□ek, J. A., Dlouh□, D., L□nsk□, V., Rynekrov□, J., Zlatohl□vek, L., Prus□kov□, M., □e□ka, R., & Ad□mkov□, V. (2012). Impact of variants within seven candidate genes on statin treatment efficacy. *Physiological Research*, 609–617. https://doi.org/10.33549/physiolres.932341
Google Scholar Worldcat Fulltext

Wang, T., Wu, J., Liu, T., Xu, L., Feng, J., Zhang, H., Shen, H., Sun, L., Li, H., & Yu, L. (2023). *The ABCB1 C3435T polymorphism is associated with triglyceride reduction in atorvastatin-treated Uyghur patients with coronary heart disease and dyslipidemia: An observational study. Endocrine, Metabolic & Immune Disorders - Drug Targets*, *23*(9), 1215–1228.
Google Scholar Worldcat Fulltext

Wang, Y., Du, X., Zhao, R., Niu, J., Wang, H., & Li, J. (2021). Association of APOE polymorphisms with lipid-lowering efficacy of statins in atherosclerotic cardiovascular diseases. *Annals of the Academy of Medicine Singapore*, *50*(6), 474–480. https://doi.org/10.47102/annals-acadmedsg.2020505
Google Scholar Worldcat Fulltext

Wei, K., & Zhang, L. (2015). Interactions Between CYP3A5*3 and POR*28 Polymorphisms and Lipid-Lowering Response with Atorvastatin. *Clinical Drug Investigation*, *35*(9), 583–591. https://doi.org/10.1007/s40261-015-0317-3
Google Scholar Worldcat Fulltext

Wei, K., Zhang, L., Zhang, Y., & Hu, X. (2010). Interactions between CYP7A1 A-204C and ABCG8 C1199A polymorphisms on lipid lowering with atorvastatin. *Journal of Clinical Pharmacy and Therapeutics*, *36*(6), 725–733. https://doi.org/10.1111/j.1365-2710.2010.01227.x
Google Scholar Worldcat Fulltext

Wilke, R. A., Moore, J. H., & Burmester, J. K. (2005). Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. *Pharmacogenetics and Genomics*, *15*(6), 415–421. https://doi.org/10.1097/01213011-200506000-00007
Google Scholar Worldcat Fulltext

Willrich, M. a. V., Hirata, M. H., Genvigir, F. D., Arazi, S. S., Rebecchi, I. M., Rodrigues, A. C., Bernik, M. M., Dorea, E. L., Bertolami, M. C., Faludi, A. A., & Hirata, R. D.

(2008). CYP3A5*3A allele is associated with reduced lowering-lipid response to atorvastatin in individuals with hypercholesterolemia. *Clinica Chimica Acta*, *398*(1–2), 15–20. https://doi.org/10.1016/j.cca.2008.07.032
Google Scholar Worldcat Fulltext

Woo, H. I., Kim, S. R., Huh, W., Ko, J., & Lee, S. (2017). Association of genetic variations with pharmacokinetics and lipid-lowering response to atorvastatin in healthy Korean subjects. *Drug Design Development and Therapy*, *Volume 11*, 1135–1146. https://doi.org/10.2147/dddt.s131487
Google Scholar Worldcat Fulltext

Yao, Y. S., Di Li, T., & Zeng, Z. H. (2020). Mechanisms underlying direct actions of hyperlipidemia on myocardium: an updated review. *Lipids in Health and Disease*, *19*(1). https://doi.org/10.1186/s12944-019-1171-8
Google Scholar Worldcat Fulltext

Yue, Y., Bai, X., Zhang, H., Li, Y., Hu, L., Liu, L., Mao, J., Yang, X., & Dila, N. (2016). Gene polymorphisms affect the effectiveness of atorvastatin in treating ischemic stroke patients. *Cellular Physiology and Biochemistry*, *39*(2), 630–638. https://doi.org/10.1159/000445654
Google Scholar Worldcat Fulltext

Zambrano, T., Hirata, M. H., Cerda, □., Dorea, E. L., Pinto, G. A., Gusukuma, M. C., Bertolami, M. C., Salazar, L. A., & Hirata, R. D. (2015). Impact of 3□UTR genetic variants in *PCSK9* and *LDLR* genes on plasma lipid traits and response to atorvastatin in Brazilian subjects: A pilot study. *International Journal of Clinical and Experimental Medicine, 8*(4), 5978–5988.
Google Scholar Worldcat Fulltext

Zhang, L., He, S., Li, Z., Gan, X., Li, S., Cheng, X., Yang, N., & Zheng, F. (2019). Apolipoprotein E polymorphisms contribute to statin response in Chinese ASCVD patients with dyslipidemia. *Lipids in Health and Disease*, *18*(1). https://doi.org/10.1186/s12944-019-1069-5
Google Scholar Worldcat Fulltext

Zhang, L., Lv, H., Zhang, Q., Wang, D., Kang, X., Zhang, G., & Li, X. (2019). Association of SLCO1B1 and ABCB1 Genetic Variants with Atorvastatin-induced Myopathy in Patients with Acute Ischemic Stroke. *Current Pharmaceutical Design*, *25*(14), 1663–1670. https://doi.org/10.2174/1381612825666190705204614
Google Scholar Worldcat Fulltext

Zhang, N., Gao, J., Liu, Y., & Sun, G. (2017). [Influence of PCSK9 gene E670G polymorphism on the risk of atherosclerotic coronary heart disease and plasma lipid level]. *PubMed*, *34*(5), 749–754. https://doi.org/10.3760/cma.j.issn.1003-9406.2017.05.028
Google Scholar Worldcat Fulltext

Zihlif, M., Otoum, S., Shhab, M. A., Almadani, Z., Momani, M., Alhawari, H., Jibrini, N. E., Jarrar, Y., Al-Ameer, H., & Imraish, A. (2022). No association between LDL receptor and CETP genetic variants and atorvastatin response in Jordanian hyperlipidemic patients. *Drug Metabolism and Personalized Therapy*, *37*(4), 369–374. https://doi.org/10.1515/dmpt-2021-0177
Google Scholar Worldcat Fulltext

Table 1

Summary of HMGCR SNPs associated with response to atorvastatin

Genetic Variation	Population Size	Effect	Reference(s)
-911C>A (rs33761740)	365 patients with CHD, Turkish Ethnicity	Linked to total cholesterol (TC) levels	(Akadam-Teker et al. 2013)
rs10474433	1984 Individuals	Strongly associated with LDL-C response to atorvastatin	(Thompson et al. 2009)
rs17671591	1984 Individuals	Strongly associated with LDL-C response to atorvastatin	(Thompson et al. 2009)
rs6453131	1984 Individuals	Strongly associated with LDL-C response to atorvastatin	(Thompson et al. 2009)
rs3846662	24 Health participants GG(n=13), AA(n=11)	GG genotype linked to higher LDL-C levels	(Chung et al. 2012)
rs12654264	895 Individuals. Male: 411, Female: 484	No significant influence on lipid-lowering therapy with statins	(Vrabl□k et al. 2012)
18T>G (rs17238540)	372 Subjects	Not associated with baseline lipid values or statin-induced LDL-C lowering response	(Chen et al. 2005)
rs17238540	1601 Patients	Associated with less favorable response to statin therapy in terms of TC and TG reduction	(Donnelly et al. 2008)
Rs12916 C/T	265 CAD patients	Synergistic effect with other loci on statin response	(Poduri et al. 2010)
SNP12 (rs17244841) and SNP29 (rs17238540)	100 CAD patients	Mutations enhance lipid-lowering effect of Atorvastatin	(Rizwan et al. 2021, Kirac et al. 2017)
rs17671591	101 Hypercholesteremic patients	T allele associated with reduced LDL cholesterol, enhanced HDL cholesterol, and greater LDL-C reductions following atorvastatin treatment	(Cuevas et al. 2016b)
(TTA)n polymorphism	64 Patients	Reduction in LDL cholesterol, triglyceride levels, and total cholesterol after atorvastatin treatment, regardless of genotype distribution	(Noriega et al. 2009)
rs3846662	326 Blacks and 596 whites.	G allele associated with increased LDL-C levels,	(Krauss et al. 2008, Hiura et al. 2010, Simon et al. 2006)

Genetic Variation	Population Size	Effect	Reference(s)
	994 Subjects (335 blacks and 609 whites). 944 African American and whites.	ethnic differences in prevalence and response	
SNP29 GG	265 CAD patients	Associated with a greater reduction in LDL-C levels	(Poduri et al. 2010)
SNP29 GG	1536 Individuals	Contrarily, associated with an increase in LDL-C levels	(Chasman et al. 2004)

Table 2

Summary of CYP450 gene polymorphism associated with atorvastatin response

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