OPEN ACCESS

Precision Medicine Communications

DOI: https://doi.org/10.55627/pmc.004.02.0556

Review Article

Atorvastatin Pharmacogenetics: What is the Evidence for Genetic Association with Efficacy & Safety?

Nimra Riaz[1], Madeeha Khan[2]*

[1]Department of Cardiology, Pakistan Atomic Energy Commision (PAEC) Hospital, Islamabad, Pakistan.
[2]Atta ur Rehman School of Applied Biosciences, National University of Sciences and Technology (NUST), Islamabad, Pakistan
***Correspondence:** madeehakkhan@gmail.com

Abstract

Hyperlipidemia, characterized by elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and/or decreased high-density lipoprotein cholesterol (HDL-C), is a key contributor to the development of cardiovascular diseases (CVD), which remain the leading cause of morbidity and mortality worldwide. Statins, especially atorvastatin, are the mainstay pharmacological agents used to lower cholesterol levels and prevent atherosclerotic complications. Atorvastatin inhibits HMG-CoA reductase, reducing hepatic cholesterol synthesis and upregulating LDL receptor expression. However, the efficacy and safety of atorvastatin therapy are significantly influenced by genetic polymorphisms in drug-metabolizing enzymes, transporters, and lipid-regulating genes. This review comprehensively examines the pharmacogenetics of atorvastatin, focusing on genetic variants influencing drug absorption, distribution, metabolism, and pharmacodynamic response. Polymorphisms in hepatic uptake transporters (SLCO1B1), efflux transporters (ABCB1, ABCG2), drug-metabolizing enzymes (CYP3A4 and CYP3A5), and lipid-regulating genes (APOE, APOA5, APOB, LDLR) are critically evaluated across diverse populations. Among these, the *SLCO1B1* c.521T>C (rs4149056) variant emerges as a key determinant of atorvastatin exposure and myopathy risk, though its clinical relevance varies by ethnicity. Pharmacogenetic studies show population-specific variations in atorvastatin outcomes, emphasizing the need for precision medicine in hyperlipidemia management.

Keywords: Atorvastatin, safety, efficacy, pharmacogenetics, personalized medicine

1. Introduction

Hyperlipidemia refers to abnormalities in the levels of circulating cholesterol including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). These can accumulate within the lining of the vascular walls, interrupting its structure and function, leading to cardiovascular, cerebrovascular, and peripheral vascular diseases (Stapleton et al.. 2010; Al-Zahrani et al.. 2021). Cardiovascular diseases (CVD) remain as the leading cause of mortality and morbidity globally (Brunham, Lonn, and Mehta 2024). In 2022, there were approximately 19.8 million deaths attributed to CVD, where ishemic heart disease had the highest global age-standardized disability-adjusted life years (DALYs) among all diseases, at 2,275.9 per 100,000 population (Mensah et al... 2023).

The global prevalence of high TC was 39% (NCD-RisC 2021). Between 1980 and 2018, there was a significant rise in plasma TC and non-HDL cholesterol levels among both men and women in the East and Southeast Asia regions (NCD-RisC 2021). According to data from the Global Health Data Exchange (GHDx), LDL-C levels exceeding 1.3 mmol/L are currently

responsible for approximately 94.92 million DALYs, with a marked exponential increase observed over the past 25 years (Hu et al.. 2023). Furthermore, 4.32 million deaths are attributable to elevated LDL-C levels (Mattiuzzi, Sanchis-Gomar, and Lippi 2020). In 2019, elevated LDL-C levels were responsible for approximately 3.78 million deaths from ischemic heart disease (IHD) globally, representing 44.3% of all IHD-related deaths (Liu, Zhao, and Qi 2022). Additionally, 0.61 million deaths from ischemic stroke were attributed to high LDL-C, accounting for 22.4% of total ischemic stroke deaths (Liu, Zhao, and Qi 2022). The global prevalence of Familial Hypercholesterolemia (FH) which corresponds to LDL-C >190mg/dL is 1:313 individuals (Beheshti et al. 2020). High TG levels (≥1.7mmol/L) are prevalent in about 30% population globally (Ruiz-García et al. 2020).

CVD remains as the leading cause of deaths in Pakistan (Pakistan Bureau of Statistics, 2020). Recent estimates show that in Pakistan about 44% individuals had high LDL-C, 53.7% had high TG, 36% had high TC and 53% had low HDL-C (Nawaz et al. 2025; Ain et al. 2025). The estimated prevalence of FH in Pakistan is higher than global prevalence estimates about 1:273 individuals (Khan et al. 2025).

2. Pathophysiology of Hyperlipidemia

Hyperlipidemia is primarily caused by genetic or familial factors including mutations in genes involved in lipid metabolism (Ahangari et al. 2018; Bhatnagar, Soran, and Durrington 2008). Primary hyperlipidemia can include common hypercholesterolemia, familial hypercholesterolemia, dysbetalipoproteinaemia and severe hypertriglyceridemia (Bhatnagar, Soran, and Durrington 2008).

Secondary causes of hypercholesterolemia can either be caused by existing disorders such as type 2 diabetes mellitus, kidney disorders, thyroid disorders or by certain drugs such as thiazide diuretics, ciclosporin etc. or by excessive intake of dietary cholesterol and smoking (Bhatnagar, Soran, and Durrington 2008).

In the normal lipid metabolism process, dietary cholesterol absorbed in the intestine is initially packaged into chylomicrons, which are broken down by lipoprotein lipase (LPL). The resulting fatty acids are delivered to muscle and adipose tissues, while the chylomicron remnants are transported to the liver. In the liver, very low-density lipoproteins (VLDL) are synthesized and secreted into circulation (Durrington and Soran 2014). VLDL is subsequently metabolized by LPL into intermediate-density lipoproteins (IDL), which are then converted into LDL. Meanwhile, the liver also produces nascent HDL particles, which mature by acquiring cholesteryl esters from peripheral cholesterol, thereby participating in reverse cholesterol transport. Through the action of cholesteryl ester transfer protein (CETP), HDL transfers these esters to LDL particles. LDL, now enriched with cholesteryl esters, delivers cholesterol to the liver and peripheral tissues. The hepatic uptake and degradation of LDL is mediated by LDL receptors on the surface of hepatocytes, maintaining cholesterol homeostasis (Durrington and Soran 2014).

FH is the most common genetic cause of primary hyperlipidemia resulting in extreme elevations of TC and LDL-C (Vrablik et al. 2020). FH is caused by pathogenic variants in genes involved in LDL metabolism including low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*) or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) leading to reduced clearance of LDL-C particles from the blood (Marks et al. 2003). Severe hypertriglyceridemia involves the elevation of TG and can be caused by pathogenic variants in genes involved in TG metabolism particularly *LPL* combined with TG raising factors such as high fat diet, obesity, diabetes and certain drugs (Simha 2020). Among secondary causes Type 1 and Type 2 Diabetes Mellitus are associated with hyperlipidemia (Durrington and Soran 2014).

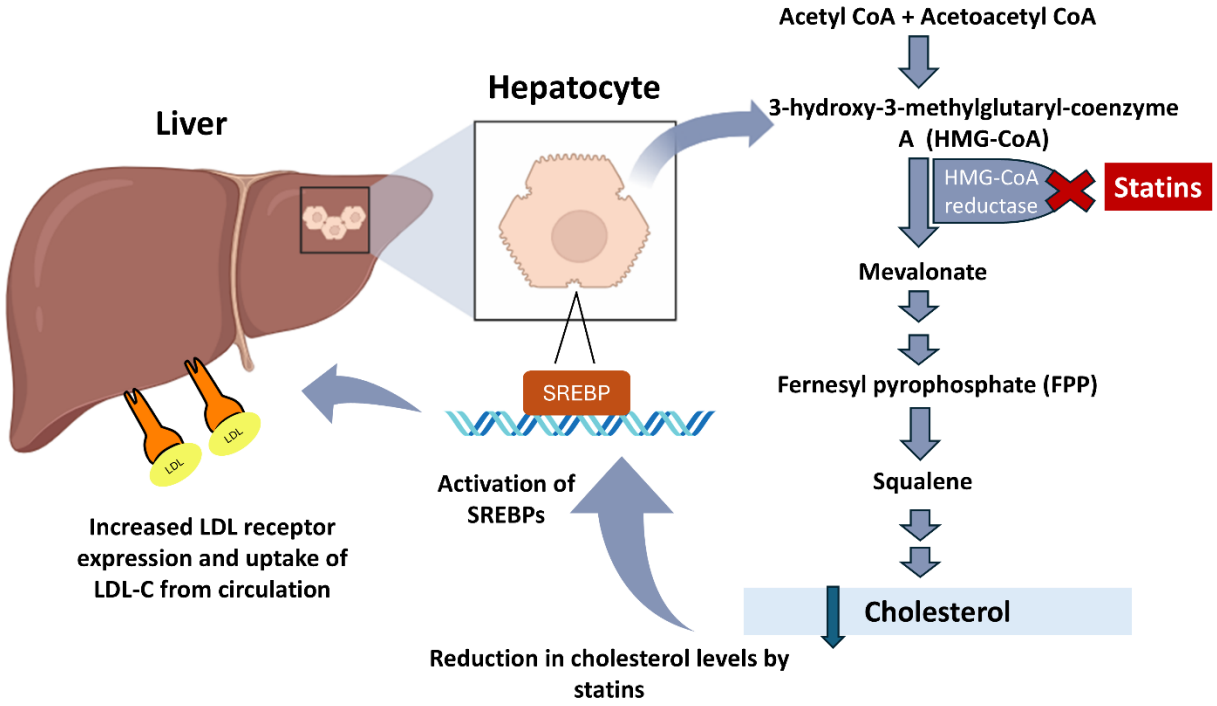

Figure 1: Mechanism of action of statins on the cholesterol biosynthesis pathway. Statins block the mevalonate pathway resulting in reduced intracellular cholesterol levels which activate SREBPs that upregulate LDL receptor expression enhancing the clearance of LDL-C from circulation (Buhaescu and Izzedine 2007).

In type 2 diabetes and obesity, insulin resistance leads to dyslipidemia by activating hormone-sensitive lipase (HSL), which increases free fatty acids (FFAs) in the blood; these FFAs promote hepatic VLDL overproduction, while reduced lipoprotein lipase (LPL) activity impairs VLDL clearance, resulting in elevated VLDL and decreased HDL levels (Yanai and Yoshida 2021; Vergès 2015). In hypothyroidism, reduced thyroid hormone levels lead to decreased expression of LDL receptors and 7 alpha-hydroxylase, impairing LDL-C clearance and cholesterol conversion to bile acids, thereby resulting in elevated LDL-C levels (Duntas and Brenta 2016).

3. Statins

The primary treatment options for the management of hypercholesterolemia are lifestyle modifications and dietary interventions (Mach et al. 2020). Statins and other lipid lowering agents including bile acid sequestrants, fibrates, etc. are a secondary treatment option for the treatment of dyslipidemia. These pharmacological therapies are typically initiated when lifestyle and dietary interventions alone fail to achieve recommended lipid targets or when patients are at high cardiovascular risk (Mach et al. 2020).

Statins reduce the total cholesterol and LDL-C in blood by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (Figure 1), the rate-limiting enzyme in cholesterol biosynthesis that catalyzes the conversion of HMG-CoA to mevalonate, that further leads to production of cholesterol and isoprenoid through a series of biochemical reactionsv (Buhaescu and Izzedine 2007). This inhibition lowers hepatic cholesterol leading to upregulation of LDL receptors and enhanced clearance of circulating LDL-C which in turn lowers their circulating levels.

The primary pharmacological effect of statins stems from their competitive inhibition of

hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis (Buhaescu and Izzedine 2007). By blocking the conversion of HMG-CoA to mevalonate, statins reduce hepatocellular cholesterol levels, triggering a compensatory response mediated by sterol regulatory element-binding proteins (SREBPs) (Endo and Beppu 2010). These transcription factors are activated via proteolytic cleavage in the Golgi apparatus, releasing their active fragments, which then migrate to the nucleus and upregulate genes involved in cholesterol synthesis and LDL uptake, particularly the LDL receptor (LDL-R) (Brown and Goldstein 1986). In hepatocytes, this enhances LDL clearance from circulation, thereby lowering serum LDL-C. In addition to lowering LDL-C, statins may also exert modest effects on triglycerides and HDL-C and have been shown to possess pleiotropic effects such as improving endothelial function, reducing inflammation, and stabilizing atherosclerotic plaques (Grundy 1998). Generally, statins can result in approximately 20% to 55% reduction in LDL-C levels with higher reductions seen with atorvastatin, rosuvastatin, and pitavastatin while lovastatin and simvastatin exhibit moderate reductions and fluvastatin and pravastatin have the lowest LDL reduction activity (Hodkinson et al. 2022; Jones et al. 1998). Despite the ability of statins to lower cholesterol and their potential to decrease cardiovascular morbidity and mortality, statin withdrawal and non-adherence is a constant problem. Statin-associated muscle symptoms (SAMSs) accounting for 72% of all the adverse side effects of statins are the major reason for discontinuation (Ward, Watts, and Eckel 2019). Other serious side effects of statin treatment can be new onset of type 2 diabetes mellitus, hepatotoxicity and renal toxicity (Beltowski, Wojcicka, and Jamroz-Wisniewska 2009).

4. Atorvastatin

Atorvastatin, introduced in 1981 as the first fully synthetic statin, was later marketed under the brand name LIPITOR (Roth 2002). Chemically, it is a calcium salt of [R-(R*, R*)] -2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carbonyl]-1H-pyrrole -1-heptanoic acid, with the empirical formula $(C_{33}H_{34}FN_2O_5)_2Ca{\cdot}3H_2O$ (Shaghaghi *et al.* 2022). As a lipophilic and tissue-selective inhibitor of HMG-CoA reductase, atorvastatin exhibits high oral bioavailability and predominantly exerts its action in the liver, spleen, and adrenal tissues (van Leuven and Kastelein 2005). Like other statins, it inhibits HMG-CoA reductase (Figure 1), the rate-limiting enzyme in cholesterol biosynthesis, thereby reducing the production of mevalonate. This decline in intracellular cholesterol levels induces the activation of SREBPs, which upregulate LDL receptor expression on hepatocytes, enhancing the clearance of LDL-C from circulation (van Leuven and Kastelein 2005).

Atorvastatin lowers LDL-C levels in a dose dependent manner resulting in reductions of 25% to 61% (Nawrocki et al. 1995). Additionally, atorvastatin lowers plasma levels of TGs and VLDL while increasing HDL concentrations. Clinically available in various doses including 10, 20, 40, and 80 mg/day, atorvastatin has demonstrated superior efficacy compared to other statins in reducing levels of LDL-C, total cholesterol, triglycerides, and VLDL particles (Lea and McTavish 1997). Atorvastatin has 30% oral absorption with 14% bioavailability due to first-pass metabolism, reaching peak plasma levels in 0.6-0.9 hours (Lennernäs 2003). Its active metabolites (via CYP3A4) provide 70% of its HMG-CoA reductase inhibition. The drug is >98% protein-bound, requires dose adjustment in liver impairment (but not renal dysfunction), and interacts with CYP3A4 inhibitors like erythromycin and cyclosporine (Lennernäs 2003).

5. Atorvastatin Pharmacogenetics

Interindividual variability in the response to atorvastatin, in terms of both lipid-lowering

efficacy and the risk of adverse effects, has been strongly linked to genetic polymorphisms affecting drug metabolism, transport, and lipid regulation (Hoste et al. 2024). A key determinant of atorvastatin pharmacokinetics is hepatic uptake, which is mediated by members of the organic anion transporting polypeptide (OATP) family. Multiple OATP isoforms, particularly those highly expressed in the liver, play a central role in the hepatic extraction of statins from the sinusoidal blood (Ho et al. 2006).

The *SLCO1B1* gene, encoding OATP1B1, has been most extensively studied. The *521T>C* (rs4149056) polymorphism is associated with reduced transporter activity, resulting in decreased hepatic uptake and elevated systemic exposure to atorvastatin, which in turn increases the risk of statin-associated myopathy, especially at higher doses (Pasanen et al. 2007).

In contrast, the *388A>G* (rs2306283) variant has been associated with enhanced transporter function and a lower risk of adverse effects (DeGorter et al. 2013). Other transporter genes, such as ATP-binding cassette B1 (*ABCB1*), which encodes P-glycoprotein involved in intestinal and hepatic drug efflux, also influence atorvastatin disposition (Neumann, Rose-Sperling, and Hellmich 2017). Polymorphisms like *2677G>T/A* and *3435C>T* have been linked to altered expression and transport activity, impacting both drug efficacy and the potential for hepatotoxicity. Similarly, *ABCC2* and *ABCG2* variants, particularly *421C>A* in *ABCG2*, are associated with increased systemic exposure and risk of adverse reactions (Bruhn and Cascorbi 2014). In terms of metabolism, atorvastatin is primarily metabolized by CYP3A4 and CYP3A5, and polymorphisms in these genes, such as *CYP3A4 1B* (290A>G) and *1G* (20230G>A), have been shown to influence plasma concentrations and therapeutic response (Mirošević Skvrce et al. 2015). Additionally, genetic variants in *APOE* and *APOA5*, which regulate lipid metabolism, affect the pharmacodynamic response to atorvastatin (Mega et al. 2009). For instance, individuals with the *APOE* ε2 allele tend to exhibit a greater reduction in LDL-C, while the ε4 allele is associated with a diminished response (Thompson et al. 2009; Mega et al. 2009).

6. Genetic Determinants of Atorvastatin Efficacy and Safety

Numerous pharmacogenetic studies have investigated the association of specific gene variants with the efficacy and safety of atorvastatin therapy. Heterogeneity in pharmacogenetic effects of each allele vary greatly among studies conducted in different ethnic groups (Table 1).

6.1. SLCO1B1

In Europeans, *rs4149056* was significantly associated with atorvastatin blood levels, identifying it as the strongest predictor of pharmacokinetic variability and risk for statin-induced myopathy (Zubiaur et al. 2021). In a cohort from the UK Biobank, *SLCO1B1* variants (*5, *15, *20) were associated with reduced LDL-lowering response, increased statin discontinuation, and muscle symptoms (Türkmen et al. 2024). In the ODYSSEY OUTCOMES trial, *rs4149056* showed no association with statin-induced adverse effects, suggesting variable effects across populations (Murphy et al. 2022). No significant association was found between *SLCO1B1 rs4149056* and adverse effects in South Indian patients (Ramakumari et al. 2018). In patients with hyperlipidemia, those carrying the *SLCO1B1* 521CC genotype showed a reduced lipid-lowering response to atorvastatin, while *MDR1* (3435C>T) polymorphism had no significant effect (Sivkov et al. 2021). In Chilean hypercholesterolemic patients, *SLCO1B1* rs2306283 was associated with greater HDL-C, while LDL-C reduction was not significantly influenced (Prado et al. 2015). In Brazilian cohort of FH patients, *SLCO1B1* variants rs2306283 and rs4149056 showed no significant association with atorvastatin-induced-myalgia or elevated

Table 1: Genetic polymorphisms Associated with Atorvastatin Efficacy/Safety

Gene	Polymorphism	Effect	Reference
SLCO1B1	rs4149056	↑Myopathy risk; ↓LDL-C response	Zubiaur et al. 2021; Türkmen et al. 2024
	rs4149056	No association with adverse effects	Murphy et al. 2022; Ramakumari et al. 2018
	rs4149056	↓Lipid-lowering response	Sivkov et al. 2021
	rs2306283	↑HDL-C; no LDL-C effect	Prado et al. 2015
	rs4149056	No association with myalgia	Santos et al. 2012
	rs4149056	↑Mild side effects and discontinuation; gene-dose effect	De Keyser et al. 2014
CYP3A4	rs35599367	↓Dose needed; ↓ metabolism	Wang et al. 2010; Klein et al. 2012
	rs2242480	↓LDL-C in ischemic stroke patients	Peng et al. 2018
	rs2740574	↑Lipid profile; ↑LDL-C; ↓LDL-C response	Rosales et al. 2012; Kajinami et al. 2004; Kadam et al. 2016
CYP3A5	rs776746	↑LDL-C reduction; ↑ myopathy risk; no association	Kivistö et al. 2004; Wilke et al. 2005; Xia et al. 2018; Ramakumari et al. 2018
ABCB1	rs2235029, rs3214119, rs1922242	↑Atorvastatin concentrations	Kim et al. 2022
	rs1045642	Influences LDL-C response	Bharath et al. 2022
	rs1128503, rs2032582	↑Risk of SAMS	Lalatović et al. 2023
APOA5	rs33984246, rs3135507	↑Atorvastatin concentrations	Kim et al. 2022
ApoB	rs676210	↑LDL-C reduction	Abdulfattah and Al-Awadi 2021
APOE	rs7412	↑LDL-C reduction;	Mega et al. 2009
	rs429358	↓Atorvastatin response	

levels of creatine kinase levels, suggesting a statin-specific genetic effect (Santos et al. 2012). In the Rotterdam Study (Netherlands), *SLCO1B1* c.521C allele carriers on high-dose atorvastatin (>20 mg) had a significantly higher risk of dose reduction or switching, suggesting a dose-dependent risk of statin intolerance linked to this variant (De Keyser et al. 2014). In the STRENGTH study, *SLCO1B1*5* (rs4149056) was associated with an increased risk of mild statin-induced side effects, including discontinuation and myalgia, with a gene-dose effect observed across statin types including atorvastatin (De Keyser et al. 2014).

6.2. CYP3A4

In statin-treated patients, carriers of the CYP3A4*22 (rs35599367 T allele) required significantly lower atorvastatin doses for lipid control due to reduced hepatic CYP3A4 expression and activity (Wang et al. 2010). The *CYP3A4 189F/S* variant was linked to increased HDL-C in Indian patients (Poduri et al. 2010).

The *CYP3A4*1G variant was associated with greater total cholesterol reduction in Chinese individuals (Gao, Zhang, and Fu 2008).

The *rs2242480* variant correlated with lower LDL-C levels in Chinese ischemic stroke patients (Peng et al. 2018). *CYP3A4*1B (rs2740574) was associated with enhanced lipid profile improvement in Chilean patients (Rosales et al. 2012) but the same allele was linked to increased LDL-C levels in Americans (Kajinami et al. 2004) and reduced LDL-C response in Indians (Kadam et al. 2016). The *CYP3A4*22 (rs35599367) allele in Finnish subjects was linked to decreased metabolism and altered efficacy of atorvastatin (Klein et al. 2012).

6.3. CYP3A5

*CYP3A5*3 homozygotes in Europeans had better LDL-C and total cholesterol reductions than *CYP3A5*1 carriers (Kivistö et al. 2004). The *CYP3A5*3/3 genotype was associated with increased risk of severe myopathy in Americans (Wilke, Moore, and Burmester 2005). The *rs776746 (CYP3A5*3)** variant was linked to higher atorvastatin concentrations and myopathy risk in Chinese individuals (Xia et al. 2018). No significant association between *CYP3A5*3/3* genotype and atorvastatin-induced adverse effects was found in South Indian patients (Ramakumari et al. 2018).

6.4. ABCB1

The *ABCB1* gene encodes P-glycoprotein, an ATP-dependent efflux transporter that plays a key role in the intestinal absorption, hepatic disposition, and systemic exposure of atorvastatin (Neumann, Rose-Sperling, and Hellmich 2017). Genetic polymorphisms in *ABCB1* can alter P-glycoprotein expression or transport activity, leading to variability in atorvastatin bioavailability, systemic exposure, and susceptibility to adverse effects.

In Koreans, variants in *ABCB1* (rs2235029_C, rs3214119_T, rs1922242_T) were associated with increased atorvastatin blood concentrations (Kim et al. 2022). In Indian coronary artery disease patients, *SLCO1B1* (rs4149056, rs4363657) and *ABCB1* (rs1045642) polymorphisms significantly influenced atorvastatin's lipid-lowering efficacy, with a synergistic effect observed in combined genotypes (Bharath et al. 2022). In Serbian population, *ABCB1* polymorphisms (1236C>T, 2677G>T/A, 3435C>T) was significantly associated with increased risk of atorvastatin-induced SAMS, highlighting the potential of *ABCB1* genotyping in clinical practice to determine the impacts of genetic variants in atorvastatin efficacy and adverse impacts (Lalatović et al. 2023).

6.5. APOA5, ApoB, ApoE

Variants in *APOA5* (rs33984246_G, rs3135507_T) in Koreans were associated with increased atorvastatin concentrations (Kim et al. 2022). In Iraqis, *ApoB* rs676210 (Pro2739Leu) AA genotype was linked to greater LDL-C reduction following atorvastatin therapy (Abdulfattah and Al-Awadi 2021). *APOE ε2* carriers experienced greater LDL-C reduction and better target attainment post-ACS than ε4 carriers (Mega et

al. 2009). In Amerindian Chilean individuals, *APOE* ε 3/4 genotype was associated with a significantly weaker LDL-C reduction in response to atorvastatin compared to E3/3 carriers, while *LDLR* rs5925 showed no effect (Lagos et al. 2015).

7. Discussion and Recommendations

Hyperlipidemia is a major modifiable risk factor for cardiovascular disease, with both genetic and environmental etiologies **(**Ahangari et al. 2018). Statins remain as the first line treatment option for treatment of hyperlipidemia (Mach et al. 2020). Atorvastatin treatment result in significant reduction in lipid levels and are being prescribed widely (Roth 2002). This review highlights the significant influence of genetic variability on the pharmacokinetics, pharmacodynamics, and safety profile of atorvastatin. Polymorphisms in genes encoding drug-metabolizing enzymes (*CYP3A4*, *CYP3A5*), transport proteins (*SLCO1B1*, *ABCG2*), and lipid regulatory pathways (*LDLR*, *APOE*) contribute substantially to interindividual differences in atorvastatin response. Among the most clinically relevant findings is the *SLCO1B1* c.521T>C (rs4149056) variant, which has been consistently associated with reduced hepatic uptake of atorvastatin and an increased risk of statin-associated muscle symptoms (SAMS) (Pasanen et al. 2007). Similarly, polymorphisms in *CYP3A5* (e.g., *CYP3A5* *3/*3) and *ABCG2* (rs2231142) have been linked to altered atorvastatin exposure, although the clinical relevance of these variants may vary across populations. However, a recent meta-analysis suggests that there might be a publication bias that overestimates the importance of the SLCO1B1 genotype, which should be considered in designing guidelines and recommendations for prescribing statins (Gougeon et al. 2025).

Despite promising advances, the translation of pharmacogenetic findings into routine clinical practice remains limited. One major challenge is the underrepresentation of certain populations, including those from South Asia and Africa, in existing studies. The frequency and impact of genetic variants can differ markedly by ethnicity, and findings from one population may not be generalizable to others. Moreover, most studies to date have focused on single polymorphisms; however, a polygenic or multi-gene approach may provide more accurate predictions of drug response (Zhai et al. 2022). Large-scale, multi-ethnic cohort studies are necessary to confirm consistent associations and understand population-specific variations.

In addition to genetic factors, non-genetic contributors, such as age, sex, diet, comorbidities, and other medications also influence atorvastatin efficacy and safety (Sainz de Medrano Sainz and Brunet Serra 2023). Therefore, while pharmacogenetic testing holds promise, it should be integrated into a broader precision medicine framework that considers both genetic and clinical variables. Integrating pharmacogenetic screening into routine clinical decision-making for statin therapy can identify patients at risk of statin-induced myopathy or poor response can help clinicians customize lipid-lowering strategies accordingly. In cases where genetic variants reduce atorvastatin efficacy, clinicians should consider alternative lipid-lowering treatments. This includes non-statin therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bempedoic acid, lomitapide etc. or combination therapies personalized to the patient's genetic and metabolic profile.

8. Conclusion

In conclusion, the relationship between pharmacogenetics and statin therapy, particularly atorvastatin, offers a possibility for optimizing hyperlipidemia treatment and improving patient outcomes. The polymorphic nature of genes such as *APOE*, *CYP3A4*, *CYP3A5*, *CETP*, *ABCB1*, *ABCG5/8*, and *SLCO1B1* has been shown to significantly influence individual responses to atorvastatin, paving the

way for personalised lipid-lowering strategies. Interethnic differences in treatment responses point to the necessity of considering population-specific data when designing therapeutic strategies. Integrating genetic screening into routine clinical practice could aid in identifying individuals most likely to benefit from atorvastatin therapy. Further studies aiming to explore a broad range of genetic markers, including less-studied SNPs and gene-gene interactions can be helpful in understanding atorvastatin pharmacogenetics. As the field of precision medicine continues to expand, integrating pharmacogenetics into routine cardiovascular care may significantly enhance patient outcomes ultimately leading to reduced ASCVD burden.

Competing Interests

The authors have no competing interests to declare.

Funding

No funding was received to assist with the preparation of this manuscript.

Ethics Approval

Not applicable, since the work does not involve any study with human participants or animals.

Consent Forms

Not Applicable

Author Contributions

Both authors contributed equally to this study. MK conceptualized the study, and NR and MK drafted the manuscript. Both authors reviewed and approved the final version of the manuscript.

Acknowledgments

The authors want to thank their respective departments for facilitating this piece of work.

References

Abdulfattah, Shaimaa Y., and Salwa J. Al-Awadi. 2021. "ApoB Gene Polymorphism (Rs676210) and Its Pharmacogenetics Impact on Atorvastatin Response among Iraqi Population with Coronary Artery Disease." Journal of Genetic Engineering and Biotechnology 19 (1): 95. https://doi.org/10.1186/S43141-021-00193-4.

Ahangari, Najmeh, Majid Ghayour Mobarhan, Amirhossein Sahebkar, and Alireza Pasdar. 2018. "Molecular Aspects of Hypercholesterolemia Treatment: Current Perspectives and Hopes." Annals of Medicine 50 (4): 303–11. https://doi.org/10.1080/07853890.2018.1457795.

Ain, Quratul, Madeeha Khan, Amjad Nawaz, Hijab Batool, Mohammad Iqbal Khan, Muhammad Ajmal, and Fouzia Sadiq. 2025. "Trends and Prevalence of Severe Hypertriglyceridemia in Pakistan: A Five-Year Analysis (2019-2023)." *Journal of Clinical Lipidology* 19(3):451-460. https://doi.org/10.1016/J.JACL.2025.02.009.

Al-Zahrani, Jamaan, Mamdouh M. Shubair, Sameer Al-Ghamdi, Abdullah A. Alrasheed, Abdulrahman A. Alduraywish, Fayez Saud Alreshidi, Saeed Mastour Alshahrani, *et al.*. 2021. "The Prevalence of Hypercholesterolemia and Associated Risk Factors in Al-Kharj Population, Saudi Arabia: A Cross-Sectional Survey." *BMC Cardiovascular Disorders* 21(1): 1–8. https://doi.org/10.1186/s12872-020-01825-2

Beheshti, Sabina O., Christian M. Madsen, Anette Varbo, and Børge G. Nordestgaard. 2020. "Worldwide Prevalence of Familial

Hypercholesterolemia: Meta-Analyses of 11 Million Subjects." *Journal of the American College of Cardiology* 75 (20): 2553–66. https://doi.org/10.1016/J.JACC.2020.03.057.

Beltowski, Jerzy, Grazyna Wojcicka, and Anna Jamroz-Wisniewska. 2009. "Adverse Effects of Statins - Mechanisms and Consequences." *Current Drug Safety* 4 (3): 209–28. https://doi.org/10.2174/157488609789006949.

Bharath, Govindaswamy, Durairaj Pandian Vishnuprabu, Loganathan Preethi, Arumugam Suriyam Nagappan, Ramia Thiagaraja Dhianeshwaran Isravanya, Lakkakula V.K.S. Bhaskar, Nagarajan Swaminathan, and Arasambattu Kannan Munirajan. 2022. "SLCO1B1 and ABCB1 Variants Synergistically Influence the Atorvastatin Treatment Response in South Indian Coronary Artery Disease Patients." *Pharmacogenomics* 23 (12): 683–94. https://doi.org/10.2217/PGS-2022-0044.

Bhatnagar, Deepak, Handrean Soran, and Paul N. Durrington. 2008. "Hypercholesterolaemia and Its Management." *BMJ* 337 (7668): 503–8. https://doi.org/10.1136/BMJ.A993.

Brown, Michael S., and Joseph L. Goldstein. 1986. "A Receptor-Mediated Pathway for Cholesterol Homeostasis." *Science* 232 (4746): 34–47. https://doi.org/10.1126/science.351331

Bruhn, Oliver, and Ingolf Cascorbi. 2014. "Polymorphisms of the Drug Transporters ABCB1, ABCG2, ABCC2 and ABCC3 and Their Impact on Drug Bioavailability and Clinical Relevance." *Expert Opinion on Drug Metabolism & Toxicology* 10 (10): 1337–54. https://doi.org/10.1517/17425255.2014.952630.

Brunham, Liam R., Eva Lonn, and Shamir R. Mehta. 2024. "Dyslipidemia and the Current State of Cardiovascular Disease: Epidemiology, Risk Factors, and Effect of Lipid Lowering." *Canadian Journal of Cardiology* 40 (8): S4–12. https://doi.org/10.1016/J.CJCA.2024.04.017.

Buhaescu, Irina, and Hassane Izzedine. 2007. "Mevalonate Pathway: A Review of Clinical and Therapeutical Implications." *Clinical Biochemistry* 40 (9): 575–84. https://doi.org/https://doi.org/10.1016/j.clinbiochem.2007.03.016.

DeGorter, Marianne K., Rommel G. Tirona, Ute I. Schwarz, Yun Hee Choi, George K. Dresser, Neville Suskin, Kathryn Myers, *et al.*. 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/-/DC1.

Durrington, Paul, and Handrean Soran. 2014. "Hyperlipidemia." In Metabolism of Human Diseases: Organ Physiology and Pathophysiology, 295–302. Springer, Vienna. https://doi.org/10.1007/978-3-7091-0715-7_43.

Endo, Akira, and Teruhiko Beppu. 2010. "A Historical Perspective on the Discovery of Statins." *Proceedings of the Japan Academy* 86 (5): 484–93. https://doi.org/10.2183/PJAB.86.484.

Gao, Yuan, Li Rong Zhang, and Qiang Fu. 2008. "CYP3A4*1G Polymorphism Is Associated with Lipid-Lowering Efficacy of Atorvastatin but Not of Simvastatin." *European Journal of Clinical Pharmacology* 64 (9): 877–82. https://doi.org/10.1007/s00228-008-0502-x.

Gougeon, A., I. Aribi, S. Guernouche, J. C. Lega, J. M. Wright, C. Verstuyft, A. Lajoinie, F. Gueyffier, and G. Grenet. "Publication bias in pharmacogenetics of statin-associated muscle symptoms: A meta-epidemiological study." *Atherosclerosis* 400 (2025): 118624. https://doi.org/10.1016/j.atherosclerosis.2024.118624

Grundy, S. M. 1998. "Consensus Statement: Role of Therapy with 'Statins' in Patients with Hypertriglyceridemia." *American Journal of Cardiology* 81 (4 A): 1B-6B. https://doi.org/10.1016/S0002-9149(98)00030-7.

Ho, Richard H., Rommel G. Tirona, Brenda F. Leake, Hartmut Glaeser, Wooin Lee, Christopher J. Lemke, Yi Wang, and Richard B. Kim. 2006. "Drug and Bile Acid Transporters in Rosuvastatin Hepatic Uptake: Function, Expression, and Pharmacogenetics." *Gastroenterology* 130 (6): 1793–1806. https://doi.org/10.1053/j.gastro.2006.02.034.

Hodkinson, Alexander, Dialechti Tsimpida, Evangelos Kontopantelis, Martin K. Rutter, Mamas A. Mamas, and Maria Panagioti. 2022. "Comparative Effectiveness of Statins on Non-High Density Lipoprotein Cholesterol in People with Diabetes and at Risk of Cardiovascular Disease: Systematic Review and Network Meta-Analysis." *The BMJ* 376. https://doi.org/10.1136/BMJ-2021-067731.

Hoste, Emilia, Vincent Haufroid, Louise Deldicque, Jean Luc Balligand, and Laure Elens. 2024. "Atorvastatin-Associated Myotoxicity: A Toxicokinetic Review of Pharmacogenetic Associations to Evaluate the Feasibility of Precision Pharmacotherapy." *Clinical Biochemistry* 124:110707. https://doi.org/10.1016/J.CLINBIOCHEM.2024.110707.

Jones, Peter, Stephanie Kafonek, Irene Laurora, and Donald Hunninghake. 1998. "Comparative Dose Efficacy Study of Atorvastatin versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia (The CURVES Study)." *American Journal of Cardiology* 81 (5): 582–87. https://doi.org/10.1016/S0002-9149(97)00965-X.

Kadam, P., T. F. Ashavaid, C. K. Ponde, and R. M. Rajani. 2016. "Genetic Determinants of Lipid-Lowering Response to Atorvastatin Therapy in an Indian Population." *Journal of Clinical Pharmacy and Therapeutics* 41 (3): 329–33. https://doi.org/10.1111/JCPT.12369.

Kajinami, Kouji, Margaret E. Brousseau, Jose M. Ordovas, and Ernst J. Schaefer. 2004. "CYP3A4 Genotypes and Plasma Lipoprotein Levels before and after Treatment with Atorvastatin in Primary Hypercholesterolemia." *American Journal of Cardiology* 93 (1): 104–7. https://doi.org/10.1016/j.amjcard.2003.08.078.

Keyser, Catherine E. De, Bas J.M. Peters, Matthijs L. Becker, Loes E. Visser, André G. Uitterlinden, Olaf H. Klungel, Céline Verstuyft, Albert Hofman, Anke Hilse Maitland-Van Der Zee, and Bruno H. Stricker. 2014. "The SLCO1B1 c.521T>C Polymorphism Is Associated with Dose Decrease or Switching during Statin Therapy in the Rotterdam Study." *Pharmacogenetics and Genomics* 24 (1): 43–51. https://doi.org/10.1097/FPC.0000000000000018.

Khan, Madeeha, Quratul Ain, Jaka Sikonja, Hijab Batool, Muhammad Qasim Hayat, Mohammad Iqbal Khan, Urh Groselj, and Fouzia Sadiq. 2025. "Prevalence of

Familial Hypercholesterolemia in Pakistan: A Pooled Analysis of 1.5 Million Individuals and Comparison with Other Countries of the Region." *Global Heart* 20 (1): 23. https://doi.org/10.5334/GH.1413.

Kim, Serim, Jong Do Seo, Yeo Min Yun, Hanah Kim, Tae Eun Kim, Taeheon Lee, Tae Rim Lee, Jun Hyung Lee, Eun Hae Cho, and Chang Seok Ki. 2022. "Pharmacokinetics and Genetic Factors of Atorvastatin in Healthy Korean Subjects." *Frontiers in Genetics* 13 (May):836970. https://doi.org/10.3389/FGENE.2022.836970/BIBTEX.

Kivistö, Kari T., Mikko Niemi, Elke Schaeffeler, Kaisu Pitkälä, Reijo Tilvis, Martin F. Fromm, Matthias Schwab, Michel Eichelbaum, and Timo Strandberg. 2004. "Lipid-Lowering Response to Statins Is Affected by CYP3A5 Polymorphism." *Pharmacogenetics* 14 (8): 523–25. https://doi.org/10.1097/01.FPC.0000114762.78957.A5.

Klein, Kathrin, Maria Thomas, Stefan Winter, Andreas K. Nussler, Mikko Niemi, Matthias Schwab, and Ulrich M. Zanger. 2012. "PPARA: A Novel Genetic Determinant of CYP3A4 In Vitro and In Vivo." *Clinical Pharmacology & Therapeutics* 91 (6): 1044–52. https://doi.org/10.1038/CLPT.2011.336.

Lagos, Jenny, Tomás Zambrano, Alexy Rosales, and Luis A. Salazar. 2015. "APOE Polymorphisms Contribute to Reduced Atorvastatin Response in Chilean Amerindian Subjects." International Journal of Molecular Sciences 16 (4): 7890–99. https://doi.org/10.3390/IJMS16047890.

Lalatović, Ninoslava, Maša Ždralević, Tanja Antunović, and Snežana Pantović. 2023. "Genetic Polymorphisms in ABCB1 Are Correlated with the Increased Risk of Atorvastatin-Induced Muscle Side Effects: A Cross-Sectional Study." *Scientific Reports* 2023 13:1 13 (1): 1–9. https://doi.org/10.1038/s41598-023-44792-2.

Lea, A. P., and D. McTavish. 1997. "Atorvastatin. A Review of Its Pharmacology and Therapeutic Potential in the Management of Hyperlipidaemias." *Drugs* 53 (5): 828–47. https://doi.org/10.2165/00003495-199753050-00011

Lennernäs, Hans. 2003. "Clinical Pharmacokinetics of Atorvastatin." Clinical *Pharmacokinetics* 42 (13): 1141–60. https://doi.org/ 10.2165/00003088-200342130-00005

Leuven, Sander I. van, and John J.P. Kastelein. 2005. "Atorvastatin." *Expert Opinion on Pharmacotherapy* 6 (7): 1191–1203. https://doi.org/10.1517/14656566.6.7.1191.

Liu, Tianxiao, Dong Zhao, and Yue Qi. 2022. "Global Trends in the Epidemiology and Management of Dyslipidemia." *Journal of Clinical Medicine* 11 (21): 6377. https://doi.org/10.3390/JCM11216377/S1.

Mach, François, Colin Baigent, Alberico L. Catapano, Konstantinos C. Koskinas, Manuela Casula, Lina Badimon, M. John Chapman, *et al.*. 2020. "2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk." *European Heart Journal* 41(1): 111-188. https://doi.org/10.1093/eurheartj/ehz455.

Marks, Dalya, Margaret Thorogood, H. Andrew W. Neil, and Steve E. Humphries. 2003. "A Review on the Diagnosis, Natural History, and Treatment of Familial Hypercholesterolaemia." *Atherosclerosis* 168 (1): 1–14. https://doi.org/10.1016/S0021-9150(02)00330-1.

Mattiuzzi, Camilla, Fabian Sanchis-Gomar, and Giuseppe Lippi. 2020. "Worldwide

Burden of LDL Cholesterol: Implications in Cardiovascular Disease." *Nutrition, Metabolism and Cardiovascular Diseases* 30 (2): 241–44. https://doi.org/10.1016/J.NUMECD.2019.09.008.

Mega, Jessica L., David A. Morrow, Alison Brown, Christopher P. Cannon, and Marc S. Sabatine. 2009. "Identification of Genetic Variants Associated with Response to Statin Therapy." *Arteriosclerosis, Thrombosis, and Vascular Biology* 29 (9): 1310–15. 10.1161/ATVBAHA.109.188474.

Mensah, George A., Yohannes Habtegiorgis Abate, Mohammadreza Abbasian, Foad Abd-Allah, Ashkan Abdollahi, Mohammad Abdollahi, Deldar Morad Abdulah, *et al.*. 2023. "Global Burden of Cardiovascular Diseases and Risks, 1990-2022." *Journal of the American College of Cardiology* 82 (25): 2350–2473. https://doi.org/10.1016/j.jacc.2023.11.007.

Mirošević Skvrce, Nikica, Viola Macolić Šarinić, Iveta Šimić, Lana Ganoci, Diana Muačević Katanec, and Nada Božina. 2015. "ABCG2 Gene Polymorphisms as Risk Factors for Atorvastatin Adverse Reactions: A Case–Control Study." *Pharmacogenomics* 16 (8): 803–15. https://doi.org/10.2217/PGS.15.47.

Nawaz, Amjad, Madeeha Khan, Quratul Ain, Muhammad Amjad, Jaka Sikonja, Hijab Batool, Mohammad Iqbal Khan, Urh Groselj, and Fouzia Sadiq. 2025. "Gender Disparity in Lipid Testing Among Over 0.5 Million Adults from Pakistan: Females Are Tested Much Later Despite Higher LDL-Cholesterol Levels." *Global Heart* 20 (1): 16. https://doi.org/10.5334/GH.1401.

Nawrocki, James W., Stuart R. Weiss, Michael H. Davidson, Dennis L. Sprecher, Sherwyn L. Schwartz, Paul J. Lupien, Peter H. Jones, Harry E. Haber, and Donald M. Black. 1995. "Reduction of LDL Cholesterol by 25% to 60% in Patients with Primary Hypercholesterolemia by Atorvastatin, a New HMG-CoA Reductase Inhibitor." *Arteriosclerosis, Thrombosis, and Vascular Biology* 15 (5): 678–82. https://doi.org/10.1161/01.ATV.15.5.67

"NCD-RisC." 2021. 2021. https://www.ncdrisc.org/index.html.

Neumann, Jennifer, Dania Rose-Sperling, and Ute A. Hellmich. 2017. "Diverse Relations between ABC Transporters and Lipids: An Overview." *Biochimica et Biophysica Acta (BBA) - Biomembranes* 1859 (4): 605–18. https://doi.org/10.1016/J.BBAMEM.2016.09.023.

"Pakistan Bureau of Statistics." 2020. Accessed April 11, 2025. https://www.pbs.gov.pk/.

Pasanen, M. K., H. Fredrikson, P. J. Neuvonen, and M. Niemi. 2007. "Different Effects of SLCO1B1 Polymorphism on the Pharmacokinetics of Atorvastatin and Rosuvastatin." *Clinical Pharmacology & Therapeutics* 82 (6): 726–33. https://doi.org/10.1038/SJ.CLPT.6100220.

Peng, Chen, Ying Ding, Xin Yi, Yupei Shen, Zhiqiang Dong, Limei Cao, Qiang Li, *et al.*. 2018. "Polymorphisms in CYP450 Genes and the Therapeutic Effect of Atorvastatin on Ischemic Stroke: A Retrospective Cohort Study in Chinese Population." *Clinical Therapeutics* 40 (3): 469-477.e2. https://doi.org/10.1016/j.clinthera.2018.02.002.

Poduri, Aruna, Madhu Khullar, Ajay Bahl, B. S. Sehrawat, Yashpaul Sharma, and Kewal K. Talwar. 2010. "Common Variants of HMGCR, CETP, APOAI, ABCB1, CYP3A4, and CYP7A1 Genes as Predictors of Lipid-Lowering Response to Atorvastatin Therapy." *DNA and Cell*

Biology 29 (10): 629–37. https://doi.org/10.1089/dna.2009.1008.

Prado, Yalena, Nicolás Saavedra, Tomás Zambrano, Jenny Lagos, Alexy Rosales, and Luis A. Salazar. 2015. "SLCO1B1 c.388A>G Polymorphism Is Associated with HDL-C Levels in Response to Atorvastatin in Chilean Individuals." *International Journal of Molecular Sciences* 16 (9): 20609–19. https://doi.org/10.3390/IJMS160920609.

Ramakumari, Nuthalapati, Bobbala Indumathi, Shiva Krishna Katkam, and Vijay Kumar Kutala. 2018. "Impact of Pharmacogenetics on Statin-Induced Myopathy in South-Indian Subjects." *Indian Heart Journal* 70 (December):S120–25. https://doi.org/10.1016/J.IHJ.2018.07.009.

Rosales, Alexy, Marysol Alvear, Alejandro Cuevas, Nicolás Saavedra, Tomaá Zambrano, and Luis A. Salazar. 2012. "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.

Roth, Bruce D. 2002. "1 The Discovery and Development of Atorvastatin, A Potent Novel Hypolipidemic Agent." *Progress in Medicinal Chemistry* 40 (C): 1–22. https://doi.org/10.1016/S0079-6468(08)70080-8.

Ruiz-García, Antonio, Ezequiel Arranz-Martínez, Beatriz López-Uriarte, Montserrat Rivera-Teijido, David Palacios-Martínez, Gema M. Dávila-Blázquez, Antonio Rosillo-González, *et al.*. 2020. "Prevalence of Hypertriglyceridemia in Adults and Related Cardiometabolic Factors. SIMETAP-HTG Study." Clinica e Investigacion En Arteriosclerosis 32 (6): 242–55. https://doi.org/10.1016/j.artere.2020.11.002.

Sainz de Medrano Sainz, Jaime I., and Mercè Brunet Serra. "Influence of pharmacogenetics on the diversity of response to statins associated with adverse drug reactions." *Advances in Laboratory Medicine/Avances en Medicina de Laboratorio* 4 (2023): 341-352. https://doi.org/10.1515/almed-2023-0123

Santos, Paulo Caleb Junior Lima, Ana Carolina Moron Gagliardi, Márcio Hiroshi Miname, Ana Paula Chacra, Raul Dias Santos, Jose Eduardo Krieger, and Alexandre Costa Pereira. 2012. "SLCO1B1 Haplotypes Are Not Associated with Atorvastatin-Induced Myalgia in Brazilian Patients with Familial Hypercholesterolemia." *European Journal of Clinical Pharmacology* 68 (3): 273–79. https://doi.org/10.1007/s00228-011-1125-1

Shaghaghi, Zahra, Maryam Alvandi, Soghra Farzipour, Mohammad Reza Dehbanpour, and Sahar Nosrati. 2022. "A Review of Effects of Atorvastatin in Cancer Therapy." *Medical Oncology* 40:1 40 (1): 1–16. https://doi.org/10.1007/S12032-022-01892-9.

Simha, Vinaya. 2020. "Management of Hypertriglyceridemia." *BMJ* 371 (October). https://doi.org/10.1136/BMJ.M3109.

Sivkov, Andrey, Natalya Chernus, Roman Gorenkov, Sergey Sivkov, Svetlana Sivkova, and Tamara Savina. 2021. "Relationship between Genetic Polymorphism of Drug Transporters and the Efficacy of Rosuvastatin, Atorvastatin and Simvastatin in Patients with Hyperlipidemia." *Lipids in Health and Disease* 20 (1): 1–9. https://doi.org/10.1186/s12944-021-01586-7

Stapleton, Phoebe A., Adam G. Goodwill, Milinda E. James, Robert W. Brock, and Jefferson C. Frisbee. 2010. "Hypercholesterolemia and Microvascular Dysfunction: Interventional Strategies." *Journal of Inflammation* 7 (1): 1–10. https://doi.org/10.1186/1476-9255-7-54.

Thompson, John F., Craig L. Hyde, Linda S. Wood, Sara A. Paciga, David A. Hinds, David R. Cox, G. Kees Hovingh, and John J.P. Kastelein. 2009. "Comprehensive Whole-Genome and Candidate Gene Analysis for Response to Statin Therapy in the Treating to New Targets (TNT) Cohort." *Circulation: Cardiovascular Genetics* 2 (2): 173–81. https://doi.org/10.1161/CIRCGENETICS.108.81806

Türkmen, Deniz, Jack Bowden, Jane A.H. Masoli, David Melzer, and Luke C. Pilling. 2024. "SLCO1B1 Exome Sequencing and Statin Treatment Response in 64,000 UK Biobank Patients." *International Journal of Molecular Sciences* 25 (8): 4426. https://doi.org/10.3390/IJMS25084426/S1.

Vergès, Bruno. 2015. "Pathophysiology of Diabetic Dyslipidaemia: Where Are We?" *Diabetologia* 58 (5): 886–99. https://doi.org/ 10.1007/s00125-015-3525-8

Vrablik, Michal, Lukas Tichý, Tomas Freiberger, Vladimir Blaha, Martin Satny, and Jaroslav A. Hubacek. 2020. "Genetics of Familial Hypercholesterolemia: New Insights." *Frontiers in Genetics* 11(2020). https://doi.org/10.3389/fgene.2020.574474.

Wang, D., Y. Guo, S. A. Wrighton, G. E. Cooke, and W. Sadee. 2010. "Intronic Polymorphism in CYP3A4 Affects Hepatic Expression and Response to Statin Drugs." *The Pharmacogenomics Journal* 11:4 11 (4): 274–86. https://doi.org/10.1038/tpj.2010.28.

Ward, Natalie C., Gerald F. Watts, and Robert H. Eckel. 2019. "Statin Toxicity." *Circulation Research* 124 (2): 328–50. https://doi.org/10.1161/CIRCRESAHA.118.312782.

Wilke, Russell A., Jason H. Moore, and James K. Burmester. 2005. "Relative Impact of CYP3A Genotype and Concomitant Medication on the Severity of Atorvastatin-Induced Muscle Damage." *Pharmacogenetics and Genomics* 15 (6): 415–21. https://doi.org/10.1097/01213011-200506000-00007.

Xia, Binbin, Yali Li, Yatong Zhang, Ming Xue, Xiaorong Li, Pingxiang Xu, Tao Xia, and Shicai Chen. 2018. "UHPLC-MS/MS Method for Determination of Atorvastatin Calcium in Human Plasma: Application to a Pharmacokinetic Study Based on Healthy Volunteers with Specific Genotype." *Journal of Pharmaceutical and Biomedical* Analysis 160 (October):428–35. https://doi.org/10.1016/J.JPBA.2018.07.033.

Yanai, Hidekatsu, and Hiroshi Yoshida. 2021. "Secondary Dyslipidemia: Its Treatments and Association with Atherosclerosis." *Global Health & Medicine* 3 (1): 15–23. https://doi.org/10.35772/GHM.2020.01078.