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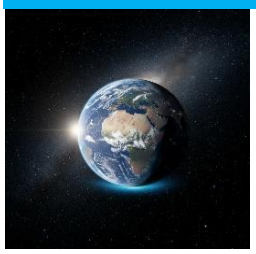

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Genetic Determinants of Inter-Individual Variability in Statin Therapy

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Abstract

Statins, or HMG-CoA reductase inhibitors, represent one of the most extensively researched and frequently prescribed pharmacological agents, primarily utilized to reduce cardiovascular risk through the modulation of serum cholesterol levels. Although their efficacy in reducing global mortality and cardiovascular events is well-established, genetic variability persists among different populations which may predispose patients to dose-related adverse effects and reduced efficancy of statin therapy. This heterogeneity has driven a shift in the scientific landscape toward exploring common genetic polymorphisms within the genes encoding genes involved in pharmacodynamic pathways. This review aims to provide a comprehensive analysis of clinically significant polymorphisms within the pharmacodynamic pathways of statins.

Methods: A systematic literature review was conducted in accordance with PRISMA guidelines. Databases including PubMed, Embase, and the Cochrane Library were searched for peer-reviewed publications from 2021 to 2025. Following a rigorous selection process based

on Evidence-Based Medicine (EBM) criteria.

Conclusions: Despite rapid progress in the field of pharmacogenomics, the role of genetic polymorphisms among genes involved in pharmacodynamic pathways of statin therapy still requires more research in order to establish robust evidence of their role in the overall lipid-lowering efficacy of statins.

Keywords: Pharmacogenomics, statins, pharmacodynamics, genetic polymorphisms.

1. Introduction

The fundamental mechanism of action of statins is primarily based on their ability to act as reversible competitive inhibitors of HMG-CoA reductase, an enzyme responsible for the reduction of HMG-CoA to mevalonic acid, a key intermediate in endogenous cholesterol synthesis. While statins inhibit the synthesis of endogenous cholesterol, their main beneficial effect is not solely dependent on impairing the ability of hepatocytes to produce cholesterol.
The most important step of the statin pharmacodynamic pathway is the upregulation of transcription of the LDLR gene. This upregulation is mediated by proteins known as SREBPs [1], which are present in the endoplasmic reticulum of cells. The increased transcription of the LDLR gene leads to an elevation in the number of LDL receptors on hepatocytes, facilitating a more efficient uptake of LDL-c particles from the blood serum.
Moreover, the therapeutic effect of statins extend beyond their impact on cholesterol synthesis and LDL receptor expression. Statins also exert pleiotropic effects, including impairment of mevalonate pathway as it plays a critical role in the synthesis of various important molecules, such as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) which are essential intermediates for the synthesis of proinflammatory interleukins. Additionaly, statins have been found to activate the sphingosine-1-phosphate pathway [2], which are known for exerting anti-inflammatory and anti-atherothrombotic effects [3].
The pharmacodynamics of statins are intricately linked to homeostatic pathways involved in lipid metabolism, and the response to statin therapy can be significantly influenced by interindividual genetic variations. Notably, genetic variations in several key genes, including ApoA, ApoB, ApoE, CETP, HMGCR, LDLR, PCSK9, and CELSR2/PSRC1/SORT1, have been identified as potential factors in modulating the therapeutic effect of statins.

2. Material and Methods

A systematic literature review was conducted in accordance with PRISMA guidelines. Databases including PubMed, Embase, and the Cochrane Library were searched for peer-reviewed publications from 2021 to 2024. Following a rigorous selection process based on Evidence-Based Medicine (EBM) criteria.

3. ApoE

Apolipoprotein E (ApoE), a protein present in chylomicrons and VLDL (very low-density lipoprotein), serves as a ligand for the LDL receptor, enabling the removal of excess cholesterol from the bloodstream by the liver. It also plays various vascular-protective roles, such as stimulating the release of nitric oxide (NO) and suppressing the formation of foam cells. [4]

In the human population, the gene encoding ApoE contains two single nucleotide polymorphisms (SNPs): rs7412 > $T^{4,075}$ (resulting in a cysteine codon) and rs429358 > $C^{3,937}$ (resulting in an arginine codon), leading to four alleles: E2 (Cys112 and Cys158), E3 (Cys112 and Arg158), E4 (Arg112 and Arg158), and e3r (Arg112 and Cys158). The e3r variant has only been detected in one family in Ibadan, Italy, and is therefore excluded from most studies.[5,6] The most common allele in the human population is E3 (wild type), while E2 and E4 are its mutations.

The E2 variant is characterized by reduced affinity (50% compared to the E3 variant) to the LDL receptor [7] which increases the risk of early-onset atherosclerosis. However, it significantly reduces the risk of Alzheimer's disease and paradoxically decreases the development of atherosclerosis through a different mechanism.

Another prominent variat of ApoE gene - E4 allele is associated with significantly higher risks of atherosclerosis, increased risks of dementia, and a markedly impaired response to statins [5]. The mentioned polymorphism encodes an ApoE variant that binds more strongly to VLDL particles than other variants, which is associated with impaired peripheral lipolysis function. Additionally, individuals with the ApoE E4 polymorphism have been observed to exhibit increased activation of phospholipase 2, an enzyme that actively promotes inflammation in the CNS [8] and vessels [9], which may contribute to accelerated atherosclerotic plaque growth.

It has been known for some time that individuals carrying the E2 variant achieve better results in reducing LDL and triglyceride levels during statin therapy. [10] This phenomenon is mainly observed in males, while in female patients, having the E2 allele was not consistently associated with lower LDL levels compared to those with the E3 or E4 variants.[6] According to a meta-analysis by Zintzaras et al. [10] conducted in 2009, the average reduction in patients with the E2 allele was 27.7%, compared to 25.1% in patients with the E4 allele. This difference has been confirmed in more recent studies, such as the study by Bi et al. (-41.2% vs. -17.6%) and the study by Zhang et al. (-29.41% vs. -23.05%). Similar conclusions were drawn in the post-hoc study on JUPITER trial, which demonstrated that individuals with the rs7412 SNP have a better response to rosuvastatin therapy.

4. ApoB

Apolipoprotein B (ApoB) is the primary lipoprotein found in LDL, VLDL, and IDL. It is considered one of the most important factors in initiating atherosclerosis [11], recognized by both the American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines. The predictive value of the ApoB/ApoA-I ratio for acute coronary syndrome (ACS) has been established by INTERHEART [12] and AMORIS [13] case-control studies which have identified a correlation between higher ApoB/ApoA-I ratios and increased risk of ACS, adjusting for the lower ApoA-I levels observed in males, the AMORIS study proposed cutoff values of <0.9 for women and <0.8 for men. The INTERHEART study further revealed a relationship between higher ApoB/ApoA-I ratios and common risk factors for ACS, such as smoking, diabetes mellitus, and hypertension. Additionally, a prospective study by Walldius et al. [14] demonstrated a significant reduction in ApoB/ApoA-I ratios of over 20-40% during statin therapy, translating to a substantial decrease in ACS risk.

Regarding genetic variations within the gene encoding ApoB protein, several polymorphisms have been associated with enhanced atherosclerotic properties and an adverse clinical profile characterized by high total cholesterol (TC), triglycerides (TG), and low HDL cholesterol (HDL-C) levels. Notably, these polymorphisms include rs693 (XbaI), rs1042031 (EcoRI), rs17240441[15], rs562338 [16], rs17240441 [17], rs1042034 [18] . However, to our knowledge there are a limited number of evidence regarding their influence on statin response, with only the rs693

(XbaI) polymorphism mentioned by *Ye P et al* [19] as potenial contributor in diminished efficacy of simvastatin treatment among its carriers.
Conversely, certain polymorphisms have been found to positively influence the lipid-lowering effects of statins. For instance, the rs676210 [20] variant of the APOB gene, highlighted in a small study conducted on an Arabian population, demonstrated significantly greater improvement in triglyceride levels (a 24.7% decrease) with atorvastatin therapy (40mg/d) compared to the wild type (34.5% decrease). Moreover, this particular polymorphism was also associated with lower levels of oxidized LDL (OxLDL).
Although ApoB does not directly impact the pharmacodynamics or pharmacokinetics of statins, a limited number of polymorphisms have been reported to exert a direct influence on the efficacy of statin therapy. However, the percentage reduction in LDL-C levels from baseline remains largely consistent among most well-known polymorphisms [21]. Nevertheless, it is important to acknowledge that genetic variants within the ApoB gene play a crucial role in predicting the effectiveness of lipid-lowering therapy and the risk of vascular pathologies.

5. CETP

Cholesteryl ester transfer protein (CETP) is a crucial protein involved in the transportation of triglycerides and cholesteryl esters between lipoproteins. Its primary function is to facilitate the exchange of triglycerides, which are abundant in chylomicrons and very low-density lipoproteins (VLDL), with cholesterol from high-density lipoprotein (HDL) and vice versa.
There are more than 206 documented polymorphisms of the CETP gene (https://databases.lovd.nl/shared/variants/CETP), most of which do not exhibit any clinically significant effects. However, a few of these polymorphisms have been associated with altered responses to statin therapy. Two of such variants are Taq1B and -629 polymorphisms, which are found in linkage disequilibrium. [22]
The Taq1B (rs708272) polymorphism is characterized by a nucleotide change at position 277 within intron 1 (277C > T), resulting in two distinct alleles, B1 and B2 [23] Post-hoc study on participants of REGRESS trial [24] observed that 16% of participants with documented atherosclerosis had the B2B2 genotype, which was also associated with higher HDL concentrations, according to *Boekholdt et al.* [25] However, the CARE [22] study provided inconclusive results regarding the correlation between B1 or B2 alleles and the efficacy of pravastatin therapy. Similarly, *Bousoula et al.*[261] found no significant influence of the Taq1B polymorphism on atorvastatin and simvastatin therapy.
The -629 polymorphism of CETP is located in the promoter region and has three different variants: C/A, A/A, and C/C. Similar to the Taq1B polymorphism, the CARE study did not find any evidence of the -629 polymorphism influencing the efficacy of pravastatin therapy. However, some reports suggest a potential positive influence of the C/C variant, especially on atorvastatin therapy [27]. Furthermore, the -629 alleles were found to potentially reduce the risk of future cardiovascular death, as reported by *Blankenberg et al.* [28]
Another notable CETP polymorphism is rs5882 (I405V), which was mentioned by *Anagnostopoulou et al.* [29] and *Kolovou et al.*[30]. Both cohort studies suggested that rs5882 is associated with better reduction of triglycerides and higher HDL-c values after simvastatin and atorvastatin therapy. However, a more recent cohort study [26] conducted by the same institution failed to find any significant influence on statin therapy. Similarly, during the TNT trial, the rs5882 SNP did not significantly influence the response to atorvastatin or the risk of cardiovascular events. While the influence of the aforementioned polymorphism on statin

therapy remains a subject of debate, there is also controversy regarding its impact on the risk of myocardial infarction [31] [32], potential higher risk of late-onset Alzheimer's disease [33], and lower risk of endometriosis [34].

Among the CETP polymorphisms that have been found to be associated with altered responses to statin therapy, rs3764261, rs708272, and rs1532624 stand out. In a recent study by *Srisawasadi et al.* [35] conducted on the Thai population, it was discovered that carriers of rs3764261 and rs708272 exhibited a higher susceptibility to atherogenic dyslipidemia following treatment with simvastatin, atorvastatin, pitavastatin, and rosuvastatin. Particularly, patients with the common CC rs3764261 genotype had the highest risk of hypo HDL-cholesterolemia (42.1%), hypertriglyceridemia (57.9%), and hyper-VLDL-cholesterolemia (66.7%). In general, carriers of the minor A allele showed a more favorable lipid profile for both rs3764261 and rs708272. Another notable polymorphism, rs1532624, which is in linkage disequilibrium with the Taq1B polymorphism, was found by *Keyser et al.* [36] to alter the response to statin therapy. Homozygotes carrying the minor A allele had higher cholesterol levels compared to homozygotes with the major C allele after initiating statin therapy, as observed among participants in the Rotterdam Study.

Guo et al. [37] reported several CETP gene polymorphisms associated with a worsened lipid profile, including rs1532624, rs173539, rs1800775, rs12149545, rs711752, and rs5883. However, the authors did not provide any clinical remarks concerning these polymorphisms.

6. HMGCR

HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) is the primary target of statins, making polymorphisms in its gene (HMGCR) crucial in shaping individual lipid profiles and potentially influencing the response to statin therapy. A multitude of variants in the HMGCR gene have been proposed to impact the clinical presentation by influencing the risk of chronic comorbidities and lipid profile.

Variants such as H4, rs2303151 [38], rs17238540 (G/T) [39], rs3846663 (C/T and T/T), rs3761740 [40] and rs12654264 [41] have been reported to worsen the clinical profile of patients by affecting their risk of chronic comorbidities and lipid levels. On the other hand, variants like H2, H7, and SNPs rs17671591, rs12916 [42] [43], rs17238484 have been associated with decreased lipid values in blood serum. Particularly rs12916 according to *Zhao X et al.* [44] might also contribute to weight gain associated with statins and an increased risk of type two diabetes.

Wong-Medina et al. [45] mentioned the H7 and H2 haplotypes, which share a common feature of containing the SNP rs3846662. These haplotypes are associated with reduced statin effectiveness, as the rs3846662 SNP leads to alternative splicing, resulting in the translation of HMG-CoA with attenuated statin sensitivity. This attenuation decreases the lipid-lowering effect of statins by 10.8% in H7 or H2 carriers and by 32% in H7/H2 genotype carriers. Although these haplotypes reduce statin efficiency, their carriers have lower baseline triglyceride (TG) values compared to the wild-type H1 haplotype [46] and are associated with an increased risk of Alzheimer's disease (AD) [41], as reported by Wong-Medina et al. Chen et al. reported that only the H4 haplotype is associated with higher TG and LDL-c levels, but no correlation between the efficiency of statin therapy and this haplotype was observed.

Another variant that has been widely reported [47] [48] to be associated with a positive response to statin therapy is rs17671591 as it has been shown to have a beneficial influence on statin therapy during the TNT trial and was later confirmed in the Chilean population by *Cuevas et al.*

A few other reported SNPs known to alter statin therapy response include rs17238540 (G/T) and rs17244841, which are in linkage disequilibrium and associated with reduced response to

pravastatin, as reported by Chasman et al. Additionally, rs12916C/T has been associated with a significantly higher reduction in LDL-c among carriers of the C and T alleles during statin therapy. [49]

7. LDLR

One of the utmost imortant component of the pharmacodynamic pathway of statins is the low-density lipoprotein receptor (encoded by the LDLR gene), which plays a crucial role in the hypolipemic effect of statins through inducement of a positive feedback loop that leads to increased synthesis of LDL receptors on hepatocytes, facilitating the removal of low-density lipoprotein cholesterol (LDL-c) from the blood serum. Mutations in the LDLR gene are among the most common causes of familial hypercholesterolemia, a genetic disorder characterized by high levels of LDL-c.

The initial reports on potential LDLR polymorphisms influencing statin therapy response in patients with familial hypercholesterolemia were published as early as in 1993 by *Leitersdof et al*. [50] who identified correlations between specific mutations (C660X, D147H, & 652delGGT) and a smaller reduction in LDL-c levels after fluvastatin treatment. In contrast, *Jeenah et al.* [51] in the same year found a correlation between a greater reduction in LDL-c levels and a specific mutation (G408A) in FH2 among patients who were undergoing simvastatin treatment.

Since those early findings, numerous other LDLR polymorphisms associated with familial hypercholesterolemia and variable responses to lipid-lowering therapy have been reported. For example, *Kajinami et al.* [52] in 1998 reported that FH patients carrying the $FH_{KANAZAWA}$ (C665T) mutation had a higher reduction in LDL-c than those with the $FH_{TONAMI-1}$ (Del exon15) mutation after statin treatment. Additionally, *Couture et al.* [53] in 1998 observed a higher reduction in LDL-c in heterozygous familial hypercholesterolemia patients with C646Y and deletion > 15 kb mutations compared to W66G mutations. Moreover, it has been noted that LDL-c reduction is more significant in patients with defective variants rather than null mutations. [5455]

Some LDLR polymorphisms have been found to potentially positively influence statin therapy but are not associated with familial hypercholesterolemia e.g. in a post-hoc study on JUPITER trial, *Chasman et al.* [56] identified two SNP polymorphisms (rs6511720 and rs11672123) correlated with greater LDL-c reduction during atorvastatin treatment - rs6511720 (-2.6% per allele; P=0.005) and rs11672123 (total LDL-c reduction by -4.4 mg/dL, P=7104). Other SNP polymorphisms (rs688, rs1433099, rs11668477) were mentioned by the authors, but their link to variable response to atorvastatin treatment was not elucidated. Nevertheless, it is worth noting that rs688 is associated with higher baseline LDL-c in pre-menopausal women according to *Zhu et al*. [57] , meanwhile in a post-hoc PROSPER study rs1433099 [58] has been linked to significantly lower baseline LDL-c levels in men and a better response to pravastatin treatment. More recent cohort study by Shaimaa et al. identified SNP polymorphisms (rs200727689 and rs72658860) associated with atorvastatin response. The researchers concluded that rs200727689 A allele carriers are more responsive to atorvastatin 40mg/d treatment with the highest decrease in LDL-c levels compared to G/G genotype carriers. Rs72658860 A/A genotype carriers were also reported to have a better response to atorvastatin treatment with a higher decrease in triglyceride (TG) levels compared to carriers of other genotypes,

Another SNPs of LDLR which are likely to modify statinotherapy efficacy were reported by *Shaimaa Y et al* [59] in a small cohort study which aimed to find correlation between SNP rs200727689; rs72658860 outcome from atorvastatin treatment. In the conclusion researchers noted that rs200727689 A allele carriers are more responsive to atorvastatin 40mg/d treatment with the highest LDL-C decrease compared to G/G genotype. Rs72658860 A/A genotype carriers are also reported to have better response to atorvastatin treatment with higher value of

decreased TG compared to rest of genotypes, although A/A carriers tended to have higher baseline LDL-c values.
LDLR L5 is a haplotype which contains several SNPs (rs14158 G, rs1433099 G, rs7254521 C, rs5742911 A, rs2738467 C) and has been reported by *Mangravite et al* [60] to have decreased lipid-lowering effect on simvastatin treatment. According to researchers together with HMGCR H2 and H7 haplotypes, LDLR L5 could potentially have an additive effect, particularly in populations with a higher prevalence of the aforementioned polymorphisms, such as individuals of African descent.

8. SREBP-SCAP pathway

The SREBP-SCAP pathway, which encompasses the sterol regulatory element-binding protein (SREBP) and SREBP cleavage-activating protein (SCAP), plays a pivotal role in cholesterol metabolism and is intricately involved in the pharmacodynamics of statins. Within a low-cholesterol environment, the SCAP protein undergoes a conformational change, enabling its binding to the SREBP molecule and facilitating its subsequent activation. The activated SREBP molecule possesses the capacity to bind to sterol response elements (SREs) on the genome, thereby promoting increased transcription of the LDL receptor gene.
Polymorphisms within the SREBP-SCAP pathway, such as the SCAP 2386G/A variant, have been identified as contributors to interindividual variations in response to statin therapy, as elucidated by *M. Fiegenbaum et al.* [61] In their study, researchers observed that carriers of the G/G genotype exhibited more favorable outcomes from simvastatin treatment compared to individuals with the A/A genotype (percentage change in total cholesterol -29.67% vs. -22.17%, $P = 0.007$).
Additionally, another polymorphism located within the genes involved in the SREBP-SCAP pathway, specifically SREBF-1a −36del/G, has been reported by *Salek et al.* [62] to significantly increase plasma apoA-I levels among individuals homozygous for the G/G genotype following fluvastatin treatment.

9. PCSK9

The initial discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) by *Abifadel et al.* [63] in 2003 opened up new perspectives in understanding hypercholesterolemia and lipid-lowering therapies. PCSK9 is primarily produced by hepatocytes and plays a critical role in cholesterol metabolism by binding to the LDL-C/LDL complex. This binding promotes the degradation of LDL-C receptors and reduces their recycling to the hepatocyte surface, leading to decreased hepatic clearance of LDL-C from the blood serum and subsequently elevated LDL-C levels [64]. Statins, through its main therapeutic effects, triggers compensatory mechanisms, including an upregulation of PCSK9 synthesis [65].
In addition to variations in ApoB and LDLR genes, polymorphisms in PCSK9 have also been identified as contributors to familial hypercholesterolemia (FH). CLINVAR reports approximately 22 pathogenic or likely pathogenic variants and over 900 variants potentially linked to FH. The RUTHERFORD-2 trial investigated the use of evolocumab in heterozygous FH patients with inadequate statin response, demonstrating a potential correlation between PCSK9 and its polymorphisms in statin-resistant familial hyperlipidemia. Evolocumab reduced LDL-C levels by 59-61% from baseline over a 12-week period.
Among the various PCSK9 gene variants not directly linked to FH but affecting statin response, rs13064411 has been reported by *de Keyser et al.* [66] to decrease the cholesterol-lowering effect of statins. Two other SNPs, rs2479409 and rs505151, have been associated with impaired

response to statin therapy, as noted by *Feng Q et al.* [67]. Additionaly *Zambrano et al.* [68]also mentioned rs505151 (E670G) and its potential negative influence on atorvastatin treatment and worse lipid profiles, which aligns with findings from other studies [69] [70] However, a more recent study conducted on the Chilean population did not replicate these findings [71].
Research conducted on animal models by *Rashid et al.* [72] indicated that the absence of PCSK9 significantly reduced cholesterol levels in the bloodstream and increased sensitivity to statins. Similar results were observed in human studies, where loss-of-function mutations, including I474V [73] and rs11591147 (R46L) [74] carriers, generally exhibited improved lipid profiles and decreased cardiovascular disease risk. Feng Q et al. reported a greater reduction in LDL-C levels during statin therapy among rs11591147 carriers, although other studies, including the post-hoc PROSPER study by *Polisecki et al.* [75], failed to confirm this correlation.

10. CELSR2/PSRC1/SORT1

CELSR2/PSRC1/SORT1 constitutes a gene cluster positioned on chromosome 1, which has been identified through numerous genome-wide association studies (GWAS) as potentially exerting influence on lipid profile and susceptibility to cardiovascular diseases [76] [77]. CELSR2, characterized as an atypical cadherin, predominantly manifests within the central nervous system (CNS), where it assumes roles in neural development and ciliogenesis[78]. Although the precise involvement of CELSR2 in lipid metabolism remains largely elusive, recent findings by *Tan et al.* [78] have shed light on its impact on lipid profile by revealing a correlation between CELSR2 depletion and a significant decrease in the expression of lipid synthesis enzymes in the liver.
SORT1 encodes sortilin 1, a glycoprotein primarily observed in the CNS but also present in numerous other tissues, including the liver [79]. It participates in intracellular transport between organelles and cellular metabolism. Both *Patel et al*. [80] and *Kjolby et al.* [81] have ascertained that hepatic sortilin 1 is implicated in the uptake of lipoproteins rich in ApoB (LDL). Moreover, it facilitates the secretion of very low-density lipoprotein (VLDL) and ApoB100, while also contributing to the downregulation and degradation of newly synthesized VLDL/ApoB100 complexes. *Gustafsen et al* [82]also noted that sortilin 1 is involved in the excretion of PCSK9 and the degradation of LDL receptors (LDLR) which might explain sortilin 1 role in formation of foam cells and atherosclerosis as noted by *Patel et al.* [80]
PSRC1 (proline/serine-rich coiled-coil 1) is responsible for the proper progression of mitosis by destabilizing microtubules. Similar to SORT1 and CELSR2, PSRC1 has a well-established [83] association with LDL-c levels and coronary artery disease (CAD). However, the exact mechanism through which PSRC1 influences lipid profile remains unclear.
Researchers have identified several polymorphisms within the CELSR2/PSRC1/SORT1 cluster that modify lipid profile and cardiovascular disease risk. A meta-analysis conducted by *Castillo-Avilla et al.* [77] thoroughly reviewed extensively studied single nucleotide polymorphisms (SNPs) such as rs646776 and rs599839, which exhibit a high level of certainty in their association with an increased risk of cardiovascular disease. *Kleber et al.* [84] also arrived at similar conclusions in their study, establishing a correlation between SNP rs599839 and a worsened lipid profile and elevated cardiovascular disease risk. In a review authored by *Goettsch et al.* [85], it was noted that rs646776 is part of a major haplotype block comprising rs599834, rs646776, rs629301, and rs12740374, all of which are associated with higher LDL-c values.
In a GWAS performed by *Hubáček et al.* [86] on the Czech population, carriers of the minor rs599838 genotype within the CELSR2/PSRC1/SORT1 cluster exhibited a significantly diminished response to statin treatment compared to common homozygotes. This was

evidenced by a reduction in LDL-c levels of -20.3% in carriers of the minor genotype, as opposed to -32.0% in common homozygotes. The Heart Protection Study, a large-scale GWAS conducted by *Hopewell et al.* [87] on 18,705 patients treated with simvastatin (40mg/day), revealed that the C allele of SNP rs646776 was associated with lower baseline LDL-c and ApoB values, as well as a greater proportional reduction in LDL-c by 0.47% and a larger reduction in ApoB by 0.76%. In a more recent meta-analysis by *Postmus et al.* [88] similar outcome was obtained as authors concluded that minor alleles within SORT1 SNPs - rs646776 and rs12740374 have been proven to be enhancing LDL-c reduction.

11. Lipoprotein(a) – Lpa(a)

Lipoprotein(a) (Lp(a)) is a LDL-like molecule that circulates in the blood plasma and contains apolipoprotein(a) (ApoA), apolipoprotein B100 (ApoB100), and a lipid component. Due to the structural similarity between ApoA and plasminogen, Lp(a) acts as a competitive inhibitor, leading to reduced fibrinolysis and an increased risk of cardiovascular disease (CVD). [89] [90]
While statins are known to decrease LDL cholesterol (LDL-c) levels by upregulating LDL receptors (LDLR), which can bind to both LDL and Lp(a) particles, many studies have reported that statins do not significantly affect Lp(a) levels and may even upregulate its synthesis [91] [92].
A genome-wide association study (GWAS) conducted by *Deshmukh et al.* on participants from the Collaborative Atorvastatin Diabetes Study (CARDS), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and the observational phase of ASCOT found that atorvastatin 10mg/day treatment did not have an effect on Lp(a) levels. However, statin therapy still exhibited a similar reduction in cardiovascular disease (CVD) in patients with high serum Lp(a) levels, indicating potential benefits of statin therapy in such patients.
Retrospective studies on large trials [87] [93], including PROSPER, CARDS, ASCOT, JUPITER, and HPS, have concluded that the SNP rs10455872, especially carriers of the minor G allele, exhibit a lower lipid-lowering response to statin therapy. Additionally, several studies, including those by *Wei Q et al.*[94], *Santos et al.*[95], and the PROCORDIS case-control study [96], suggest that individuals with the aforementioned SNP have a higher residual risk of coronary heart disease (CHD). In the GWAS by *Deshmukh et al.*[97], it was observed that the G allele was associated with a 5 percentage points lower apparent response to atorvastatin (45% in "GG" and "AG" genotypes vs. 40% in the "AA" genotype). This study also confirmed the association of the "A" allele with a lower response to pravastatin 40mg/day treatment. Similar results were obtained in a GWAS by *Postmus et al.* [88], which was conducted on participants from the JUPITER trial.
Furthermore, the HPS retrospective study by Hopewell et al. mentioned the minor allele of the SNP rs3798220 [87], which was associated with decreased LDL-c and ApoB reduction during statin therapy (-2.30% and -2.09%, respectively). Additionally other study has also suggested [98] a correlation between rs3798220 and an increased risk of CVD, similar to rs10455872, indicating its potential as a marker for CVD.
Additionally HPS retrospective study by *Hopewell et al* also mentioned about minor allel of SNP rs3798220 which decreased LDL-C and Apo-B reduction of statinotherapy by -2.30% and −2.09% correspondingly. Moreover other studies including previously mentioned PROCORDIS study mention about correlation between rs3798220 and increased risk of CVD similarly to rs10455872 and might have potential for being a marker for CVDs.
Other variants of the LPA gene associated with a higher risk of CHD include rs6415084 and rs12194138 [99] but to our knowledge, there is no established correlation between these variants and statin response, and their influence on the risk of CHD is still under discussion [100]. Some

variant, however, have been linked to lower risk of CHD e.g. rs41272114 which is a loss-of-function type [101] SNP, found during PROCARDIS case-control study [96]

12. Other factors

To our knowledge there are plethora of factors potentially contributing to altered statin response have been reported throughout years which are not directly linked to either main pharmacodynamic or pharmacokinetic pathways.

Gene	Polymorphism	Association
ACE	Insertion/Deletion	Deletion/Deletion genotype is associated with higher chance of ACS despite of statin treatment
Hepatic lipase [24]	(-514 C/T)	CC genotype associated with regression, TT genotype with progression during statin therapy
LILRB5 [102]	rs12975366	C allele carriers have better absolute reduction
QPRT [103]	rs13331798	Significantly associated with lipid-lowering response
SULT1E1 [103]	c.-64C>T (rs3736599)	Associated with lipid-lowering response
SULT1E1 [103]	c.-9-469A>G (rs3822172)	Associated with lipid-lowering response
MTTP [104]	rs1800591	Associated with poor response to statin among Filipinos
BUD13-ZPR1-APOA5 [104]	rs1558861	Associated with poor response to statin among Filipinos
KIF-6 [105]	rs20455 c.2155T>C	C/C homozygotes have smaller reduction in LDL cholesterol levels
CYP7A1 [106]	A-204C	C allele associated with poor response to statin therapy
NPC1L1 [107]	-18A>C, L272L, V1296V, U3_28650A>G	Minor allele homozygotes associated with higher TC, LDL-C, and apoB levels at baseline
NPC1L1[108]	non-2/2 haplotype	2/2 haplotype associated with greater reduction in LDL-c and Apo-B levels
FXR [109]	-1G>T	G allele carriers among Chinese population have better response to atorvastatin treatment
ABCG5/8 [106]	D19H	Wild-type homozygotes associated with poor response to statin therapy

13. Summary

Statins remain highly effective drugs for managing cardiovascular diseases and in overall blood cholesterol level reduction, irrespective of genetic variations within the pharmacokinetic and pharmacodynamic pathways of statin metabolism. In our opinion, the interindividual response to statins, widely recognized as a clinical phenomenon, may be influenced by the cumulative effects of numerous variables, including environmental factors and the presence of multiple polymorphisms across various genes, ultimately impacting the final outcome of statin treatment [110]. This highlights the complex nature of individual genetic factors in influencing the efficacy of lipid-lowering therapies.

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