Review article

Genetic Polymorphisms and Statin-Associated Side Effects: The Role of SLCO1B1 and Additional Risk Factors

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Abstract

Statins are first-line agents for managing dyslipidemia, primarily prescribed to reduce low-density lipoprotein cholesterol (LDL-C) and prevent atherosclerotic cardiovascular disease (ASCVD). Despite their proven efficacy, there is significant interindividual variability in statin response, with some patients experiencing adverse events such as statin-associated muscle symptoms (SAMS) and hepatotoxicity. These effects are partly attributable to genetic polymorphisms, particularly in the SLCO1B1 gene, which encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) responsible for hepatic statin uptake. The SLCO1B1 rs4149056 polymorphism is associated with impaired transporter function, leading to elevated statin plasma concentrations and a higher risk of statin-induced myopathy, especially with simvastatin. Non-genetic factors, such as hypothyroidism, can exacerbate statin intolerance by impairing lipid metabolism and increasing the risk of myopathy and rhabdomyolysis due to reduced hepatic statin clearance. Vitamin D deficiency has also been linked to increased susceptibility to SAMS, as vitamin D plays a role in muscle function and statin metabolism through CYP enzyme modulation. Coenzyme Q10 (CoQ10) depletion, a consequence of statin therapy due to inhibition of the mevalonate pathway, may further contribute to mitochondrial dysfunction and muscle injury. Incorporating pharmacogenetic testing and addressing modifiable risk factors such as thyroid dysfunction and vitamin D deficiency may optimize statin therapy, reducing adverse effects while maintaining cardiovascular protection.

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Introduction

Dyslipidemia is a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), the leading global cause of morbidity and mortality. Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, remain the cornerstone of dyslipidemia treatment because of their proven efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels and decreasing ASCVD risk (1). However, their clinical utility is often limited by significant interindividual variability in both therapeutic response and the occurrence of adverse drug reactions (ADRs), such as statin-associated muscle symptoms (SAMS) and hepatotoxicity. This variability in statin efficacy and tolerability is strongly influenced by pharmacogenomic factors, particularly polymorphisms in the SLCO1B1 gene, which encodes the hepatic organic anion transporting polypeptide OATP1B1. This transporter plays a critical role in statin uptake and metabolism, and certain allelic variants, such as SLCO1B1 c.521T>C, are associated with elevated systemic statin concentrations and an increased risk of ADRs (2). Additionally, non-genetic factors, including endocrine dysfunctions (e.g., hypothyroidism) and micronutrient deficiencies (e.g., vitamin D deficiency), further contribute to reduced statin tolerability and suboptimal lipid-lowering efficacy (3,4). This review explores the complex interplay between genetic determinants and non-genetic modulators in shaping the pharmacokinetic and pharmacodynamic profiles of statins, with particular emphasis on their clinical implications for optimizing personalized dyslipidemia management strategies and reducing the burden of ADRs associated with statin therapy.

Literature search strategy

This article is a narrative review. A comprehensive literature search was conducted using PubMed/MEDLINE, Scopus, and Web of Science to identify relevant studies published in English up to July 2025. Search terms included combinations of keywords related to statins, statin-associated muscle symptoms, pharmacogenetics, SLCO1B1, ABCG2, CYP enzymes, vitamin D, hypothyroidism, and coenzyme Q10. Reference lists of selected articles were also screened to identify additional relevant publications. Studies were selected based on their relevance to statin pharmacokinetics, pharmacogenetics, and factors influencing statin efficacy and safety.

Mechanism of statin therapy and clinical efficacy

Statins are a widely prescribed class of lipid-lowering agents used as first-line therapy for dyslipidemia, with the specific goal of reducing low-density lipoprotein cholesterol (LDL-C) levels. Their mechanism of action involves the competitive inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the mevalonate pathway responsible for hepatic cholesterol biosynthesis. Due to their efficacy in lowering LDL-C, statins play a pivotal role in both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) (1). Clinical evidence indicates that a reduction in LDL-C by 1 mmol/L correlates with a 22% decrease in the five-year risk of major cardiovascular events (5). The recommended LDL-C levels vary depending on the risk category. For individuals at very high risk, the LDL-C level should be less than 1.4 mmol/L, with a reduction of initial LDL values by at least 50%. For those at high risk, the recommended LDL-C level is less than 1.8 mmol/L, also with at least a 50% reduction in initial LDL values. Individuals at moderate risk should maintain LDL-C levels below 2.6 mmol/L. For people at low risk, the recommended LDL-C level is below 3 mmol/L (6). Research has shown that statins can reduce LDL-C by 20–50%, triglycerides by 10–20%, and may potentially increase HDL cholesterol by 5–10% (7). According to the latest data from the World Health Organization (WHO), cardiovascular diseases are the leading cause of death globally, responsible for 17.9 million deaths each year. Over 80% of these deaths are caused by cerebrovascular accidents or myocardial infarctions, with one-third occurring in individuals under the age of 70 (8). Long-term

statin therapy is believed to be effective in reducing the risk of myocardial infarction by as much as 25%, while the risk of cerebrovascular accident decreases by approximately 15% (7). In clinical practice, atorvastatin and rosuvastatin are the most commonly prescribed statins, differing in their lipophilicity, LDL-C lowering efficacy, and metabolism. Atorvastatin is more lipophilic and is primarily metabolized by the CYP3A4 enzyme, whereas rosuvastatin is more hydrophilic, more effective at lowering LDL-C, and less reliant on CYP enzymes for metabolism. A recent study involving patients with coronary artery disease found that both rosuvastatin and atorvastatin were equally effective in reducing the composite risk of all-cause mortality, myocardial infarction, stroke, or coronary revascularization over a three-year period.

Statin-associated adverse effects

Although statins demonstrate clinical efficacy, patient responses to statin therapy vary considerably. Some individuals achieve target therapeutic outcomes without adverse effects, while others experience significant complications. The most common of these are statin-associated muscle symptoms (SAMS), which range from myalgia, myopathy, and myositis with elevated creatine kinase (CK) levels to rhabdomyolysis, the most severe manifestation. SAMS typically presents as a symmetrical condition affecting the large proximal muscles, particularly in the lower limbs. Symptoms may occur at rest or shortly after physical activity and commonly develop within the first month of starting therapy or after a dose escalation (9). Additional musculoskeletal side effects include tendinopathies, tendon disorders, and arthralgias, although these are infrequently assessed in large randomized controlled trials (9,10). The incidence of myopathy varies; some studies estimate it occurs in 1.5–5% of cases, depending on the type and dose of statin used, though the true numbers are believed to be much higher. In one cohort study, an incidence of 9.6% was reported, with myopathy being more frequent in women, younger individuals, and those who are more physically active (11). The dosage of statins is the strongest independent risk factor for developing myopathy. The risk of SAMS is approximately six times higher in patients on high-dose statin therapy compared to those on lower doses. Among all statins, increasing evidence suggests that the dose-dependent effect is most pronounced with simvastatin (12). Lipophilic statins, including simvastatin, atorvastatin, and lovastatin, carry the highest risk due to their ability to nonselectively diffuse into extrahepatic tissues such as skeletal muscle. Conversely, hydrophilic statins such as pravastatin and fluvastatin demonstrate lower muscle penetration, which is associated with a reduced risk of SAMS (9). A recent meta-analysis comparing lipophilic and hydrophilic statins did not identify a clinically or statistically significant difference in the overall prevalence of adverse effects. The same study showed that side effects were significantly more common in older individuals and women. The impact of chronic diseases on the occurrence of side effects was also examined, with the strongest positive correlation observed in individuals with diabetes, hypothyroidism, and obesity, while arterial hypertension was not identified as a risk factor for these side effects (13). Statins may also induce a mild, asymptomatic elevation in hepatic transaminases, which typically resolves within 12 weeks of initiation. In rare cases, statins can result in a clinically significant elevation in transaminases or acute hepatic failure, necessitating discontinuation of therapy. These hepatic events are usually dose-dependent and occur within the first three months of treatment, with minimal risk of long-term hepatic dysfunction. Notably, the incidence of statin-induced hepatotoxicity appears consistent across different statin formulations (10,14). A recent study compared the impact of atorvastatin and rosuvastatin on liver enzyme levels. In most cases, the elevations were less than two times the upper limit of normal (ULN). However, more significant increases were observed with atorvastatin at a dosage of 40 mg/day compared to rosuvastatin at an equivalent dose of 20 mg/day (15). Other, potentially more severe side effects of statin therapy include the development of type 2 diabetes mellitus, neurological and cognitive

impairments, kidney damage, and various other complications (9). The development of type 2 diabetes mellitus is one of the more well-documented non-muscular adverse effects of statins. While rosuvastatin was linked to lower LDL-C levels, it also carried a higher risk of new-onset diabetes mellitus requiring treatment with antidiabetic medications and an increased incidence of cataract surgery compared to atorvastatin (16). The proposed mechanisms include increased insulin resistance and impaired β-cell function, potentially mediated by decreased expression of GLUT-4 glucose transporters in skeletal muscle and altered cholesterol metabolism within pancreatic cells. This effect is more pronounced at higher doses of statins and with lipophilic statins such as atorvastatin and simvastatin (17,18). Neurological and cognitive impairments, though rare, have also been reported. Lipophilic statins are hypothesized to cross the blood-brain barrier more easily, potentially altering cholesterol-dependent processes essential for synaptic plasticity and neurotransmission. However, evidence remains inconsistent, with most studies indicating these effects are mild, reversible, and infrequent (19,20). Kidney damage associated with statins typically results from severe rhabdomyolysis, which leads to the release of myoglobin into the bloodstream. Myoglobin can obstruct renal tubules and induce oxidative stress, potentially causing acute kidney injury. This risk increases with high-dose statin therapy or the concurrent use of medications that raise the risk of myopathy, such as fibrates (21). Other reported complications include gastrointestinal symptoms, fatigue, and rare immune-mediated necrotizing myopathies (IMNM). IMNM is an autoimmune condition associated with anti-HMGCR antibodies and requires immunosuppressive treatment (22). These non-muscular adverse effects, along with statin-associated muscle symptoms (SAMS), are among the most common reasons for statin discontinuation. However, the overall risk of severe complications remains low, and the benefits of statin therapy in reducing cardiovascular morbidity and mortality generally outweigh these risks in appropriately selected patients (9,13).

Genetic variability and statin therapy

Genetic factors play a key role in modulating the metabolism and efficacy of statins, as well as the occurrence of side effects. The organic anion-transporting polypeptide 1B1 (OATP1B1), encoded by the SLCO1B1 gene, plays a significant role in the transport and elimination of certain statins (23). Reduced activity of the OATP1B1 transporter results in lower statin efficacy and a higher likelihood of side effects. OATP1B1 is located on the basolateral membrane of hepatocytes and is important not only for statin transport into hepatocytes but also for the pharmacokinetics of methotrexate, rifampin, sirolimus, repaglinide, nateglinide, irinotecan, and mycophenolic acid. Genome-wide association studies (GWAS) have shown that, among all investigated polymorphisms of metabolic enzymes and transporters, the strongest impact on adverse statin-related side effects is associated with the rs4149056 polymorphism (c.521T>C, p.V174A) in the SLCO1B1 gene (24). Three genotypes of the SLCO1B1 rs4149056 polymorphism have been identified and classified based on their impact on statin metabolism in the liver: TT (wild type), TC, and CC (24-26). The C allele is associated with decreased hepatic uptake of statins. Some findings suggest that the c.521T>C polymorphism is primarily associated with simvastatin-induced myopathy rather than myopathy caused by atorvastatin. This may be due to differences in the involvement of other organic anion-transporting polypeptides (OATPs) in hepatic uptake. Simvastatin relies heavily on OATP1B1 for liver absorption, whereas atorvastatin is a substrate for both OATP1B1 and OATP2B1, which could explain the observed differences (27). In a clinical study where participants were administered 80 mg of simvastatin, CC homozygotes exhibited an 18% cumulative incidence of statin-induced myopathy, with most cases manifesting within the first year of treatment. The CT genotype was correlated with an approximate 3% cumulative risk, while TT homozygotes had a markedly lower risk, at only 0.6%. Overall, over 60% of myopathy cases were attributable to the rs4149056 C variant in the SLCO1B1 gene (24).

While the findings suggest a link between the SLCO1B1 polymorphism and adverse drug reactions, the clinical trials reviewed did not show a clear benefit of routine SLCO1B1 genotyping for improving statin therapy outcomes or minimizing side effects. Based on the current evidence, the study concludes that routine genotyping of SLCO1B1 prior to statin treatment is not recommended in clinical practice (28).

In addition to the SLCO1B1 gene, enzymes from the cytochrome P450 family, particularly CYP3A4 and CYP2C9, play a pivotal role in statin metabolism. Among widely prescribed statins, simvastatin and atorvastatin are predominantly metabolized by CYP3A4. However, simvastatin undergoes extensive pre-systemic metabolism, leading to reduced bioavailability and making it more prone to pharmacokinetic drug interactions compared to atorvastatin (7). The CYP3A4*22 (rs35599367, g.20493C>T) variant, which occurs predominantly in the Caucasian population with an allele frequency of approximately 5%, is linked to decreased CYP3A4 gene expression in hepatocytes. Research indicates that carriers of the T allele exhibit altered statin metabolism, including a 49% increase in simvastatin bioavailability and a 35% reduction in atorvastatin metabolite concentrations. Additionally, this polymorphism has been associated with a more pronounced lipid-lowering effect of simvastatin. However, no definitive evidence has been established regarding its influence on reducing myocardial infarction risk (29).

The ABCG2 gene encodes the ATP-binding cassette transporter G2 (BCRP), a membrane efflux transporter predominantly expressed in the liver, intestines, kidneys, and at the blood-brain barrier. It plays a pivotal role in the excretion of various endogenous substrates and xenobiotics, including statins. This transporter significantly influences drug bioavailability, distribution, and clearance.

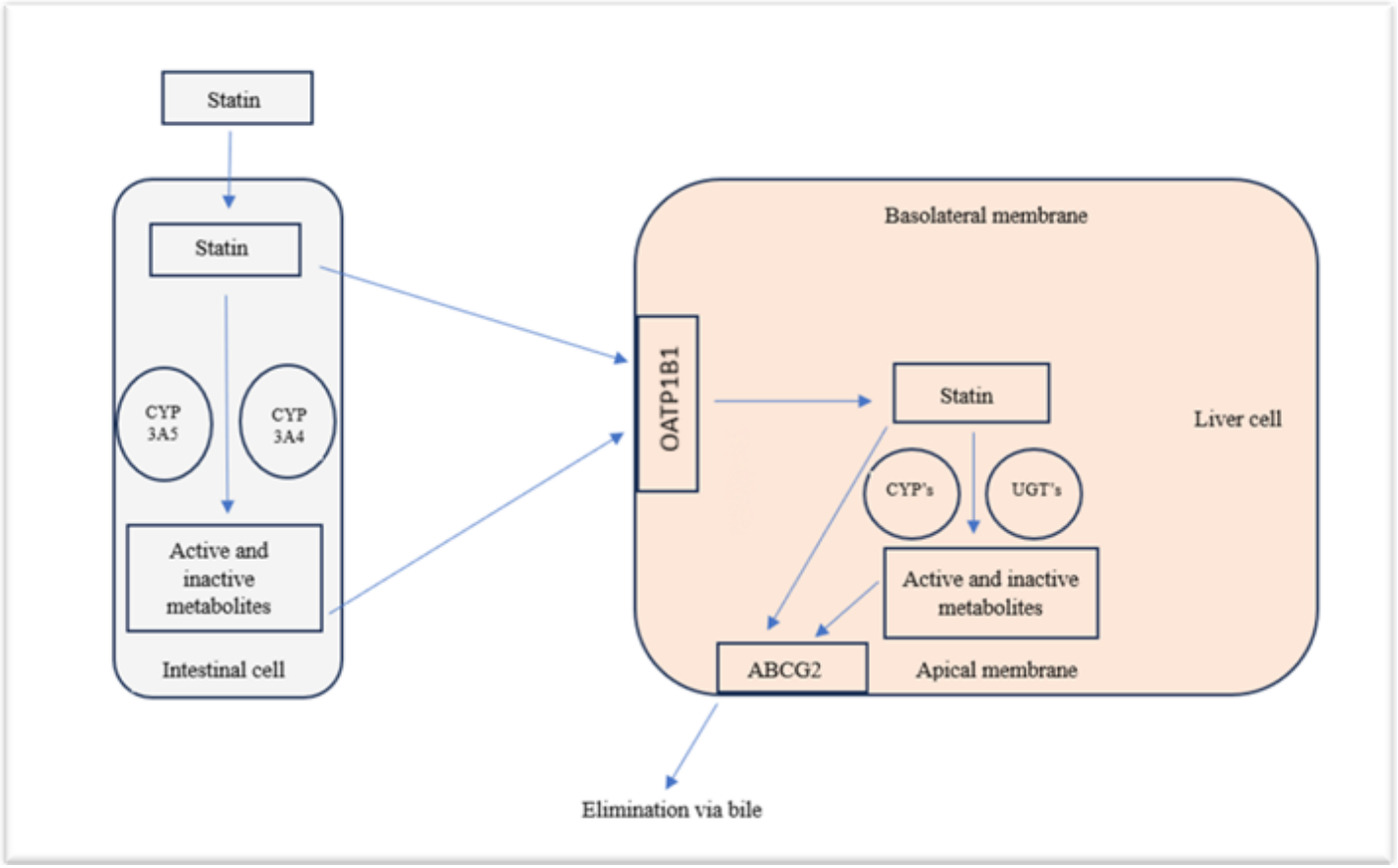

Figure 1. Pharmacokinetic pathways of statins highlighting the roles of OATP1B1 and ABCG2.

Among the identified polymorphisms in ABCG2, the most extensively studied variant, rs2231142 (c.421C>A, p.Q141K), involves a substitution of glutamine with lysine at codon 141. This polymorphism, characterized by the A allele, results in a 30–40% reduction in protein expression and transporter activity compared to the wild-type C allele. Consequently, individuals carrying the A allele experience increased systemic drug exposure due to impaired efflux function (12). Several studies have investigated the impact of c.421C>A on statin pharmacokinetics, with a primary focus on rosuvastatin, a substrate of BCRP. One meta-analysis demonstrated that carriers of the A allele exhibited approximately 50% higher $AUC_{0-\infty}$ (area under the curve, reflecting overall drug exposure) and Cmax (peak plasma concentration) compared to individuals with the CC genotype. This finding was consistent across multiple cohorts, highlighting the substantial effect of the ABCG2 c.421C>A variant on rosuvastatin pharmacokinetics (27). The pharmacokinetic pathways of statins, with a focus on SLCO1B1 and ABCG2, are illustrated in Figure 1.

Pharmacological profiles of individual statins

Atorvastatin is a lipophilic statin that, when administered orally, is rapidly and almost completely absorbed (>98%). It is primarily metabolized in the liver via the cytochrome system, particularly through the CYP3A4 isoenzyme. As a result, atorvastatin has a high potential for drug-drug interactions mediated by CYP, especially with CYP3A4 inhibitors. Multiple single nucleotide polymorphisms (SNPs) in efflux (ABCB1, ABCC1, ABCC2, ABCC4, and ABCG2) and influx (SLCO1B1, SLCO1B3, and SLCO2B1) transporters have been studied for their association with modulation of atorvastatin pharmacokinetics or the development of statin-related myotoxicities (SRM) (30). Most clinical trials of atorvastatin have focused on genetic polymorphisms in the SLCO1B1 gene. The two most studied single nucleotide variants (SNPs) of this gene are SLCO1B1 c.521T>C (rs4149056) and c.388A>G (rs2306283). For the SLCO1B1 c.521T>C variant, the area under the curve (AUC) for TC or CC genotypes was 40–81% higher compared to the TT genotype. In vitro studies suggest that SLCO1B1 c.521T>C reduces the transport activity of atorvastatin due to mislocalization of the transporter, causing decreased expression of OATP1B1 on the plasma membrane. As a result, the SLCO1B1 c.521T>C mutation may increase atorvastatin plasma concentrations by reducing its uptake into the liver (7,31).

Rosuvastatin is metabolized to a limited extent (approximately 10%). In vitro metabolism studies on human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450 enzymes. The primary isoenzyme involved in rosuvastatin metabolism is CYP2C9, while isoenzymes CYP2C19, CYP3A4, and CYP2D6 play minor roles (32,33). Pharmacogenetic studies on rosuvastatin have mainly focused on mutations in two genes, SLCO1B1 and ABCG2, specifically on two SNPs: SLCO1B1 c.521T>C and ABCG2 c.421C>A. The effect of the SLCO1B1 c.521T>C mutation on the AUC for rosuvastatin increases by 19–68%. However, this effect appears to be weaker for rosuvastatin than for atorvastatin (19–68% vs. 40–81%), despite rosuvastatin being more hydrophilic. Rosuvastatin is a substrate for several other transporters, including OATP1B3, OATP2B1, and OATP1A2, which are also expressed in the liver. These transporters may compensate for the reduced activity of OATP1B1, explaining the relatively modest impact of the SLCO1B1 polymorphism on rosuvastatin pharmacokinetics. ABCG2 c.421C>A, which results in an amino acid change Gln141Lys, is one of the most well-studied sequence variations in the ABCG2 gene. Several studies have shown that the ABCG2 421AA genotype has a greater impact on rosuvastatin AUC compared to the genetic polymorphisms of other transporters (7,32). For individuals with poor ABCG2 function, a starting dose of rosuvastatin ≤ 20 mg is

recommended. However, if a higher dose is required to achieve the desired efficacy, an alternative statin or combination therapy (e.g., statin plus ezetimibe) is advised. Although the risk of myopathy is unknown, some studies show that rosuvastatin exposure (AUC) was 144% higher in individuals with the 421AA genotype compared to those with the 421CC (wild-type) genotype. Therefore, this recommendation is primarily based on pharmacokinetic data (12).

Table 1. Pharmacogenetic impact of SLCO1B1 and ABCG2 polymorphisms on statin therapy (7,12,54)

Gene polymorphism	Statin	Pharmacokinetic effects	Clinical Implications and summary of recommendations
SLCO1B1 (c.521T>C, rs4149056)	**Atorvastatin**	The SLCO1B1 gene encodes the hepatic OATP1B1 transporter responsible for the hepatic uptake of atorvastatin. The c.521T>C polymorphism results in reduced transporter function, leading to decreased hepatic clearance and elevated systemic atorvastatin concentrations.	This polymorphism increases the risk of statin-associated muscle symptoms (SAMS), particularly myopathy and rhabdomyolysis. Therapeutic recommendations: Prescribe ≤20mg for patients with SLCO1B1 poor function phenotype and ≤40mg for patients with SLCO1B1 decreased or possible decreased phenotype as a starting dose. Adjust doses of atorvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for 40 mg dose.
SLCO1B1 (c.521T>C, rs4149056)	**Rosuvastatin**	The impact of the c.521T>C polymorphism on rosuvastatin pharmacokinetics is moderate. Plasma concentrations of rosuvastatin are elevated, but to a lesser extent than atorvastatin and simvastatin. Rosuvastatin undergoes less hepatic uptake via OATP1B1, which minimizes the impact of SLCO1B1 variants.	Though the risk of SAMS is lower with rosuvastatin in patients carrying this variant, dose titration is recommended. Regular monitoring of creatine kinase (CK) levels is advised, especially at higher doses (≥20 mg).
SLCO1B1 (c.521T>C, rs4149056)	**Simvastatin**	Simvastatin is highly dependent on OATP1B1 for hepatic uptake. Reduced transporter activity due to the c.521T>C polymorphism significantly increases simvastatin systemic exposure (up to 221% increase in AUC), leading to prolonged drug exposure.	Patients with the SLCO1B1 c.521T>C variant are at a markedly higher risk of myopathy, especially at higher doses (e.g., 80 mg). Guidelines recommend avoiding high-dose simvastatin, with preference given to lower doses or alternative statins (pravastatin, fluvastatin, rosuvastatin). If simvastatin therapy is warranted in patients with SLCO1B1 decreased or possible decreased phenotype, limit dose to <20 mg/day.
ABCG2 (c.421C>A, rs2231142)	**Rosuvastatin**	ABCG2 encodes the Breast Cancer Resistance Protein (BCRP) efflux transporter, which mediates the biliary excretion of rosuvastatin. The c.421C>A polymorphism results in a functional loss of the BCRP transporter, leading to reduced biliary excretion and an increase in rosuvastatin plasma concentration.	Patients with the ABCG2 c.421C>A variant are at increased risk of adverse effects, such as muscle toxicity (myopathy, rhabdomyolysis), particularly at higher doses of rosuvastatin (>20 mg). For individuals who have ABCG2 poor function, a rosuvastatin starting dose of ≤20mg is recommended; however, if a dose greater than 20mg is needed for desired efficacy, an alternative statin or combination therapy (e.g., statin + ezetimibe) is recommended.
****CYP2C9 (c.430C>T, *2; c.1075A>C, 3)**	**Simvastatin**	CYP2C9 polymorphisms (notably *2 and *3) result in decreased enzyme activity, leading to slower metabolism of simvastatin. This causes a significant increase in simvastatin plasma concentration and reduced clearance, increasing the overall drug exposure (AUC).	CYP2C9 *2 and *3 variants significantly increase the risk of statin-induced myopathy. Patients with these variants may require a lower simvastatin dose or consideration of an alternative statin like pravastatin or rosuvastatin. Pharmacokinetic monitoring and regular assessment of CK levels are advised.

Simvastatin is rapidly absorbed in humans, but due to extensive first-pass metabolism in the liver and intestines, its absolute bioavailability is less than 5%. Simvastatin metabolism is primarily mediated by the cytochrome P450 enzyme CYP3A4, making the drug highly susceptible to interactions with CYP3A4 inhibitors, which can dramatically increase its plasma concentration (34). Simvastatin, a lipophilic drug, primarily reaches the liver via passive diffusion, where it is metabolized into its active form, simvastatin acid. However, genetic variations in the SLCO1B1 gene can substantially influence its pharmacokinetics. Specifically, the SLCO1B1 c.521T>C polymorphism significantly elevates the area under the curve (AUC) for simvastatin acid, resulting in greater systemic exposure and a heightened risk of dose-dependent adverse effects, particularly myotoxicity (7). In one meta-analysis, the odds of myopathy were 2.8 times higher for the CC genotype and 1.8 times higher for the TC genotype (35). In contrast, the SLCO1B1 c.388A>G variant does not significantly alter simvastatin acid levels (7).

The pharmacogenetic impact of SLCO1B1 and ABCG2 polymorphisms on statin therapy, including their effects on drug metabolism and clinical implications, is summarized in Table 1.

Factors influencing statin efficacy and safety

According to some studies, individuals with lower vitamin D concentrations are at higher risk of developing statin-induced myopathy. The recommended levels of 25(OH)D are 30–50 ng/mL (75–125 nmol/L). Vitamin D insufficiency is indicated by levels below 30 ng/mL (75 nmol/L), while deficiency is defined as concentrations below 20 ng/mL (50 nmol/L). Severe deficiency occurs at levels below 10 ng/mL (30 nmol/L). Observational studies have shown that over 40% of Europeans are deficient in vitamin D (36,37). Among older adults, the numbers are even more concerning, with some research indicating that only 15% of the elderly have optimal vitamin D status (38). Inadequate vitamin D levels are associated with muscle weakness, functional impairment, depression, and increased risk of falls and fractures. Risk factors for deficiency include darker skin, limited sun exposure, older age, obesity, and certain medications (39,40). Studies have demonstrated improvements in muscle-related side effects in individuals who supplemented with vitamin D. In a recent study involving patients with SAMS and vitamin D deficiency, vitamin D supplementation was administered over six months. The results showed a 63% reduction in pain intensity, along with improvements in all quality-of-life indicators. Additionally, in the rechallenge subgroup, 75% of patients successfully tolerated high-intensity statins during follow-up (41). Another large study demonstrated that vitamin D supplementation improved statin tolerance in 83.9% of patients across the reported studies, highlighting its potential role in managing statin-associated muscle symptoms (42). There may also be a link between statin lipophilicity and the incidence of statin-induced myopathy in relation to vitamin D levels. Evidence suggests that less lipophilic statins (such as rosuvastatin) may be better tolerated in patients who previously experienced statin-induced myopathy and had low vitamin D levels when re-challenged. Some smaller, short-term studies have shown that more lipophilic statins (such as simvastatin) can increase certain vitamin D metabolites, while less lipophilic statins do not appear to improve vitamin D levels (43). Furthermore, recent studies suggest that atorvastatin and rosuvastatin can increase serum vitamin D concentrations (4). The exact mechanism linking statin-induced myopathy to vitamin D deficiency remains unclear. One plausible explanation is a synergistic effect, where vitamin D deficiency exacerbates myopathy, supported by the pleiotropic effects of statins on skeletal muscle and the role of vitamin D receptors (VDRs) in muscle protein synthesis. Another theory proposes that vitamin D may influence statin metabolism by inducing CYP enzymes, particularly CYP3A4 and CYP2C9, which are activated by vitamin D. Higher vitamin D levels could enhance enzyme activity, leading to faster statin metabolism and reduced bioavailability (4,44,45). Consistent with these proposed biological mechanisms, observational data also suggest a relationship between vitamin D status

and muscle-related outcomes in specific clinical populations. In one observational study involving obese individuals, low vitamin D levels were prevalent regardless of hypertension status; however, a positive association between serum vitamin D concentrations and muscle mass was observed specifically in hypertensive patients. This finding suggests a context-dependent interaction between vitamin D status, muscle composition, and cardiometabolic burden (46).

Although several observational and interventional studies suggest an association between vitamin D deficiency and statin-associated muscle symptoms, there are currently no formal clinical guidelines recommending routine assessment or correction of vitamin D status before initiating statin therapy. Furthermore, vitamin D supplementation is not guideline-recommended for the prevention of statin-associated adverse effects, and its use should be considered on an individual basis, particularly in patients with documented deficiency.

Hypothyroidism significantly affects statin therapy due to its effects on lipid metabolism and the increased risk of adverse drug reactions. In clinical practice, thyroid dysfunction is routinely assessed during the evaluation of hyperlipidemia, as hypothyroidism is a common cause of secondary dyslipidemia and is independently associated with an increased risk of statin-associated muscle symptoms and rhabdomyolysis. Reduced production of thyroid hormones (T3 and T4) in hypothyroidism leads to elevated total cholesterol and LDL-C levels, primarily due to decreased expression of LDL receptors in the liver, which reduces LDL clearance from circulation (47). This impaired lipid metabolism can diminish the efficacy of statin therapy, as statins rely on upregulation of LDL receptors to lower cholesterol levels. Consequently, in patients with untreated or inadequately managed hypothyroidism, higher statin doses may be necessary to achieve therapeutic goals in managing hyperlipidemia (47,48). In addition to reduced efficacy, hypothyroidism increases the risk of statin-induced myopathy and rhabdomyolysis. This elevated risk is attributed to reduced hepatic metabolism of statins in hypothyroid patients, resulting in higher plasma drug concentrations. Studies indicate that hypothyroid individuals are more vulnerable to muscle-related side effects, including myopathy and rhabdomyolysis, even at standard statin doses (3). This increased susceptibility makes it essential to ensure proper thyroid function before initiating or adjusting statin therapy to minimize adverse reactions and optimize treatment outcomes (49).

Coenzyme Q10 (CoQ10) has been proposed as a potential therapeutic agent for managing statin-associated muscle symptoms (SAMS) due to its role in mitochondrial energy production and its depletion caused by statin therapy. Statins inhibit the mevalonate pathway, which not only reduces cholesterol synthesis but also decreases endogenous CoQ10 levels, potentially leading to mitochondrial dysfunction and muscle damage (50). Based on this mechanism, CoQ10 supplementation has been suggested as a strategy to alleviate SAMS. CoQ10 supplementation is hypothesized to restore mitochondrial function by replenishing intracellular CoQ10 levels, improving energy metabolism, and reducing oxidative stress in muscle tissue. Beyond its role in managing SAMS, CoQ10 has shown additional benefits in patients with hyperlipidemia, including improvements in inflammatory markers, lipid profiles, and blood pressure (50,51). In one meta-analysis, CoQ10 supplementation improved statin-associated muscle symptoms, suggesting that CoQ10 may serve as a complementary approach in managing statin-induced myopathy. However, no significant reduction in plasma CK levels was observed following CoQ10 supplementation (52). Despite this, many studies have failed to demonstrate an effect of CoQ10 supplementation on the side effects of statin therapy. In a recent multicenter study, CoQ10 was not significantly associated with the resolution of SAMS (49). In another randomized study, CoQ10 supplementation had no effect on muscle CoQ10 levels or mitochondrial function and did not alleviate myalgia symptoms (53). A previous meta-analysis also found no clear benefit of CoQ10 supplementation for statin-

induced myopathy (43). While some studies suggest potential relief of muscle symptoms, the evidence remains inconsistent. Larger, well-designed trials are needed to confirm its efficacy. Until then, CoQ10 should be used cautiously, recognizing the limitations of existing research.

Conclusion

In summary, statins remain a cornerstone in the management of dyslipidemia, consistently lowering LDL cholesterol and reducing cardiovascular risk. Despite their well-established safety profile, statin-associated muscle symptoms (SAMS) are the most common reason for discontinuing therapy. Although temporary withdrawal and rechallenge are often attempted, many patients do not resume treatment, leading to persistently elevated LDL cholesterol levels and increased cardiovascular risk. Growing evidence supports the role of SLCO1B1, ABCG2, and CYP2C9 polymorphisms in modulating systemic statin exposure and susceptibility to SAMS. As a result, genotype-guided recommendations aim to minimize adverse effects while maintaining therapeutic efficacy (13). Addressing additional modifiable factors, such as thyroid dysfunction and vitamin D deficiency, may further improve statin tolerability and treatment outcomes. Future efforts should prioritize integrating pharmacogenetic testing and individualized risk assessment into clinical practice to achieve an optimal balance between cardiovascular protection and drug safety, paving the way for truly personalized lipid-lowering therapy.

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Genetski polimorfizmi i nuspojave povezane s upotrebom statina: Uloga SLCO1B1 I dodatni čimbenici rizika

Sažetak

Statini su lijekovi prvog izbora u liječenju dislipidemije, s primarnim ciljem sniženja lipoproteina niske gustoće (LDL-kolesterola) i prevencije aterosklerotske kardiovaskularne bolesti (ASCVD). Unatoč dokazanoj učinkovitosti, odgovor na terapiju statinima pokazuje veliku interindividualnu varijabilnost, a dio bolesnika razvija nuspojave poput mišićnih simptoma povezanih sa statinima (SAMS) i hepatotoksičnosti. Takvi učinci dijelom su posljedica genetskih polimorfizama, osobito u genu SLCO1B1, koji kodira organski anionski transportni polipeptid 1B1 (OATP1B1), ključan za unos statina u hepatocite. Polimorfizam SLCO1B1 rs4149056 povezan je sa smanjenom funkcijom transportera, povišenim plazmatskim koncentracijama statina i povećanim rizikom od statinom inducirane miopatije, osobito kod primjene simvastatina. Od negenetskih čimbenika, hipotireoza može pogoršati netoleranciju na statine ometanjem metabolizma lipida i smanjenjem klirensa statina u jetri, što povećava rizik od miopatije i rabdomiolize. Slično tome, nedostatak vitamina D povezan je s većom osjetljivošću na SAMS, budući da vitamin D sudjeluje u funkciji skeletnih mišića i metabolizmu statina putem modulacije CYP enzima. Dodatno, smanjena razina koenzima Q10 (CoQ10), koja nastaje kao posljedica inhibicije mevalonatnog puta tijekom terapije statinima, može pridonijeti mitohondrijskoj disfunkciji i oštećenju mišića.

Uvođenje farmakogenetskog testiranja te prepoznavanje i korekcija promjenjivih čimbenika rizika poput bolesti štitnjače i nedostatka vitamina D moglo bi optimizirati terapiju statinima, smanjiti učestalost nuspojava i smanjiti učestalost nuspojava.

Ključne riječi: inhibitori hidroksimetilglutaril-KoA reduktaze; gen SLCO1B1; hiperkolesterolemija; miopatija izazvana statinima; farmakogenomika