Original article

UDC: 575.2:615.27
doi: 10.5633/amm.2025.0303

IMPACT OF *ABCG2 421 C>A AND SLCO1B1 521T>C* GENE POLYMORPHISM ON THE CONTROL OF LIPID STATUS IN PATIENTS ON ATORVASTATIN AND ROSUVASTATIN TREATMENT

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Single nucleotide polymorphisms (SNPs) of SLCO1B1 gene (521T>C), encoding OATP1B1 transporter, and ABCG2 gene (421C>A), encoding BCRP transporter, may have impact on statin metabolism, consequently affecting their pharmacodynamic effects. This study aimed to examine the association between transporter gene polymorphisms and lipid status control in relation to the doses of statin administered. In addition, the serum activity levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were compared among carriers of different transporter genotypes. This cross-sectional pharmacogenetic study enrolled 102 patients with dyslipidemia who had been on atorvastatin or rosuvastatin treatment for more than 4 weeks. The values of lipid status parameters were collected from routine patient check-ups, and the transporter SNP was determined using the real-time PCR method. The frequencies of the mutant 521C and 421A alleles were 32.35% and 19.61%, respectively. Patients carrying the mutant A allele of ABCG2 421C>A, who were taking higher doses of atorvastatin, had significantly lower LDL-c than patients with the wild-type genotype. In addition, the presence of the variant 521C allele of the SLCO1B1 polymorphism resulted in better control of HDL-c in patients receiving higher doses of rosuvastatin. The obtained results did not show an association between AST and ALT activity and the examined SNPs. Our study demonstrates that the presence of the examined SNPs may be linked to the regulation of specific lipid parameters. Further research with a larger cohort and blood drug concentration measurements of statins is needed to better understand the polymorphism-dose-effect relationship.

Acta Medica Medianae 2025;64(3): 24–33.

Key words: *atorvastatin, rosuvastatin, ABCG2, SLCO1B1, gene polymorphism, lipid status*

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Introduction

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, demonstrate high efficiency in the management of dyslipidemia (1). Enzyme HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis; therefore, its inhibition reduces intracellular cholesterol levels, lowering low-density lipoprotein cholesterol (LDL-c) levels, while potentially increasing high-density lipoprotein cholesterol (HDL-c) levels (2). The beneficial effects of statins on reducing cardiovascular morbidity and mortality are not solely due to their impact on lipid regulation; pleiotropic effects also play a role. These pleiotropic effects contribute to their widespread use in both primary and secondary prevention of cardiovascular events related to atherosclerotic changes in blood vessels (3).

The most commonly prescribed statins in clinical practice are atorvastatin and rosuvastatin. While both drugs are administered in their active acid form, they differ in structure and pharmacokinetic properties. Atorvastatin is a lipophilic drug that undergoes a significant first-pass effect. It is metabolized in the liver by cytochrome P450 (CYP) enzymes, primarily

CYP3A4, and its metabolites are subsequently excreted in the bile (4). In contrast to atorvastatin, rosuvastatin is more hydrophilic and is only partially metabolized by cytochrome P450 enzymes, primarily CYP2C9 and CYP2C19 (5). Apart from CYP isoenzymes, transporters also play a key role in the distribution and elimination of both statins. These include the organic anion-transporting polypeptide (OATP), an influx transporter primarily located on the basolateral membrane of hepatocytes, and the breast cancer resistance protein (BCRP), an efflux transporter found in the liver, intestine, kidney, and other tissues. Their expression is influenced by single nucleotide polymorphisms (SNP), Solute Carrier Organic Anion Transporter Family Member 1B—SLCO1B1 (OATP1B1 transporter) 521T>C (rs41490565) and Adenosine triphosphate (ATP) Binding Cassette G2—ABCG2 (BCRP transporter) 421C>A (rs2231142). In accordance with previous studies, these SNPs may have an impact on statin bioavailability, uptake in the liver and excretion into the bile, consequently affecting the concentration of these drugs in the blood (6–8).

It has been shown that the SLCO1B1 521T>C can lead to increased plasma concentrations of both atorvastatin (a 2.4-fold increase) and rosuvastatin (a 1.7-fold increase) (4). A potential explanation for the influence of this gene polymorphism on statin pharmacokinetics is provided by *in vitro* studies followed by *in vivo* studies (9). It has been shown that the amino acid change from valine to alanine at codon 174, characteristic of the SLCO1B1 521T>C polymorphism, results in decreased function of the OATP1B1 transporter, reduced uptake of statins into liver cells, and consequently, higher drug concentrations in the blood (10). Given the significant frequency of the 521C allele in various populations (9, 11), it is important to examine the frequency of this polymorphism in our study participants and its impact on statin kinetics in order to determine the optimal dosing regimen for effective lipid control. The ABCG2 transporter is a multidrug transporter that handles a wide range of substrates and belongs to a superfamily of 48 human ATP-dependent transporters. It has been found that the ABCG2 rs2231142 variant, located in the nucleotide-binding domain, plays an important role in protein stability (12). The 421C>A results in an amino acid change from glutamine to lysine at codon 141 (Q141K), which is associated with reduced ABCG2 transport activity, either by lowering transporter expression on the plasma membrane or by decreasing its ATPase activity (13). Additionally, researchers found that subjects carrying the variant allele had plasma rosuvastatin levels more than 100% higher than those with the wild-type genotype (1). Given this, it is expected that SNPs in transporter genes may influence the lipid-lowering effects of statins. The aim of this study was to examine the association between transporter gene polymorphisms and lipid status control in relation to the administered doses of atorvastatin or rosuvastatin. Additionally, we compared the serum activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) between carriers of different transporter genotypes.

Materials and Methods

The cross-sectional pharmacogenetic study was conducted from September to November 2024 at the Clinic of Nephrology and the Clinic of Cardiology, University Clinical Centre Niš, and the Research Centre for Biomedicine, Faculty of Medicine, University of Niš, Serbia. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees, as well as the 1964 Helsinki Declaration and its subsequent amendments, or comparable ethical standards. The protocols were approved by the Ethics Committee of the Faculty of Medicine, University of Niš (No 12-8310-1/2-8 from July 10, 2024) and Ethical Committee of the University Clinical Centre Niš (No 17321/2 from June 19, 2024). This study included 102 patients with dyslipidemia who had been on atorvastatin or rosuvastatin treatment for more than 4 weeks. All patients were enrolled in this study during regular controls at the mentioned clinics. Of all recruited patients, data for 93 patients were complete regarding statin dosing regimen and were included in the further study. Inclusion criteria were applied: age (> 18 years), use of a statin (atorvastatin or rosuvastatin), availability of a dosage regimen, and time since the last dose was taken, as well as recent control of lipid status. The values of lipid status parameters, along with other important biochemical markers such as alanine aminotransferase (ALT), aspartate amino-transferase (AST), serum creatinine, urea, and glucose levels, were collected from routine patient check-ups at one of the mentioned clinics. The pharmacodynamic effect of statins was measured in terms of lipid status control. Desired levels of lipid parameters for which it is considered that the control of the lipid status is optimal, according to the reference laboratory values, were as follows: total cholesterol (TC) ≤ 5.2 mmol/l, low-density lipoprotein cholesterol (LDL-c) ≤ 3.4 mmol/l, high-density lipoprotein cholesterol (HDL-c) ≥ 1 mmol/l, and triglycerides (TG) ≤ 1.7 mmo/l.

Genotyping ABCG2 421C>A and SLCO1B1 521T>C Gene Polymorphism

A fasting blood sample was collected from each patient during the routine control at the Clinic of Nephrology and the Clinic of Cardiology, University Clinical Centre Niš. DNA was extracted from the whole blood (200 µL) with EDTA as an anticoagulant using Genomic DNA Purification Kit (Thermo Scientific, Vilnius, Lithuania) according to the manufacturer's instructions. The ABCG2 421C>A (rs2231142) and SLCO1B1 521T>C

(rs4149056) genotyping was performed using TaqMan® Drug Metabolism Genotyping Assays, C_15854163_70 and C__30633906_10, respectively (Applied Biosystems, Carlsbad, CA, USA) on the 7500 Fast Real-Time PCR System (Applied Biosystems), according to the manufacturer's instructions.

Statistical Analysis

The distribution of genotypes for each polymorphism was assessed for deviation from Hardy–Weinberg equilibrium (HWE), given in Figure 1 and Figure 2. Continuous data were expressed as mean with standard deviation and median with interquartile range, and categorical variables were expressed as counts and percentages. Student's t-test (normally distributed data) and Mann–Whitney U test (not normally distributed data) were employed for the comparison of continuous variables between groups. Chi-square ($\chi 2$) test was used to compare data between groups, when data were defined as categorical. All analyses were performed using SPSS statistical analysis software, version 20.0 (SPSS, IBM Corp, Armonk, NY, USA) at the significance level set at $p < 0.05$.

Results

The study included 102 patients with dyslipidemia who were taking atorvastatin (50 of 102 patients) or rosuvastatin (52 of 102 patients). Also, the research population consisted of 41 women (40.2%) and 61 men (59.8%). Baseline characteristics of the patients, along with the genotypic frequencies of the ABCG2 421C>A and SLCO1B1 521T>C gene polymorphisms, are presented in Table 1.

Most common comorbidities among the studied population were ischemic heart disease 59.80% (n = 61), arterial hypertension 55.88% (n = 57), insulin-independent diabetes mellitus 36.27% (n = 37) and renal insufficiency 34.31% (n = 35). It was observed that the frequency of wild-type genotypes was 70.59% (n = 72) and 81.37% (n = 83) for SLCO1B1 521T>C and ABCG2 421C>A gene polymorphism, respectively (Figures 1 and 2).

Table 1. Baseline characteristics and laboratory findings of the examined population

Parameter	Mean ± standard deviation or median (Q1–Q3) or N (%)		
	All patients	Atorvastatin	Rosuvastatin
Male/female	61/41 (59.8/40.2%)	30/20 (60/40%)	31/21 (59.6/40.4%)
Number of patients	102 (100%)	50 (49.02%)	52 (50.98%)
Age	62.4 ± 12.6	63.5 ± 13.56	60.74 ± 11.94
Obesity	20 (19.79%)	11 (22%)	9 (17.31%)
Total Cholesterol (mmol/L)	5.15 ± 1.73 5 (3.81–6.175)	5.00 ± 1.80 5.7 (3.75–5.97)	5.28 ± 1.67 5.15 (3.88–6.34)
High-density lipoprotein cholesterol (mmol/L)	1.25 ± 0.34 1.24 (1–1.47)	1.26 ± 0.36 1.3 (1–1.5)	1.25 ± 0.33 1.25 (1.04–1.44)
Low-density lipoprotein cholesterol (mmol/L)	2.96 ± 1.38 2.66 (1.86–3.79)	2.9 ± 1.49 2.6 (1.84–3.65)	3.02 ± 1.18 2.77 (2.02–3.87)
Triglycerides (mmol/L)	2.09 ± 1.68 1.61 (1.11–2.33)	1.82 ± 1.06 1.53 (1.17–2.25)	2.34 ± 2.1 1.7 (1.09–2.79)
Aspartate aminotransferase (U/L)	46.9 ± 74.08 25 (20–36)	32.91 ± 26.68 25 (20.25–34.5)	61.2 ± 100.41 26 (20–28)
Alanine aminotransferase (U/L)	44.78 ± 77.99 25.5 (19.75–39.25)	34.57 ± 35.00 26 (20–37.5)	54.57 ± 103.26 26 (20–48)
Urea (mmol/L)	10.79 ± 9.21 7.2 (5.35–12.88)	14.36 ± 11.23* 10.85 (6.4–18.7)	7.35 ± 4.71 6.15 (4.83–8.27)
Creatinine (mmol/L)	190.12 ± 222.87 101.3 (81.43–151.25)	276.35 ± 283.01* 141.75 (89.52–360.25)	107.21 ± 84.34 90.65 (75.67–104.17)
Glucose (mmol/L)	7.23 ± 2.81 6.2 (5.3–8.5)	6.77 ± 2.35 5.8 (5.1–8.5)	7.67 ± 3.15 6.5 (5.47–8.5)

SNP— single nucleotide polymorphism; Serum levels of examined parameters are expressed as mean ± standard deviation or median (interquartile range Q1–Q3)
* atorvastatin vs. rosuvastatin, $p < 0.001$

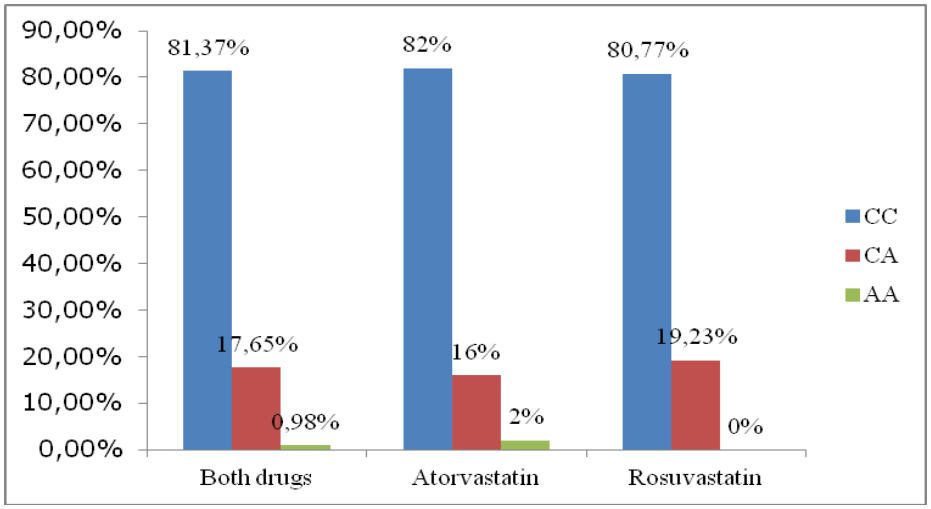

Figure 1. Frequency of ABCG2 421C>A genotypes among studied population (n = 102)
HWE: χ^2 = 0.0005, p = 0.98 (p > 0.05)

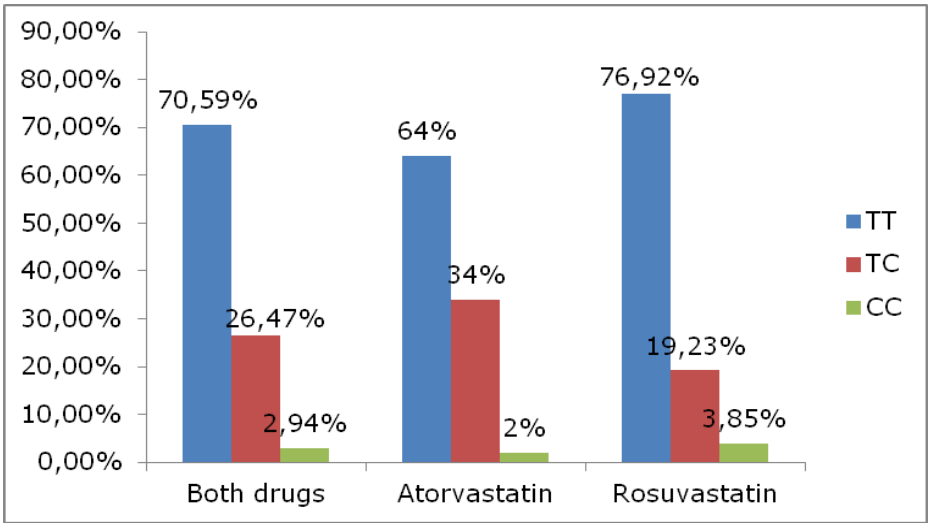

Figure 2. Frequency of SLCO1B1 521T>C genotypes among studied population (n = 102)
HWE: χ^2 = 0.0584, p = 0.81 (p > 0.05)

The frequency of mutant 521C and 421A alleles was 32.35% and 19.61%, respectively. Mean values with standard deviation, as well as median and interquartile range of lipid parameters, are given in Table 1. Serum values of examined biochemical parameters: ALT, AST, creatinine and urea, in some patients showed a drastic deviation, which affected the mean value and standard deviation. For this reason, the median and interquartile difference are more accurate and precise indicators of the value of these parameters in the studied population. Serum creatinine and urea levels were significantly elevated in patients undergoing atorvastatin therapy. This finding can be attributed to the fact that patients receiving atorvastatin were predominantly recruited from the Nephrology Clinic, where the majority of individuals have pre-existing or existing kidney conditions. Consequently, the observed differences in these parameters were anticipated. Atorvastatin was more commonly used in patients with impaired kidney function because the drug is primarily eliminated by metabolism. In addition, differences in serum levels of AST and ALT were examined among the different genotypes of the studied polymorphisms (Table 2). Carriers of the mutant 421A allele exhibited nearly significant (p = 0.082) higher serum AST levels compared to individuals with the wild-type genotype.

Patients were divided into two groups based on the median dose taken which was 20 mg for both atorvastatin and rosuvastatin. Patients who were taking lower doses—5, 10 or 20 mg of

atorvastatin or rosuvastatin, were selected in group I. The II group included patients with 40 or 80 mg atorvastatin or 40 mg rosuvastatin prescribed. Lipid parameters of each patient were considered according to the reference values of each of the investigated parameters individually and expressed as controlled and uncontrolled lipid parameter status (Table 3). Table 3 shows the number of patients with controlled and uncontrolled parameters of lipid status, divided according to dosage regimen (group I and II as previously explained) and according to ABCG2 C>A and SLCO1B1 521T>C genotype.

It was noticed that patients who were carriers of the mutant A allele of ABCG2 C>A in group II had significantly lower LDL-c than patients with the wild-type genotype. This indicates that the presence of the ABCG2 gene polymorphism affected the pharmacodynamic effects of atorvastatin on LDL-c lowering in patients who were taking higher doses. None of the patients carrying the A allele had an uncontrolled lipid status, which indicates greater efficacy of atorvastatin in these patients. There were no significant differences in other parameter values between the other groups of examined gene polymorphisms in patients taking atorvastatin.

Table 4 is structured in the same way as Table 3, with data for rosuvastatin provided. Patients with higher doses of rosuvastatin and the TC/CC SLCO1B1 521T>C genotypes had better-controlled HDL-c (values > 1 mmol/L) compared to patients in the same dosage group with the TT genotype. This suggests increased efficacy of rosuvastatin in patients carrying the C allele, particularly those on higher doses, in terms of elevating HDL-cholesterol plasma levels. No significant differences were observed between the other groups of examined gene polymorphisms in patients taking rosuvastatin.

Table 2. A comparison of groups stratified based on genetic polymorphisms regarding the values of AST and ALT

Gene polymorphism	Genotype	AST	ALT
ABCG2 421C>A	CC	24 (20–36)	25 (19–34)
	CA/AA	30.5 (22.75–86.25)	27.5 (20.25–61.75)
Statistics		Z = -1.737, p = 0.082	Z = -0.550, p = 0.583
SLCO1B1 521T>C	TT	24.5 (20–37.75)	24.5 (18.75–36)
	TC/CC	26 921.5–34)	26 (21–42)
Statistics		Z= -0.678, p = 0.498	Z = 0.583, p = 0.560

AST— aspartate aminotransferase (U/L); ALT— alanine aminotransferase (U/L)
Values are expressed as median with interquartile range (Q1– Q3)

Table 3. Patients taking **atorvastatin**— comparison of groups according to the control of lipid status (controlled/uncontrolled parameter) in relation to the dose of atorvastatin and the investigated gene polymorphism

		ABCG			SLCO1B1		
		CC	CA/AA	Statistics	TT	TC/CC	Statistics
TC	I group	13/8	3/1	χ^2 = 0.250, p = 0.617	12/7	4/2	χ^2 = 0.024, p = 0.876
	II group	6/14	3/2	χ^2 = 1.563, p = 0.211	8/12	1/4	χ^2 = 0.694, p = 0.405
LDL-c	I group	15/6	3/1	χ^2 = 0.021, p = 0.884	13/6	5/1	χ^2 = 0.503, p = 0.478
	II group	7/13	5/0	**χ^2 = 6.771, p = 0.009**	10/10	2/3	χ^2 = 0.160, p = 0.689
HDL-c	I group	18/3	3/1	χ^2 = 0.287, p = 0.592	17/2	4/2	χ^2 = 1.765, p = 0.184
	II group	16/4	3/2	χ^2 = 0.877, p = 0.349	15/5	4/1	χ^2 = 0.055, p = 0.815
TG	I group	11/10	2/2	χ^2 = 0.008, p = 0.930	10/9	3/3	χ^2 = 0.013, p = 0.910
	II group	10/10	2/3	χ^2 = 0.160, p = 0.689	10/10	2/3	χ^2 = 0.160, p = 0.689

I group—patients taking lower doses of atorvastatin (5 mg, 10 mg, 20 mg); II group—patients taking higher doses of atorvastatin (40 mg, 80 mg) TC: total cholesterol, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol; TG: triglycerides; ABCG2 SNP: Adenosine triphosphate (ATP)-binding cassette transporter single nucleotide polymorphism; SLCO1B1: Solute carrier organic anion transporter family member 1B1 single nucleotide polymorphism. Results are expressed as the total number of patients who had controlled lipid status (TC ≤ 5.2 mmol/l, LDL-c ≤ 3.4 mmol/l, HDL ≥ 1 mmol/l, TG ≤ 1.7 mmol/l) and uncontrolled lipid status (TC > 5.2 mmol/l, LDL-c > 3.4 mmol/l, HDL < 1 mmol/l, TG > 1.7 mmol/l)

Table 4. Patients taking **rosuvastatin**—comparison of groups according to the control of lipid status (controlled/uncontrolled parameter) in relation to the dose of atorvastatin and the investigated gene polymorphism

		ABCG2			SLCO1B1		
		CC	CA / AA	Statistics	TT	TC / CC	Statistics
TC	I group	12/12	3/2	χ^2 = 0.166, p = 0.684	8/9	7/5	χ^2 = 0.358, p = 0.550
	II group	8/4	2/0	χ^2 = 0.933, p = 0.334	8/2	2/2	χ^2 = 1.260, p = 0.262
LDL-c	I group	15/9	3/2	χ^2 = 0.011,p = 0.917	11/6	7/5	χ^2 = 0.121, p = 0.728
	II group	9/3	2/0	χ^2 = 0.636, p = 0.425	9/1	2/2	χ^2 = 2.715,p = 0.099
HDL-c	I group	22/2	3/2	χ^2 = 3.490, p = 0.062	16/1	9/3	χ^2 = 2.162, p = 0.141
	II group	7/5	1/1	χ^2 = 0.049, p = 0.825	4/6	4/0	**χ^2 = 4.200, p = 0.040**
TG	I group	16/8	2/3	χ^2 = 1.250, p = 0.264	10/7	8/4	χ^2 = 0-184, p = 0.668
	II group	4/8	1/1	χ^2 = 0.207, p = 0.649	4/6	1/3	χ^2 = 0.280, p = 0.597

I group—patients taking lower doses of rosuvastatin (5 mg, 10 mg, 20 mg)**;** II group—patients taking a higher dose of rosuvastatin (40 mg) TC: total cholesterol, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol; TG: triglycerides; ABCG2 SNP: Adenosine triphosphate (ATP)-binding cassette transporter single nucleotide polymorphism; SLCO1B1: Solute carrier organic anion transporter family member 1B1 single nucleotide polymorphism. Results are expressed as the total number of patients who had controlled lipid status (TC ≤ 5.2 mmol/l, LDL-c ≤ 3.4 mmol/l, HDL ≥ 1 mmol/l, TG ≤ 1.7 mmol/l) and uncontrolled lipid status (TC > 5.2 mmol/l, LDL-c > 3.4 mmol/l, HDL < 1 mmol/l, TG > 1.7 mmol/l)

Discussion

Pharmacogenetic testing has expanded in recent years and plays a crucial role in personalized medicine. Personalized medicine was initially intended to be implemented in clinical practice for drugs with a narrow therapeutic index and/or potentially severe side effects (14). However, even for drugs with a wide therapeutic range, pharmacogenetic testing can be important for adjusting doses and avoiding side effects, thereby improving patient compliance and enhancing the effectiveness of therapy. It has already been mentioned that, in addition to CYP enzymes, efflux and influx transporters in the liver may play an important role in exposure to statins. Although various studies have investigated different genes encoding transporters, not all gene polymorphisms have been shown to affect the expression and/or function of transporters, or these polymorphisms may not be present in the population at a frequency sufficient to monitor their effects (15, 16).

Several studies have revealed that the gene polymorphisms ABCG2 421C>A and SLCO1B1 521T>C impact the systemic exposure of atorvastatin and rosuvastatin (17–20). Therefore, it is not surprising that the 2022 updated guidelines of the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend SLCO1B1 and ABCG2 genotyping, given their strong association with increased systemic exposure to statins (21).

The frequency of minor alleles of examined genes varied among different populations. Tomilson et al. found that the frequency of the 421A variant allele among Asian patients with hypercholesterolemia was 30.5%, which is a higher frequency than in our studied population (19.61%). A slightly higher frequency of the mutant Aallele is also present in the population of Mexicans compared to ours, about 25% (22). On the other hand, the ABCG2 421A variant was found to have the lowest frequency in African populations, ranging from 0% to 5% (23). On the other hand, variant ABCG2 421A had the lowest frequency in African populations, 0–5%. The African population has also been shown to have a low frequency of the SLCO1B1 521C variant allele, ranging from 0% to 7%. A study conducted in the Netherlands had comparable SLCO1B1 521C variant frequency (30.57%) with our results, 32.35% (24).

The impact of the ABCG2 421C>A gene polymorphism has already been mentioned for reducing transporter activity in A allele carriers. Lower efflux transporter activity leads to increased statin absorption in the gastrointestinal tract while reducing drug elimination via the hepatobiliary pathway. Increased absorption and reduced elimination of statins can lead to higher concentrations of the drug in the blood, thereby enhancing its effect. However, it is important to consider that higher drug concentrations in the blood may increase the risk of statin-related side effects. The results of our study indicate a near-significant difference in serum AST levels between the different genotypes of the ABCG2 421C>A polymorphism. It has been suggested that individuals carrying the mutant A allele may have

an increased likelihood of experiencing statin-induced liver toxicity (25). During the first months of statin therapy, a temporary increase in transaminase levels (AST, ALT) can occur. Aminotransferase changes have been observed as early as a few hours after initial statin exposure, extending up to eight months following treatment initiation (26). However, only 3% of patients experience a permanent rise in these enzyme activities (27). Elevated transaminase levels are more common in patients taking higher doses of statins (28). According to current guidelines, statin use does not need to be discontinued if aminotransferase levels increase by ≤ 3 UNL (upper normal limit), but it is recommended to stop statin therapy if levels exceed 3 UNL (29). The temporary increase in liver transaminases may be due to changes in the lipid membranes of liver cells, which increase permeability and cause enzyme leakage. These changes in enzyme levels are considered adaptive, rather than a sign of liver damage (26). Reduced activity of the ABCG2 transporter causes statins to accumulate in liver cells, potentially affecting cell membranes. This may explain why transaminase levels are higher in patients with the 421AA/421CA genotype.

A large study published in September 2024, which enrolled 139,508 Taiwanese participants, found that individuals with the ABCG2 rs2231142 AA genotype had higher HDL-c and lower triglyceride (TG) levels, but no difference in LDL-c levels was observed (30). This study indicates a better lipid profile in AA genotype carriers, primarily reflected in a decrease in TG and an increase in HDL-c, though these changes were not statistically significant in our study. These results highlight the importance of clearly determining the effect of this gene polymorphism on each lipid parameter.

Although most research has focused on the impact of ABCG2 polymorphism on statin metabolism, it is noteworthy that statin therapy also affects the expression of the ABCG2 transporter. Rodrigues et al. investigated baseline mRNA expression levels of ABC and SLCO transporters in peripheral blood mononuclear cells. They reported that atorvastatin treatment significantly downregulated the gene expression of these influx and efflux transporters (31).

The Rotterdam study investigated the impact of SLCO1B1 521T>C and found that patients taking atorvastatin at a starting dose greater than 20 mg had a higher risk of dose reduction or switch if they carried the C allele, compared to those with the TT genotype (24). Although this was not the primary objective of the trial, these results are comparable to those in our group II, where patients also used atorvastatin doses greater than 20 mg and showed a greater reduction in LDL cholesterol. This suggests that higher doses of atorvastatin are more effective in C allele carriers.

Regarding the influence of this polymorphism on the pharmacodynamic effect of rosuvastatin, some studies (20, 32) have shown that the presence of the 521C allele negatively affects the control of LDL cholesterol reduction. It is important to highlight that carriers of the TT genotype had lower drug concentrations in plasma, which correlated with a reduced incidence of side effects. In contrast, carriers of the CC genotype, despite having higher drug concentrations, exhibited poorer control of lipid levels. Therefore, it is essential to better understand the relationship between gene polymorphisms, plasma drug concentrations, and pharmacodynamic effects.

Our study indicated that higher doses of atorvastatin or rosuvastatin in patients with the variant allele had improved response to statin therapy. This is reflected by a more significant reduction in LDL-c and an increase in HDL-c. However, a statistically significant difference was observed only in the better control of LDL-c in patients with the variant 421A allele of the ABCG2 polymorphism on atorvastatin therapy, and in better control of HDL-c in patients with the variant C521C allele of the SLCO1B1 polymorphism during rosuvastatin treatment. It remains unclear why the polymorphisms affect only some lipid parameters, while no statistically significant differences were observed for others. A potential explanation could be that statins exert cholesterol-lowering effects by inhibiting HMG-CoA reductase in hepatocytes. Therefore, when uptake from the blood into the liver is reduced due to the SLCO1B1 c.521T>C variant, it may be associated with reduced pharmacological efficacy. On the other hand, increased systemic exposure may increase the risk of enhanced side effects, which were not specifically investigated in this study but should be considered in future research. It is also important to note that some of the patients enrolled in the study had chronic kidney disease. The data suggest that lowering LDL cholesterol helps prevent major heart-related events in patients with chronic kidney disease and kidney transplant recipients (33). On the other hand, it must be mentioned that patients with chronic kidney disease require careful attention. Chronic kidney disease is a common risk factor for the development of statin-induced myopathy. The risk of this complication increases when other significant factors, such as advanced age, female gender, liver dysfunction, and diabetes mellitus, are present (34).

Some limitations of the study need to be mentioned, in the first row, the small number of patients enrolled in the study. Further research involving a larger cohort of patients is needed, with a more detailed and precise stratification by dosage. In addition, it is important to have measured drug concentrations in the blood, which would provide a more comprehensive understanding of the polymorphism-dose-effect relationship. This study serves as a foundation for future investigations into the pharmacokinetics and pharmacodynamics of rosuvastatin and atorvastatin.

Conclusion

In conclusion, examining the influence of ABCG2 and SLCO1B1 gene polymorphisms on lipid control in relation to the administered statin dose, statistically significant differences were observed in some lipid parameters among patients with polymorphic alleles. These findings could serve as a basis for adjusting statin doses based on the presence of specific polymorphisms. However, more extensive research is needed to provide a clearer understanding of how transporter gene polymorphisms affect individual lipid parameters.

Acknowledgments

The authors would like to thank the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grant No: 451-03-137/2025-03/200113 and Grant No: 451-03-136/2025-03/200113).

References

1. Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, Niemi M. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2009;86(2):197-203. [CrossRef][PubMed]
2. Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol 2020;16(9):809-22. [CrossRef][PubMed]
3. Oesterle A, Liao JK. The Pleiotropic Effects of Statins - From Coronary Artery Disease and Stroke to Atrial Fibrillation and Ventricular Tachyarrhythmia. Curr Vasc Pharmacol 2019;17(3):222-32. [CrossRef][PubMed]
4. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82(6):726-33. [CrossRef][PubMed]
5. Silveira AMR, Duarte GHB, Fernandes AMAP, Garcia PHD, Vieira NR, Antonio MA et al. Serum Predose Metabolic Profiling for Prediction of Rosuvastatin Pharmacokinetic Parameters in Healthy Volunteers. Front Pharmacol 2021;12:752960. [CrossRef][PubMed]
6. DeGorter MK, Tirona RG, Schwarz UI, Choi YH, Dresser GK, Suskin N, et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. Circ Cardiovasc Genet 2013;6(4):400-8. [CrossRef][PubMed]
7. Lee HK, Hu M, Lui SSh, Ho CS, Wong CK, Tomlinson B. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. Pharmacogenomics 2013;14(11):1283-94. [CrossRef][PubMed]
8. Guan ZW, Wu KR, Li R, Yin Y, Li XL, Zhang SF, et al. Pharmacogenetics of statins treatment: Efficacy and safety. J Clin Pharm Ther 2019;44(6):858-67. [CrossRef][PubMed]
9. Romaine SP, Bailey KM, Hall AS, Balmforth AJ. The influence of SLCO1B1 (OATP1B1) gene polymorphisms on response to statin therapy. Pharmacogenomics J 2010;10(1):1-11. [CrossRef][PubMed]
10. Ieiri I, Higuchi S, Sugiyama Y. Genetic polymorphisms of uptake (OATP1B1, 1B3) and efflux (MRP2, BCRP) transporters: implications for inter-individual differences in the pharmacokinetics and pharmacodynamics of statins and other clinically relevant drugs. Expert Opin Drug Metab Toxicol 2009;5(7):703-29. [CrossRef][PubMed]
11. Sychev DA, Shuev GN, Chertovskih JV, Maksimova NR, Grachev AV, Syrkova OA. The frequency of SLCO1B1*5 polymorphism genotypes among Russian and Sakha (Yakutia) patients with hypercholesterolemia. Pharmgenomics Pers Med 2016;9:59-63. [CrossRef][PubMed]
12. Cleophas MC, Joosten LA, Stamp LK, Dalbeth N, Woodward OM, Merriman TR. ABCG2 polymorphisms in gout: insights into disease susceptibility and treatment approaches. Pharmgenomics Pers Med 2017;10:129-42. [CrossRef][PubMed]
13. Morisaki K, Robey RW, Ozvegy-Laczka C, Honjo Y, Polgar O, Steadman K, et al. Single nucleotide polymorphisms modify the transporter activity of ABCG2. Cancer Chemother Pharmacol 2005;56(2):161-72. [CrossRef][PubMed]
14. Sainz de Medrano Sainz JI, Brunet Serra M. Influence of pharmacogenetics on the diversity of response to statins associated with adverse drug reactions. Adv Lab Med 2023;4(4):341-52. [CrossRef][PubMed]
15. Lehtisalo M, Taskinen S, Tarkiainen EK, Neuvonen M, Viinamäki J, Paile-Hyvärinen M, et al. A comprehensive pharmacogenomic study indicates roles for SLCO1B1, ABCG2 and SLCO2B1 in rosuvastatin pharmacokinetics. Br J Clin Pharmacol 2023;89(1):242-52. [CrossRef][PubMed]
16. Choi HY, Bae KS, Cho SH, Ghim JL, Choe S, Jung JA, et al. Impact of CYP2D6, CYP3A5, CYP2C19, CYP2A6, SLCO1B1, ABCB1, and ABCG2 gene polymorphisms on the pharmacokinetics of

simvastatin and simvastatin acid. Pharmacogenet Genomics 2015;25(12):595-608. [CrossRef][PubMed]
17. Zhang D, Ding Y, Wang X, Xin W, Du W, Chen W, et al. Effects of ABCG2 and SLCO1B1 gene variants on inflammation markers in patients with hypercholesterolemia and diabetes mellitus treated with rosuvastatin. Eur J Clin Pharmacol 2020;76(7):939-46. [CrossRef][PubMed]
18. Liu Y, Chen Y, Wei B, Li H, Peng Y, Luo Z. Impacts of ABCG2 loss of function variant (p. Gln141Lys, c.421 C > A, rs2231142) on lipid levels and statin efficiency: a systematic review and meta-analysis. BMC Cardiovasc Disord 2024;24(1):202. [CrossRef][PubMed]
19. Tomlinson B, Hu M, Lee VW, Lui SS, Chu TT, Poon EW, et al. ABCG2 polymorphism is associated with the low-density lipoprotein cholesterol response to rosuvastatin. Clin Pharmacol Ther 2010;87(5):558-62. [CrossRef][PubMed]
20. Tachibana-Iimori R, Tabara Y, Kusuhara H, Kohara K, Kawamoto R, Nakura J, et al. Effect of genetic polymorphism of OATP-C (SLCO1B1) on lipid-lowering response to HMG-CoA reductase inhibitors. Drug Metab Pharmacokinet 2004;19(5):375-80. [CrossRef][PubMed]
21. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022;111:1007–21. [CrossRef][PubMed]
22. Vargas-Morales JM, Guevara-Cruz M, Aradillas-García C, G Noriega L, Tovar A, Alegría-Torres JA. Polymorphisms of the genes ABCG2, SLC22A12 and XDH and their relation with hyperuricemia and hypercholesterolemia in Mexican young adults. F1000Res 2021;10:217. [CrossRef][PubMed]
23. Soko ND, Chimusa E, Masimirembwa C, Dandara C. An African-specific profile of pharmacogene variants for rosuvastatin plasma variability: limited role for SLCO1B1 c.521T>C and ABCG2 c.421A>C. Pharmacogenomics J 2019;19(3):240-48. [CrossRef][PubMed]
24. de Keyser CE, Peters BJ, Becker ML, Visser LE, Uitterlinden AG, Klungel OH, et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24(1):43-51. [CrossRef][PubMed]
25. Choi SA, Kim JS, Park YA, Lee DH, Park M, Yee J, et al. Transporter Genes and statin-induced Hepatotoxicity. Cardiovasc Drugs Ther 2025;39(4):801-810. [CrossRef][PubMed]
26. Averbukh LD, Turshudzhyan A, Wu DC, Wu GY. Statin-induced Liver Injury Patterns: A Clinical Review. J Clin Transl Hepatol 2022;10(3):543-52. [CrossRef][PubMed]
27. Bhardwaj SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. Clin Liver Dis 2007;11(7):597–613. [CrossRef][PubMed]
28. Villani R, Navarese EP, Cavallone F, Kubica J, Bellanti F, Facciorusso A, et al. Risk of Statin-Induced Hypertransaminasemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Mayo Clin Proc Innov Qual Outcomes 2019;3(2):131-40. [CrossRef][PubMed]
29. Kim HS, Lee SH, Kim H, Lee SH, Cho JH, Lee H, et al. Statin-related aminotransferase elevation according to baseline aminotransferases level in real practice in Korea. J Clin Pharm Ther 2016;41(3):266-72. [CrossRef][PubMed]
30. Lee CK, Chen IC, Lin HJ, Lin CH, Chen YM. Association of the ABCG2 rs2231142 variant with the Framingham Cardiovascular Disease Risk score in the Taiwanese population. Heliyon 2024;10(18):e37839. [CrossRef][PubMed]
31. Rodrigues AC, Hirata MH, Hirata RD. Impact of cholesterol on ABC and SLC transporters expression and function and its role in disposition variability to lipid-lowering drugs. Pharmacogenomics 2009;10(6):1007-16. [CrossRef][PubMed]
32. Zakria M, Hussain A, Ahmad N, Ahmed N, Rauf MA, Siraj S. The lipid-lowering efficacy of rosuvastatin is associated with variations in SLCO1B1: a 12-month prospective cohort study. Eur Rev Med Pharmacol Sci 2023;27(10):4708-17. [CrossRef][PubMed]
33. Ferro CJ, Mark PB, Kanbay M, Sarafidis P, Heine GH, Rossignol P, et al. Lipid management in patients with chronic kidney disease. Nat Rev Nephrol 2018;14(12):727-49. [CrossRef][PubMed]
34. Verdoodt A, Honore PM, Jacobs R, De Waele E, Van Gorp V, De Regt J, et al. Do Statins Induce or Protect from Acute Kidney Injury and Chronic Kidney Disease: An Update Review in 2018. J Transl Int Med 2018;6(1):21-5. [CrossRef][PubMed]

Originalni rad **UDC: 575.2:615.27**
doi: 10.5633/amm.2025.0303

UTICAJ *ABCG2 421 C>A I SLCO1B1 521T>C* GENSKOG POLIMORFIZMA NA KONTROLU LIPIDNOG STATUSA BOLESNIKA LEČENIH ATORVASTATINOM I ROSUVASTATINOM

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Polimorfizmi gena za transportere lekova SLCO1B1 (OATP1B1 transporter) 521T>C i ABCG2 421C>A (BCRP transporter) mogu imati uticaja na metabolizam statina i, posledično, na farmakodinamičke efekte ovih lekova. Cilj ove studije bio je da se ispita povezanost između genskih polimorfizama za transportere lekova i kontrole lipidnog statusa kod bolesnika u čijem su lečenju korišćene različite doze statina. Dodatno, poredili smo serumsku aktivnost aspartat aminotransferaze (engl. aspartate aminotransferase – AST) i alanin aminotransferaze (engl. *alanine aminotransferase* – ALT) kod nosilaca različitih genotipova ispitivanih polimorfizama. Farmakogenetička studija preseka obuhvatila je sto dva bolesnika sa dislipidemijom koji su bili na terapiji atorvastatinom ili rosuvastatinom najmanje četiri nedelje. Vrednosti lipidnih parametara prikupljene su prilikom rutinske kontrole bolesnika. Za ispitivanje genskih polimorfizama korišćena je metoda *Real-Time* PCR. Frekvencije mutiranih alela 521C i 421A bile su 32,35% i 19,61%, redom. Pokazalo se da bolesnici koji su nosioci mutiranog A-alela ABCG2 421C>A i koji uzimaju više doze atorvastatina imaju statistički značajno niže vrednosti LDL holesterola od bolesnika koji imaju *wild type* genotip. Osim toga, prisustvo varijantnog 521C alela SLCO1B1 polimorfizma uticalo je na bolju kontrolu serumskih vrednosti HDL holesterola kod bolesnika koji uzimaju veće doze rosuvastatina. Dobijeni rezultati nisu pokazali statistički značajnu povezanost između aktivnosti AST-a i ALT-a i ispitivanih genskih polimorfizama. Studija je pokazala da prisustvo ispitivanih genskih polimorfizama može biti povezano s kontrolom određenih "parametara lipida". Neophodna su dalja istraživanja na većem broju ispitanika. Takođe, poželjno je određivanje koncentracije leka u krvi da bi se dobila potpunija slika o vezi između genskih polimorfizama, doze i efekta statina.

Acta Medica Medianae 2025; 64(3): 24–33.

***Ključne reči**: atorvastatin, rosuvastatin, ABCG2, SLCO1B1, genski polimorfizmi, lipidni status*