

Original article

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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 (SNP) 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. The aim of this study was to examine the association between transporter gene polymorphisms and lipid status control in relation to the doses of statin administered. Also, we compared the serum activity of AST and ALT between carriers of different transporter genotypes. The 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 transporter SNP was determined using Real-Time PCR method. Frequency of mutant 521C and 421A allele was 32.35% and 19.61%, respectively. It was noticed that patients who are carriers of mutant A-allele of *ABCG2* 421C>A and taking higher doses of atorvastatin had significantly lower LDL-c than patients with wild-type genotype. In addition, presence of the variant 521C allele of the *SLCO1B1* polymorphism resulted in better control of HDL-c in patients with higher dosage during rosuvastatin treatment. The obtained results did not show association between AST and ALT activity and 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.

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

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. Theirs 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. Also, we compared the serum activity of AST and ALT between carriers of different transporter genotypes.

Patients 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 Nis (No 12-8310-1/2-8 from 10.07.2024.) and Ethical Committee of the University Clinical Center Nis (No 17321/2 from 19.06.2024.). 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), used drug (atorvastatin or rosuvastatin), availability of dosage regimen and time since last dose taken and recent control of lipid status. The values of lipid status parameters, along with other important biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, urea, and glucose levels, were collected from routine patient check-ups at one of the mentioned clinics. 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, Triglycerides (TG) ≤ 1.7 mmol/l.

Genotyping ABCG2 421C>A and SLC01B1 521T>C gene polymorphism

A fasting blood sample was collected from each patient during the routine control at one of the Clinics. DNA was extracted from the whole blood (200 μ L) 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) for and SLC01B1 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) Mann-Whitney U test (not normally distributed data) was employed for the comparison of continuous variables between groups. Chi-square (χ^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 are 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.

Table 1. Baseline characteristics and laboratory findings of 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, $p < 0.001$

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 SLC01B1 521T>C and ABCG2 421C>A gene polymorphism, respectively (Figure 1, Figure 2).

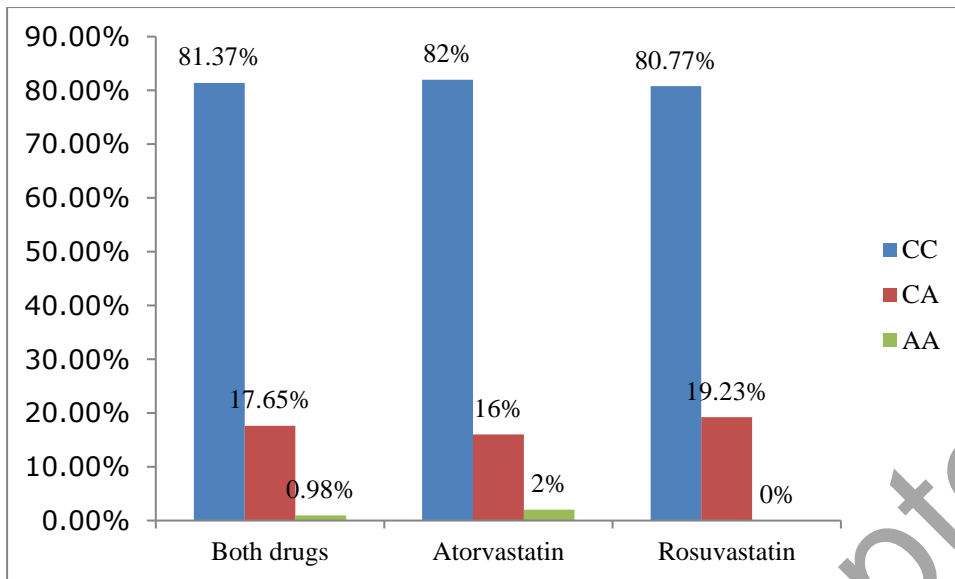


Figure 1. Frequency of ABCG2 421C>A genotypes among studied population (n=102)
HWE: $\chi^2=0.0005$, $p=0.98$ ($p>0.05$)

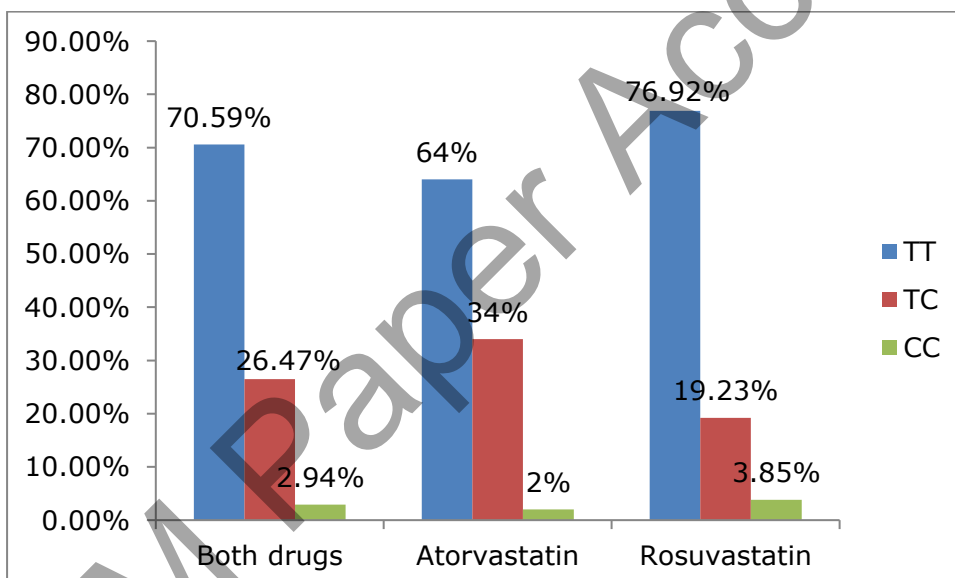


Figure 2. Frequency of SLCO1B1 521T>C genotypes among studied population (n=102)
HWE: $\chi^2=0.0584$, $p=0.81$ ($p>0.05$)

Frequency of mutant 521C and 421A allele was 32.35% and 19.61%, respectively. Mean values with standard deviation, so 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 are 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.

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)

Patients were divided into two groups according to the median of taken dose (median for atorvastatin was 20mg, so as for rosuvastatin). Patients who were taking lower doses - 5, 10 or 20mg of atorvastatin, such as 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 are carriers of mutant A-allele of ABCG2 C>A in group II had significantly lower LDL-c than patients with wild-type genotype. This indicates

that presence of ABCG2 gene polymorphism affects pharmacodynamic effects of atorvastatin on LDL-c lowering in patients who are taking higher doses. None of patients carrying the A-allele had 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 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

		ABCG2			SLCO1B1		
		CC	CA AA	Statistics	TT	TC CC	Statistics
TC	I group	13/8	3/1	$\chi^2=0.250, p=0.617$	12/7	4/2	$\chi^2=0.024, p=0.876$
	II group	6/14	3/2	$\chi^2=1.563, p=0.211$	8/12	1/4	$\chi^2=0.694, p=0.405$
LDL-c	I group	15/6	3/1	$\chi^2=0.021, p=0.884$	13/6	5/1	$\chi^2=0.503, p=0.478$
	II group	7/13	5/0	$\chi^2=6.771, p=0.009$	10/10	2/3	$\chi^2=0.160, p=0.689$
HDL-c	I group	18/3	3/1	$\chi^2=0.287, p=0.592$	17/2	4/2	$\chi^2=1.765, p=0.184$
	II group	16/4	3/2	$\chi^2=0.877, p=0.349$	15/5	4/1	$\chi^2=0.055, p=0.815$
TG	I group	11/10	2/2	$\chi^2=0.008, p=0.930$	10/9	3/3	$\chi^2=0.013, p=0.910$
	II group	10/10	2/3	$\chi^2=0.160, p=0.689$	10/10	2/3	$\chi^2=0.160, p=0.689$

I group - patients who are taking lower dose of atorvastatin (5 mg, 10mg, 20mg); II group - patients who are taking higher dose of atorvastatin (40 mg, 80mg)

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 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 was 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 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	$\chi^2=0.166$, $p=0.684$	8/9	7/5	$\chi^2=0.358$, $p=0.550$
	II group	8/4	2/0	$\chi^2=0.933$, $p=0.334$	8/2	2/2	$\chi^2=1.260$, $p=0.262$
LDL-c	I group	15/9	3/2	$\chi^2=0.011$, $p=0.917$	11/6	7/5	$\chi^2=0.121$, $p=0.728$
	II group	9/3	2/0	$\chi^2=0.636$, $p=0.425$	9/1	2/2	$\chi^2=2.715$, $p=0.099$
HDL-c	I group	22/2	3/2	$\chi^2=3.490$, $p=0.062$	16/1	9/3	$\chi^2=2.162$, $p=0.141$
	II group	7/5	1/1	$\chi^2=0.049$, $p=0.825$	4/6	4/0	$\chi^2=4.200$, $p=0.040$
TG	I group	16/8	2/3	$\chi^2=1.250$, $p=0.264$	10/7	8/4	$\chi^2=0.184$, $p=0.668$
	II group	4/8	1/1	$\chi^2=0.207$, $p=0.649$	4/6	1/3	$\chi^2=0.280$, $p=0.597$

I group - patients who are taking lower dose of rosuvastatin (5 mg, 10mg, 20mg); II group - patients who are taking 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 total number of patients who had controlled lipid status ($TC \leq 5.2$ mmol/l, $LDL-c \leq 3.4$ mmol/l, $HDL \geq 1$ mmol/l, $TG \leq 1.7$ 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).

Frequency of minor alleles of examined genes varied among different populations. Tomilson et al. found that the frequency of 421A variant allele among Asians patients with hypercholesterolemia was 30.5%, which is higher frequency than in our studied population (19.61%). A slightly higher frequency of the mutant A allele is also present in the population of Mexicians 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 been shown to also have a low frequency of SLCO1B1 521C variant allele, ranging from 0 to 7%. Study conducted in the Netherlands had comparable SLCO1B1 521C variant frequency (30.57%) with our results, 32.35% (24).

The impact of ABCG2 421C>A gene polymorphism is already 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 activity (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 increases permeability and causes 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 and 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 on 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.

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.

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Uticaj *ABCG2* 421 C>A i *SLCO1B1* 521T>C genskog polimorfizma na kontrolu lipidnog statusa kod pacijenata na terapiji 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 uticaj na metabolizam statina i posledično na farmakodinamske efekte ovih lekova. Cilj ove studije bio je ispitivanje povezanosti između genetskih polimorfizama za transportere i kontrole lipidnog statusa kod pacijenata na terapiji različitim dozama statina. Dodatno, poredili smo serumsku aktivnost AST i ALT kod nosioca različitih genotipova ispitivanih polimorfizama. Farmakogenetska studija preseka obuhvatila je 102 pacijenta sa dislipidemijom, koji su bili najmanje 4 nedelje na terapiji atorvastatinom ili rosuvastatinom. Vrednosti lipidnih parametara prikupljene su tokom rutinske kontrole pacijenata. Ispitivanje genetskih polimorfizama vršeno je primenom *Real-Time PCR* metode. Frekvencije mutiranih alela 521C i 421A bile su 32.35% i 19.61%, redom. Pokazano je da pacijenti koji su nosioci mutiranog A alela ABCG2 421C>A, koji uzimaju više doze atorvastatina imaju statistički značajno niže vrednosti LDL-holesterola od pacijenata sa *wild type* genotipom. Dodatno, prisustvo varijantnog 521C alela SLCO1B1 polimorfizma uticalo je na bolju kontrolu serumskih vrednosti HDL-holesterola kod pacijenata na terapiji višim dozama rosuvastatina. Dobijeni rezultati nisu pokazali statistički značajnu povezanost između aktivnosti AST i ALT i ispitivanih genskih polimorfizama. Studija je pokazala da prisustvo ispitivanih genskih polimorfizama može biti povezano sa kontrolom određenih lipidnih parametara. Neophodna su dalja istraživanja na većem broju ispitanika i poželjno određivanje koncentracije leka u krvi, da bi se dobila potpuniya slika o vezi između genskih polimorfizama, doze i efekta statina.

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