






ORIGINAL ARTICLE

A comprehensive pharmacogenomic study indicates roles for *SLCO1B1*, *ABCG2* and *SLCO2B1* in rosuvastatin pharmacokinetics

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Aims: The aim was to comprehensively investigate the effects of genetic variability on the pharmacokinetics of rosuvastatin.

Methods: We conducted a genome-wide association study and candidate gene analyses of single dose rosuvastatin pharmacokinetics in a prospective study ($n = 159$) and a cohort of previously published studies ($n = 88$).

Results: In a genome-wide association meta-analysis of the prospective study and the cohort of previously published studies, the *SLCO1B1* c.521 T > C (rs4149056) single nucleotide variation (SNV) associated with increased area under the plasma concentration–time curve (AUC) and peak plasma concentration of rosuvastatin ($P = 1.8 \times 10^{-12}$ and $P = 3.2 \times 10^{-15}$). The candidate gene analysis suggested that the *ABCG2* c.421C > A (rs2231142) SNV associates with increased rosuvastatin AUC ($P = .0079$), while the *SLCO1B1* c.388A > G (rs2306283) and *SLCO2B1* c.1457C > T (rs2306168) SNVs associate with decreased rosuvastatin AUC ($P = .0041$ and $P = .0076$). Based on *SLCO1B1* genotypes, we stratified the participants into poor, decreased, normal, increased and highly increased organic anion transporting polypeptide (OATP) 1B1 function groups. The OATP1B1 poor function phenotype associated with 2.1-fold (90% confidence interval 1.6–2.8, $P = 4.69 \times 10^{-5}$) increased AUC of rosuvastatin, whereas the OATP1B1 highly increased function phenotype associated with a 44% (16–62%; $P = .019$) decreased rosuvastatin AUC. The *ABCG2* c.421A/A genotype associated with 2.2-fold (1.5–3.0; $P = 2.6 \times 10^{-4}$) increased AUC of rosuvastatin. The *SLCO2B1* c.1457C/T genotype associated with 28% decreased rosuvastatin AUC (11–42%; $P = .01$).

Conclusion: These data suggest roles for *SLCO1B1*, *ABCG2* and *SLCO2B1* in rosuvastatin pharmacokinetics. Poor *SLCO1B1* or *ABCG2* function genotypes may increase

The authors confirm that the Principal Investigator for this paper is Mikko Niemi and that he had direct clinical responsibility for study participants.

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the risk of rosuvastatin-induced myotoxicity. Reduced doses of rosuvastatin are advisable for patients with these genotypes.

KEYWORDS

ABCG2, pharmacogenomics, rosuvastatin, *SLCO1B1*, *SLCO2B1*

1 | INTRODUCTION

Rosuvastatin is commonly used as a cholesterol-lowering drug in the primary and secondary prevention of cardiovascular diseases.^{1,2} It inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase, thus limiting the rate of cholesterol synthesis and lowering plasma cholesterol levels.³ Rosuvastatin therapy is generally well tolerated. Among its well-known adverse effects, however, are muscle symptoms varying in severity from mild myalgia to potentially fatal rhabdomyolysis.^{4–8} The risk of rosuvastatin-induced myotoxicity is dose-dependent,⁵ and increased rosuvastatin concentrations due to drug–drug interactions or variability in genes related to rosuvastatin pharmacokinetics may predispose patients to myotoxicity. Understanding the factors that may affect rosuvastatin exposure is therefore important.

Being a hydrophilic compound, rosuvastatin needs active transport by uptake and efflux transporters to effectively cross cell membranes.^{6,9,10} The oral bioavailability of rosuvastatin is approximately 20%.^{11,12} Absorption of rosuvastatin is limited by the **breast cancer resistance protein** (BCRP, official name ABCG2, encoded by ABCG2), expressed on the apical membrane of enterocytes.^{5,13} BCRP mediates the efflux of rosuvastatin back into the small intestinal lumen, and decreased BCRP function may lead to increased rosuvastatin exposure. For example, the area under the plasma rosuvastatin concentration–time curve (AUC) was 144% higher in healthy volunteers homozygous for the ABCG2 c.421C > A (rs2231142, p.Gln141Lys) decreased function variant, compared with the c.421C/C homozygotes.¹⁴ Concomitant use of BCRP-inhibiting drugs such as cyclosporine, eltrombopag or febuxostat markedly increases rosuvastatin concentrations.^{15–18}

Rosuvastatin is administered in the active acid form and is subject to only limited metabolism.³ Its main metabolites are active N-desmethylosuvastatin, formed by CYP2C9, and inactive rosuvastatin lactone. Approximately 90% of orally administered rosuvastatin is excreted unchanged into bile and urine.^{5,12} The uptake of rosuvastatin into hepatocytes is primarily mediated by **organic anion transporting polypeptide** (OATP) 1B1 (encoded by *SLCO1B1*). In addition, other members of the solute carrier superfamily, OATP1B3, OATP2B1 and, to a lesser extent, the sodium-dependent taurocholate cotransporting polypeptide NTCP (encoded by *SLCO1B3*, *SLCO2B1* and *SLC10A1*, respectively), transport rosuvastatin into hepatocytes.^{9,19,20} Changes in the function of these uptake transporters may affect systemic and liver exposures to rosuvastatin. For example, homozygosity for the reduced function c.521 T > C (rs4149056, p.Val174Ala) single

What is already known about this subject

- Rosuvastatin pharmacogenetics has been studied in targeted candidate gene analyses.
- Due to the targeted nature and limited sample sizes of previous studies, relevant genetic variants could have been left unidentified.
- This is the largest pharmacogenetic study on rosuvastatin pharmacokinetics in healthy volunteers thus far, and the first comprehensive study.

What this study adds

- The *SLCO1B1* genotype predicting poor organic anion transporting polypeptide 1B1 function and the ABCG2 genotype predicting poor breast cancer resistance protein function double rosuvastatin exposure.
- The *SLCO2B1* c.1457C > T variant associates with decreased rosuvastatin exposure.
- Lower rosuvastatin starting and maximum doses are advised for patients with poor organic anion transporting polypeptide 1B1 or breast cancer resistance protein function.

nucleotide variation (SNV) in *SLCO1B1* is associated with a 1.8–2.7-fold increase in rosuvastatin peak plasma concentration (C_{max}) and a 1.6–2.2-fold increase in rosuvastatin AUC.^{21,22} The c.521 T > C SNV is also associated with a potentially increased risk of rosuvastatin-associated myotoxicity.^{23,24}

Understanding of genetic variability in rosuvastatin pharmacokinetics has so far been based on targeted candidate gene studies, and genetic variants affecting rosuvastatin pharmacokinetics may therefore still be unidentified. Therefore, we considered it important to conduct a comprehensive pharmacogenetic study on rosuvastatin pharmacokinetics. To that end, we carried out a genome-wide association study of rosuvastatin pharmacokinetics in 247 healthy volunteers, and a candidate gene analysis of 16 genes previously found to be involved in rosuvastatin pharmacokinetics.

2 | METHODS

2.1 | Subjects and study design

The study sample consists of a prospective rosuvastatin pharmacokinetic study and a cohort of previously published studies with rosuvastatin pharmacokinetic data. Following written informed consent, a total of 159 unrelated, healthy white Finnish volunteers (79 men and 80 women, mean \pm standard deviation: age 25 ± 4 y, height 174 ± 9 cm, weight 70 ± 13 kg and body mass index 23 ± 3 kg/m²) participated in the prospective study. The participants' health was confirmed by medical history, physical examination and routine laboratory tests before they entered the study. None used continuous medication, including hormonal contraception, and all were nonsmokers.

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District (record number 86/13/03/00/2015) and the Finnish Medicines Agency Fimea (EudraCT number 2015-000540-41). Following an overnight fast, the volunteers ingested a single oral dose of 40 mg rosuvastatin (Crestor; AstraZeneca UK Ltd., Cheshire, UK). A standardized warm meal was served 4 hours, and light meals 7 and 10 hours after rosuvastatin administration. Timed venous blood samples were drawn prior to and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 24 hours after the ingestion of rosuvastatin. The samples were 4 or 9 mL each and they were collected in EDTA-containing tubes that were placed on ice immediately after sampling. Plasma was separated within 30 minutes and aliquots were stored at -70°C until analysis. Use of any other drugs was prohibited from 1 week before to 3 days after rosuvastatin administration. The participants were not allowed to use alcohol from 1 day before to 2 days after the day of rosuvastatin administration, and grapefruit products from 2 days before to 2 days after rosuvastatin administration.

The cohort of previously published studies consisted of 88 unrelated, healthy white Finnish volunteers (38 women and 50 men, mean \pm standard deviation age 23 ± 3 y, height 175 ± 9 cm, weight 69 ± 11 kg and body mass index 22 ± 2 kg/m²) who had participated in previously published single-dose pharmacokinetic studies on either 10 mg ($n = 37$) or 20 mg ($n = 51$) rosuvastatin.^{14,18,25,26} In the studies, the rosuvastatin plasma concentrations were determined either prior to and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 34 and 48 hours after rosuvastatin ingestion,^{14,25,26} or prior to and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 23 and 47 hours after rosuvastatin ingestion.¹⁸ The participants in the cohort of previously published studies were unrelated to the prospective study participants. The study protocols, including the present genetic analyses, were approved by competent ethics committees and the Finnish Medicines Agency, Fimea. All participants gave written informed consent.

2.2 | Analysis of drug concentrations in plasma samples

Rosuvastatin reference standard and deuterated internal standard (rosuvastatin-D₆) were purchased from Toronto Research Chemicals

(North York, Ontario, Canada). Prior to analysis, plasma (150 μL) proteins were precipitated with acetonitrile (450 μL) containing the internal standard, and the sample mixture was drawn through the Phree Phospholipid Removal 96-well extraction plate (Phenomenex, Torrance, CA, USA) according to the manufacturer's protocol. The supernatant was then evaporated and the residue was reconstituted in 100 μL of 0.1% formic acid:acetonitrile (80:20, v:v).

Rosuvastatin concentrations were determined using a Shimadzu Nexera liquid chromatography system (Shimadzu Corporation, Kyoto, Japan) coupled to an API 3000 tandem mass spectrometer interfaced with electrospray ion source (AB Sciex, Toronto, Ontario, Canada). The mobile phase consisted of 0.1% formic acid in water (A) and acetonitrile (B) (gradient separation, 15–95% B, total run time 7.5 min). The mobile phase flow was set at 300 $\mu\text{L}/\text{min}$ and the injection volume was 10 μL . The quantification was based on positive multiple reactions monitoring of the mass-to-charge transitions 482–258 and 488–264 for rosuvastatin and rosuvastatin-D₆. The lower and upper limits of quantification in plasma were 0.1 and 50 ng/mL. Samples in which rosuvastatin concentration exceeded 50 ng/mL were diluted with blank plasma. The day-to-day coefficient of variation was below 15% at relevant rosuvastatin concentrations.

2.3 | Pharmacokinetics

The pharmacokinetic variables (C_{max} ; time to C_{max} ; T_{max} ; AUC from zero to infinity, $\text{AUC}_{0-\infty}$; elimination half-life, $t_{1/2}$) of rosuvastatin, were calculated using standard noncompartmental methods using Phoenix WinNonlin, version 8.2 (Certara, Princeton, NJ, USA).

2.4 | Genotyping

Genomic DNA was extracted from EDTA whole blood samples using the Maxwell 16 LEV Blood DNA Kit on a Maxwell 16 Research automated nucleic acid extraction system (Promega, Madison, WI, USA). Whole genome genotyping was carried out with the Infinium Core Exome (prospective study, $n = 159$) or Global Screening Array (the cohort of previously published studies, $n = 88$) microchips (Illumina, San Diego, CA, USA) at the Technology Centre of the Institute for Molecular Medicine, Finland (University of Helsinki, Finland). Hardy–Weinberg equilibrium $P > 10^{-5}$ and proportion missing ≤ 0.03 were used as quality thresholds for including data in the genome-wide association study.

To supplement missing data and to verify genotype calls, the participants were genotyped for 28 relevant SNVs with TaqMan genotyping assays on a QuantStudio 12 K Flex Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA; Table S1). Haplotype computations for *SLCO1B1**1 (previously known as *1A, c.388A-c.463C-c.521 T-c.1929A), *5 (c.388A-c.463C-c.521C-c.1929A), *14 (c.388G-c.463A-c.521 T-c.1929A), *15 (c.388G-c.463C-c.521C-c.1929A), *20 (previously also known as *35, c.388G-c.463C-c.521 T-c.1929C) and *37 (previously known as *1B, c.388G-c.463C-c.521 T-c.1929A) were performed with PHASE v2.1.1.^{27,28}

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.²⁹

2.6 | Statistical analysis

Data are presented as geometric means with geometric coefficient of variation or 90% confidence intervals (CI), or estimated marginal means with 90% CI. Statistical analyses were carried out using the statistical programs JMP Genomics 8.0 (SAS Institute, Inc., Cary, NC, USA) and IBM SPSS Statistics for Windows, version 27 (Armonk, NY, USA). Before analysis, the pharmacokinetic variables analysed ($AUC_{0-\infty}$, C_{max} , $t_{1/2}$) were logarithmically transformed. For the cohort of previously published studies, the $AUC_{0-\infty}$ and C_{max} values were adjusted linearly to a 40 mg rosuvastatin dose. Sex and logarithmically transformed bodyweight were tested as demographic covariates in the prospective study using stepwise linear regression analysis, with P value thresholds of .05 for entry and .10 for removal.

For the genome-wide association and candidate gene analyses, a stepwise linear regression analysis fixed for significant demographic covariates was used to investigate possible associations of genetic variants with rosuvastatin pharmacokinetic variables. Genome-wide meta-analysis of the prospective study and the cohort of previously published studies was carried out by weighting the regression coefficients from each study by the inverse variance. Additive coding was employed for genetic variants, and multiallelic variants were expanded. Only SNVs included in both the prospective study and the cohort of previously published studies were included in the meta-analysis and the candidate gene analysis. SNVs with minor allele frequencies ≤ 0.05 (genome wide association analysis) or ≤ 0.01 (candidate gene analysis) were excluded from the analyses. A P value below 5×10^{-8} was considered genome-wide significant. Thresholds of .05 for entry and .10 for removal were used in the candidate gene analysis.

Further gene-based analyses were carried out using analysis of variance, adjusting for covariates, with pairwise comparisons with the Fisher's least significant difference method. Study (prospective study or cohort of previously published studies) was set as a random factor in the analysis. Since it is possible to achieve greater statistical power by combining variants with similar effects, *SLCO1B1* was analysed as 5 genotype-predicted OATP1B1 function classes: poor function (two decreased function alleles); decrease function (one decreased and 1 normal or increased function allele); normal function (two normal function alleles); increased function (one increased and 1 normal function allele); or highly increased function (two increased function alleles).^{30,31} *SLCO1B1**1 and *37 were considered normal function alleles, *5 and *15 as decreased function alleles, and *14 and *20 as increased function alleles. A P value $< .05$ was considered statistically significant.

3 | RESULTS

The $AUC_{0-\infty}$ of rosuvastatin varied 10-fold and C_{max} 25-fold among the participants of the prospective study (Table 1). Body weight was associated with decreased rosuvastatin C_{max} and $AUC_{0-\infty}$ (-4.5% per 10% increase in body weight; $P = .016$ and $P = .003$) in the prospective study and was used as a covariate for these variables in all further analyses. Among the total group of 247 participants, rosuvastatin $AUC_{0-\infty}$ varied 13-fold and C_{max} 37-fold after adjusting the values to a 40-mg rosuvastatin dose.

3.1 | Genome-wide association study

In the genome-wide association analysis of the prospective study, no SNV showed a genome-wide significant association with rosuvastatin pharmacokinetics. In the meta-analysis with the cohort of previously published studies with rosuvastatin pharmacokinetic data, the *SLCO1B1* c.521 T > C SNV associated with rosuvastatin $AUC_{0-\infty}$ and C_{max} at the genome-wide significance level (Figure 1). The $AUC_{0-\infty}$ of

TABLE 1 Pharmacokinetic variables of rosuvastatin in 247 healthy volunteers

Variable	Prospective study (n = 159)		Cohort of previously published studies (n = 88)		Total (n = 247)	
	Geometric mean (geometric CV)	Range	Geometric mean (geometric CV)	Range	Geometric mean (geometric CV)	Range
Dose-adjusted C_{max} (ng/mL)	17.8 (66%)	4.1–103.8	16.0 (61%)	2.8–56.4	17.1 (64%)	2.8–103.8
T_{max} (h) ^a	4	0.5–8	5	0.5–7	5	0.5–8
Dose-adjusted $AUC_{0-\infty}$ (ng × h/mL)	159.6 (52%)	53.6–535.8	142.2 (53%)	40.2–417.2	153.2 (53%)	40.2–535.8
$t_{1/2}$ (h)	10.4 (31%)	4.1–37.8	11.9 (48%)	1.7–45.5	10.9 (38%)	1.7–45.5

Rosuvastatin dose in the prospective study was 40 mg, and 10–20 mg in the previously published studies. The $AUC_{0-\infty}$ and C_{max} values from the cohort of previously published studies were adjusted to 40-mg dose. The observed AUC covered the $AUC_{0-\infty}$ well, except for 2 outliers. The geometric mean (geometric CV) % extrapolated AUC was 3.6% (79%). $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 hour to infinity; CI, confidence interval; CV, coefficient of variation; C_{max} , peak plasma concentration; T_{max} time to C_{max} ; $t_{1/2}$, elimination half-life.

^a T_{max} data given as median.

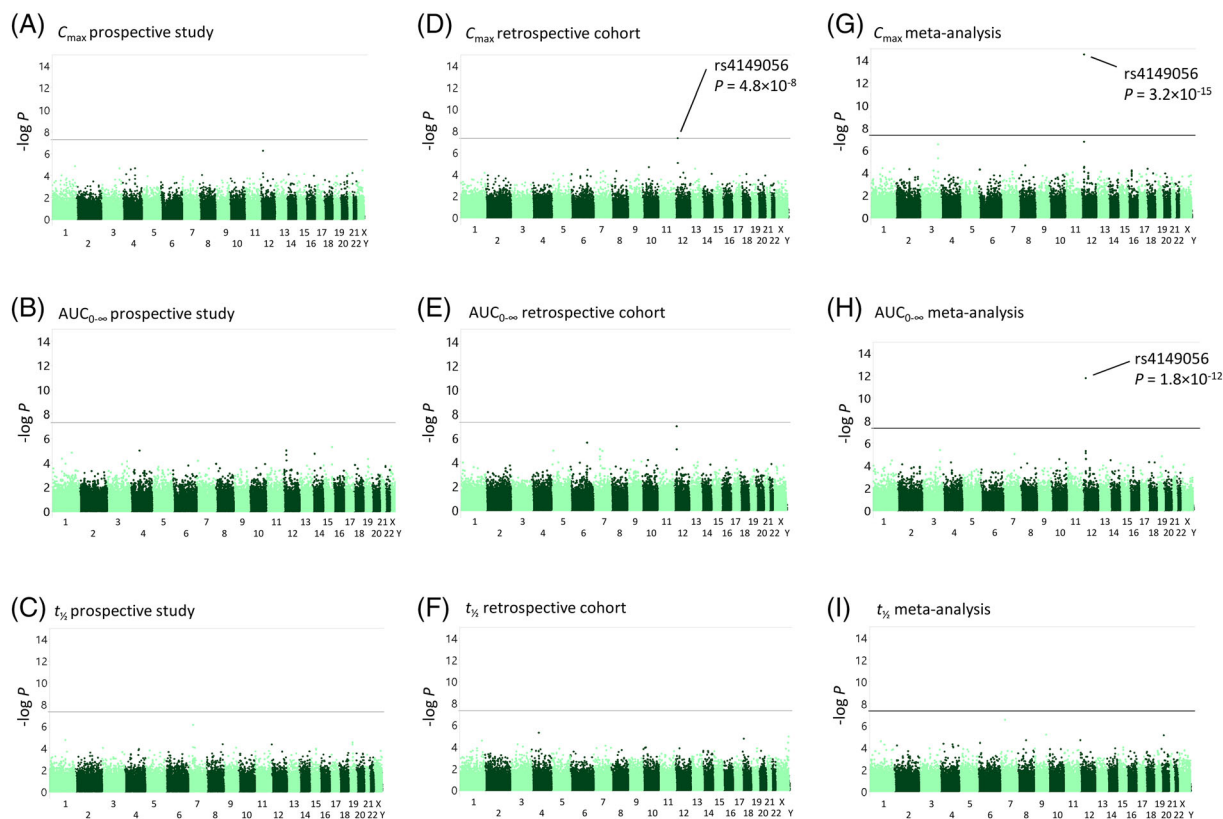


FIGURE 1 Manhattan plots of pharmacokinetic variables of rosuvastatin. The results of the genome-wide association analysis of the prospective study for peak plasma concentration (C_{\max}) (a), area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) (b), and elimination half-life ($t_{1/2}$) (c) are shown on the left, the results of the cohort of previously published studies for peak plasma concentration (C_{\max}) (d), $AUC_{0-\infty}$ (e), and elimination half-life ($t_{1/2}$) (f) are shown in the middle, and the results of the meta-analysis of the prospective study and the cohort of previously published studies for C_{\max} (g), $AUC_{0-\infty}$ (h), and $t_{1/2}$ (i) on the right. Horizontal lines indicate the genome-wide significance level of 5×10^{-8}

rosuvastatin was 42% ($P = 1.8 \times 10^{-12}$) and the C_{\max} 59% ($P = 3.2 \times 10^{-15}$) larger per copy of the c.521C allele. No other variants showed genome-wide significant associations with rosuvastatin exposure, even after adjusting for the *SLCO1B1* c.521 T > C variant. No associations were observed with rosuvastatin $t_{1/2}$.

3.2 | Candidate gene analysis

To identify which of the 16 candidate genes associate with rosuvastatin pharmacokinetics and to mitigate the risk of false negatives due to the conservative multiple testing correction in the genome-wide analyses, a linear regression analysis of 42 missense and functional variants was conducted. In the analysis, the *SLCO1B1* c.521 T > C and the *ABCG2* c.421C > A (tentatively named *ABCG2*2*) SNVs associated with increased rosuvastatin $AUC_{0-\infty}$ (Table 2). In contrast, the *SLCO1B1* c.388A > G (rs2306283, p.Asn130Asp), the *ABCG2* c.34G > A (rs2231137, p.Val12Met) and the *SLCO2B1* 1457C > T (rs2306168, p.Ser486Phe) SNVs associated with decreased $AUC_{0-\infty}$. As the *ABCG2* c.34G > A SNV showed only a borderline significant association without correction for multiple testing and has shown an

opposite association with rosuvastatin pharmacokinetics in a previous study,³² it was excluded from further analyses.

3.3 | Gene-based analyses

We next performed an analysis of variance to estimate the effect sizes of different *SLCO1B1*, *ABCG2* and *SLCO2B1* genotypes on rosuvastatin pharmacokinetics. For this purpose, the participants were divided into different classes based on their *SLCO1B1* genotype-predicted OATP1B1 phenotype, *ABCG2* c.421C > A (*ABCG2*2*) genotype and *SLCO2B1* c.1457C > T genotype. The largest AUC values were seen in individuals with poor OATP1B1 function phenotype as well as those with the *ABCG2*2* allele (Figure 2). In contrast, AUC was smallest in the groups with increased or highly increased OATP1B1 function. The *SLCO2B1* c.1457C/T genotype also seemed to be more common in individuals with smaller AUC values.

In a gene-based analysis adjusted for the *ABCG2* and *SLCO2B1* genotypes, OATP1B1 poor function phenotype associated with increased rosuvastatin $AUC_{0-\infty}$ and C_{\max} , whereas the OATP1B1 highly increased function phenotype associated with decreased

TABLE 2 Results of the candidate gene analyses on rosuvastatin $AUC_{0-\infty}$ in 247 healthy volunteers

Covariate/SNV	Effect ^a		P-value	Bonferroni adjusted P-value	Adjusted R ² for each step
	Average (%)	90% CI			
Weight	-6.1	-8.5, -3.6	9.7×10^{-5}		0.031
SLCO1B1 c.521 T > C	52.4	38.6, 67.7	4.1×10^{-12}	1.8×10^{-10}	0.181
SLCO1B1 c.388A > G	-12.4	-18.8, -5.5	.0041	.18	0.214
ABCG2 c.421C > A	18.8	6.8, 32.1	.0079	.34	0.236
SLCO2B1 c.1457C > T	-25.3	-37.6, -10.7	.0076	.33	0.258
ABCG2 c.34G > A	-11.9	-20.7, -2.1	.048	>.99	0.267

$AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; SNV, single nucleotide variation.

^aPer minor allele copy or 10% increase in body weight.

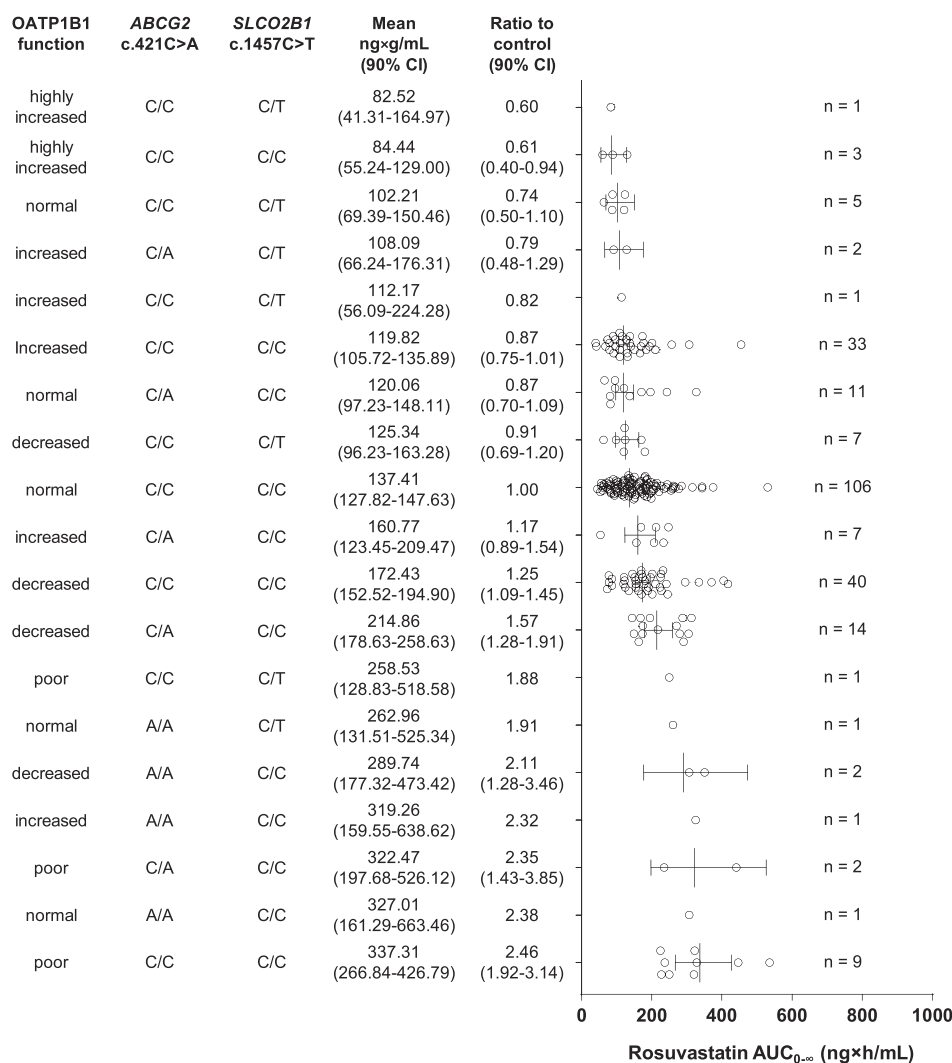


FIGURE 2 Rosuvastatin area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) values in individuals divided into different classes based on the *SLCO1B1* phenotype, *ABCG2* diplotype and *SLCO2B1* c.1457C > T genotype. Data are estimated marginal means with 90% confidence interval (CI). HIF, highly increased function; IF, increased function; NF, normal function; DF, decreased function; PF, poor function

rosuvastatin $AUC_{0-\infty}$ (Table 3). The mean $AUC_{0-\infty}$ and C_{max} were increased 2.1-fold (90% CI 1.6, 2.8; $P = 4.69 \times 10^{-5}$) and 2.8-fold (90% CI 2.0, 3.9; $P = 1.75 \times 10^{-6}$) in the poor function group, compared with the normal function group. The highly increased function group had 44% (90% CI 16%, 62%; $P = .019$) decreased mean $AUC_{0-\infty}$ compared with the normal function group.

The *ABCG2**2 allele associated with increased concentrations of rosuvastatin in an analysis adjusted for *OATP1B1* function and *SLCO2B1* genotype (Table 4). Individuals who were *ABCG2**2 homozygotes, predicting poor BCRP function, showed 116% larger $AUC_{0-\infty}$ (90% CI 53%, 203%; $P = 2.6 \times 10^{-4}$) and 104% higher C_{max} (90% CI 37%, 203%; $P = .0036$) compared with the control, *1/*1 group.

TABLE 3 Pharmacokinetics of rosuvastatin in individuals with different *SLCO1B1* genotype-predicted OATP1B1 functions

Variable	Highly increased (n = 4)		Increased (n = 44)	
	Mean (90% CI)	Ratio to normal (90% CI) P-value	Mean (90% CI)	Ratio to normal (90% CI) P-value
C_{max} (ng/mL)	10.4 (6.8–15.9)	0.64 (0.40–1.02) P = .12	14.8 (11.8–18.4)	0.91 (0.68–1.22) P = .59
$AUC_{0-\infty}$ (ng × h/mL)	83.8 (58.2–120.7)	0.56 (0.38–0.84) P = .019	140.9 (116.7–170.1)	0.95 (0.73–1.22) P = .71
$t_{1/2}$ (h)	12.1 (8.9–16.5)	1.11 (0.79–1.56) P = .62	11.7 (10.0–13.8)	1.07 (0.87–1.32) P = .60

Data are estimated marginal means adjusted for weight ($AUC_{0-\infty}$ and C_{max}), *SLCO2B1* c.1457C > T genotype and *ABCG2* c.421C/A genotype. $AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; C_{max} , peak plasma concentration; $t_{1/2}$, elimination half-life.

TABLE 3 (Continued)

Variable	Normal (n = 124)	Decreased (n = 63)		Poor (n = 12)	
	Mean (90% CI)	Mean (90% CI)	Ratio to normal (90% CI) P-value	Mean (90% CI)	Ratio to normal (90% CI) P-value
C_{max} (ng/mL)	16.2 (13.4–19.7)	19.6 (17.1–22.6)	1.21 (0.95–1.54) P = .19	45.0 (33.9–59.9)	2.77 (1.97–3.91) P = 1.75×10^{-6}
$AUC_{0-\infty}$ (ng × h/mL)	149.0 (126.3–176.0)	180.5 (160.0–203.8)	1.21 (0.99–1.49) P = .13	312.0 (244.4–398.6)	2.09 (1.56–2.81) P = 4.69×10^{-5}
$t_{1/2}$ (h)	11.0 (9.5–12.6)	11.1 (10.0–12.3)	1.00 (0.85–1.20) P = .93	11.2 (9.1–13.7)	1.02 (0.79–1.30) P = .91

Data are estimated marginal means adjusted for weight ($AUC_{0-\infty}$ and C_{max}), *SLCO2B1* c.1457C > T genotype and *ABCG2* c.421C/A genotype. $AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; C_{max} , peak plasma concentration; $t_{1/2}$, elimination half-life.

In addition, the *SLCO2B1* c.1457C > T SNV associated with lower concentrations and prolonged $t_{1/2}$ of rosuvastatin (Table 5). The analysis was adjusted for OATP1B1 function and *ABCG2* genotype. The mean $AUC_{0-\infty}$ was 28% (90% CI 11%, 42%; $P = .011$) and the C_{max} 33% (90% CI 14%, 48%; $P = .008$) lower, and the $t_{1/2}$ 29% longer (90% CI 8%, 54%; $P = .02$) in C/T heterozygotes than in noncarriers. No participant was homozygous for the *SLCO2B1* c.1457C > T variant.

4 | DISCUSSION

The aim of this study was to investigate the effects of genetic variability on the pharmacokinetics of the cholesterol-lowering drug rosuvastatin using a genome-wide approach. The results give new information on how functional variants in *SLCO1B1*, *ABCG2* and *SLCO2B1* affect rosuvastatin pharmacokinetics in humans. In the genome-wide meta-analysis, the *SLCO1B1* c.521 T > C SNV associated with increased rosuvastatin $AUC_{0-\infty}$ and C_{max} . A candidate gene analysis revealed 4 more SNVs in the *SLCO1B1*, *ABCG2* and *SLCO2B1* genes associating with rosuvastatin $AUC_{0-\infty}$. In gene-based analyses of these 3 genes, the *SLCO1B1* genotypes that predict poor OATP1B1 function and the *ABCG2* c.421A/A genotype that predicts poor BCRP function showed the strongest associations with rosuvastatin exposure, with mean $AUC_{0-\infty}$ and C_{max} values being more than doubled in these genotype groups. In addition, the *SLCO2B1* c.1457C/T genotype associated with decreased rosuvastatin concentrations and a prolonged rosuvastatin $t_{1/2}$.

The strongest associations with rosuvastatin pharmacokinetics were observed with *SLCO1B1* c.521 T > C SNV. *SLCO1B1* encodes the uptake transporter OATP1B1 expressed on the basolateral membrane of human hepatocytes.^{20,33} OATP1B1 is the primary transporter to mediate rosuvastatin uptake into hepatocytes. The c.521 T > C SNV has been shown to lead to reduced OATP1B1 function and has been associated with raised plasma concentrations of rosuvastatin and a potentially higher risk of rosuvastatin-induced myotoxicity.²⁴ In the present study, which is the largest pharmacogenetic study on rosuvastatin pharmacokinetics so far, the c.521 T > C SNV associated genome-wide significantly with increased $AUC_{0-\infty}$ and C_{max} of rosuvastatin.

In the candidate gene analysis, besides the c.521 T > C, the *SLCO1B1* c.388A > G SNV showed a significant association with rosuvastatin AUC. To evaluate the combined effects of *SLCO1B1* functional variants, *SLCO1B1* was included in the gene-based analysis as 5 genotype-predicted OATP1B1 function phenotype classes.^{30,31} In this analysis, the poor function phenotype associated with 2.1-fold increased AUC and 2.8-fold increased C_{max} values of rosuvastatin as compared with normal function OATP1B1. This falls within the range of estimates from previous studies, which have indicated a 1.6–2.2-fold increase in rosuvastatin AUC in individuals with the c.521C/C genotype.^{21,22,25} Interestingly, rosuvastatin AUC was lower in individuals with highly increased OATP1B1 function than in those with normal OATP1B1 function. A similar association was recently observed with simvastatin acid AUC.³¹

As in previous studies,²⁵ the *SLCO1B1* genotype was not associated with the $t_{1/2}$ of rosuvastatin in our study. Because OATP1B1

TABLE 4 Pharmacokinetics of rosuvastatin in individuals with different *ABCG2* c.421C > A (*ACBG2**2) genotypes

Variable	<i>ABCG2</i> c.421C/C (n = 206)	<i>ABCG2</i> c.421C/A (n = 36)		<i>ABCG2</i> c.421A/A (n = 5)	
	Mean (90% CI)	Mean (90% CI)	Ratio to c.421C/C (90% CI); P-value	Mean (90% CI)	Ratio to c.421C/C (90% CI); P-value
C_{\max} (ng/mL)	16.4 (14.4–18.6)	16.8 (14.1–20.0)	1.03 (0.83–1.27); P = .85	33.3 (22.8–48.6)	2.04 (1.37–3.03); P = .0036
$AUC_{0-\infty}$ (ng × h/mL)	138.7 (124.4–154.5)	159.0 (137.0–184.5)	1.15 (0.95–1.38); P = .22	298.6 (215.9–413.1)	2.16 (1.53–3.03); P = 2.6×10^{-4}
$t_{1/2}$ (h)	11.5 (10.5–12.6)	11.4 (10.1–12.9)	0.99 (0.85–1.16); P = .94	10.6 (8.0–13.9)	0.92 (0.69–1.23); P = .64

Data are estimated marginal means adjusted for weight ($AUC_{0-\infty}$ and C_{\max}), *SLCO2B1* c.1457C > T genotype and *SLCO1B1* genotype-predicted OATP1B1 function. $AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; C_{\max} , peak plasma concentration; $t_{1/2}$, elimination half-life.

TABLE 5 Pharmacokinetics of rosuvastatin in individuals with different *SLCO2B1* c.1457C > T genotypes

Variable	<i>SLCO2B1</i> c.1457C/T (n = 18)		<i>SLCO2B1</i> c.1457C/C (n = 229) Mean (90% CI)
	Mean (90% CI)	Ratio to c.1457C/C (90% CI); P-value	
C_{\max} (ng/mL)	13.9 (11.1–17.4)	0.67 (0.52–0.86); P = .0080	20.7 (18.7–23.0)
$AUC_{0-\infty}$ (ng × h/mL)	128.3 (105.7–155.7)	0.72 (0.58–0.89); P = .011	178.6 (163.6–195.1)
$t_{1/2}$ (h)	13.4 (11.4–15.8)	1.29 (1.08–1.54); P = .022	10.4 (9.7–11.2)

Data are estimated marginal means adjusted for weight ($AUC_{0-\infty}$ and C_{\max}), *SLCO1B1* genotype-predicted OATP1B1 function and *ABCG2* c.421C > A genotype. None of the study participants was homozygous for the *SLCO2B1* c.1457C > T variant. $AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; C_{\max} , peak plasma concentration; $t_{1/2}$, elimination half-life.

transports rosuvastatin from the blood into the hepatocytes, poor OATP1B1 function may be assumed to reduce the hepatic extraction ratio of rosuvastatin. For the AUC to double, as was seen in our study, the hepatic extraction ratio of rosuvastatin should be reduced from the normal 63%¹¹ to 46%. Such a change in the extraction ratio would increase oral bioavailability 1.46-fold and decrease clearance (Cl) by 27%. As the $t_{1/2}$ depends on both the distribution volume (V_d) and Cl ($t_{1/2} = \ln 2 \times V_d / Cl$), the results suggest that poor OATP1B1 function reduces both the V_d and Cl of rosuvastatin.

In the candidate gene analyses, 2 SNVs in the *ABCG2* gene associated with changes in rosuvastatin exposure. We tentatively named the c.421A allele *2, similarly to the star allele names commonly used with cytochrome P450 and *SLCO1B1* variants. Using simpler names when referring to this allele would be reasonable since the *ABCG2**2 has been widely studied and found to be functionally relevant.

In this study, the gene-based analyses adjusting for *SLCO1B1* and *SLCO2B1* genotypes showed significant associations for the *2/*2 genotype. The *ABCG2**2/*2 genotype predicting poor BCRP function associated with increased AUC and C_{\max} . The $t_{1/2}$ of rosuvastatin remained unchanged over the *ABCG2* genotype groups. These findings indicate that changes in rosuvastatin concentrations are likely to be the result of altered rosuvastatin bioavailability, following changes in the BCRP-mediated efflux of rosuvastatin in the small intestine. Homozygosity for the decreased function *2 allele associated with 2.2-fold increase in rosuvastatin AUC. This effect size lies in the vicinity of what has been seen in previous pharmacogenetic studies.^{14,32,34}

A similar 2.1-fold increase in rosuvastatin AUC without changes in $t_{1/2}$ has also been seen when rosuvastatin was administered after pre-treatment with the BCRP-inhibiting drug febuxostat.¹⁸

The evidence on the function of the other *ABCG2* allele, c.34G > A, is controversial. In some studies, no effect on BCRP transporter activity or expression was observed in vitro.^{35–37} By contrast, the c.34G > A allele has been shown to disturb the cell membrane localization of BCRP.³⁸ In a previously published pharmacokinetic study in 62 healthy Chinese men, the AUC and C_{\max} of rosuvastatin were increased in patients with the c.34A/A genotype.³² In our candidate gene analysis, the c.34A/A genotype associated with a decreased rosuvastatin AUC and C_{\max} . Therefore, and since the association was only marginally below the level of statistical significance without correction for multiple testing, we excluded the c.34G > A SNV from further analyses.

Another candidate gene with significant association with rosuvastatin pharmacokinetics was *SLCO2B1*, encoding the OATP2B1 transporter. In our study, the *SLCO2B1* c.1457C/T genotype associated with decreased rosuvastatin AUC and C_{\max} . Similarly, the c.1457C > T SNV has associated with reduced AUC and C_{\max} of the OATP2B1 substrates fexofenadine and celirololol.^{39,40} Previous studies have shown that OATP2B1 is expressed, e.g., in the small intestine, on the sinusoidal membrane of hepatocytes, and in heart and skeletal muscle.^{41,42} Interestingly, the OATP2B1-inhibiting drug ronacaleret decreased rosuvastatin exposure by approximately half in healthy volunteers,⁴³ suggesting that decreased function of OATP2B1 may

limit the oral bioavailability of rosuvastatin. Taken together, the data suggest that the *SLCO2B1* c.1457C > T SNV reduces the oral bioavailability of rosuvastatin by impairing its transport from the gut lumen into enterocytes.

In our study, rosuvastatin $t_{1/2}$ was 29% longer in the *SLCO2B1* c.1457C/T heterozygotes than in the C/C homozygotes. A similar difference has also been seen for 3S,5R-fluvastatin.⁴⁴ Interestingly, a previous study showed that apple juice reduces the AUC and C_{max} and prolongs the $t_{1/2}$ of the OATP2B1 substrate fexofenadine.³⁹ The authors suggested that the changes in fexofenadine AUC and C_{max} indicate decreased fexofenadine bioavailability through OATP2B1 inhibition, and that the prolonged $t_{1/2}$ might be due to *flip-flop* pharmacokinetics caused by sustained absorption of fexofenadine. A similar mechanism might explain the prolongation of the rosuvastatin $t_{1/2}$ in the carriers of the *SLCO2B1* c.1457C > T variant in our study. More studies are needed to further elucidate the role of *SLCO2B1* in rosuvastatin pharmacokinetics.

The normal dose range of rosuvastatin is 5–40 mg/d. Given that the risk of statin-induced muscle toxicity increases with systemic statin concentrations, taking the genetic variability in rosuvastatin pharmacokinetics into consideration could help prevent cases of myotoxicity.⁶ In patients with poor OATP1B1 or BCRP function genotypes, rosuvastatin concentrations may be twice as high as in noncarriers of these variants. It could therefore be advisable to use a lower-than-normal starting dose of rosuvastatin, and to avoid the usual maximum dose of 40 mg in these patients. These recommendations are consistent with the current dosing recommendations for patients of Asian ethnicity, whose rosuvastatin exposure is known to be approximately double that of Caucasian patients.^{21,45} In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, there was no association between *SLCO1B1* genotype and the rate of clinical myalgia in patients receiving 20 mg rosuvastatin daily.⁴⁶ A maximum dose of 20 mg rosuvastatin could therefore be a safe choice for patients with poor OATP1B1 or BCRP function genotypes. This corroborates the recent recommendation by the Clinical Pharmacogenetics Implementation Consortium,⁴⁷ which was based on previously published data from targeted candidate gene pharmacokinetic studies with relatively small numbers of participants.

In the JUPITER trial, an intronic SNV in *ABCG2* associated with a larger reduction in low-density lipoprotein (LDL) cholesterol levels in patients receiving 20 mg rosuvastatin.⁴⁸ This SNV is in a strong linkage disequilibrium with the *ABCG2* c.421C > A SNV. In contrast, the *SLCO1B1* c.521 T > C SNV has associated either with no change or a slightly impaired LDL cholesterol-lowering efficacy of statins.^{48–50} Reduced OATP1B1 function may therefore increase the risk of myotoxicity of rosuvastatin without an increase in LDL cholesterol-lowering efficacy, whereas reduced BCRP function may increase both the risk of myotoxicity and the efficacy of rosuvastatin.

In this study, there were no participants homozygous for both the *SLCO1B1* c.521 T > C and *ABCG2* c.421C > A SNVs. The combined effects of these 2 variants cannot be directly extrapolated from the present results. However, according to pharmacokinetic principles,

their effects can be assumed to be additive. Systemic rosuvastatin exposure may therefore be increased more than 4-fold in these patients compared with noncarriers of the variant alleles. Cyclosporine, which inhibits both BCRP and OATP1B1 as well as OATP1B3 and NCTP, increases rosuvastatin AUC up to 7.1-fold.¹⁵ The patients with both OATP1B1 and BCRP poor function genotypes could therefore be predisposed to myotoxicity even when using lower rosuvastatin doses.

The allele frequencies in the study population may affect the results from this study. In our prospective study, the minor allele frequencies of the SNVs with significant associations were 17% for *SLCO1B1* c.521 T > C, 41% for *SLCO1B1* c.388A > G, 7% for *ABCG2* c.421C > A, 10% for *ABCG2* c.34G > A and 4% for *SLCO2B1* c.1457C > T. It may be possible that the effects of some SNVs or genotypes could have remained undetected due to their low frequencies in the Finnish population.

This was a single-dose study carried out in healthy participants. Since rosuvastatin shows linear pharmacokinetics,^{51,52} the results can be extrapolated to continuous dosing. Variability in rosuvastatin pharmacokinetics in patients with hypercholesterolaemia and/or previous cardiovascular events, who often have multiple medications, may be greater than in the group of young, healthy volunteers in our study. In addition to genetic variation, drug–drug interactions, increased age and impaired renal function, for example, may predispose patients to statin-induced myotoxicity.^{4,53,54} Therefore, it is even more important to be able to anticipate higher than average rosuvastatin concentrations in these patients.

In conclusion, this study suggests that the *SLCO1B1*, *ABCG2* and *SLCO2B1* genotypes affect rosuvastatin pharmacokinetics. The mechanisms underlying the effects are likely changes in rosuvastatin bioavailability (*ABCG2*, *SLCO2B1*) and hepatic uptake of rosuvastatin (*SLCO1B1*). Taking these genotypes into consideration when prescribing rosuvastatin could help to reduce dose-dependent adverse effects such as myotoxicity and ensure the efficacy of rosuvastatin therapy. In particular, patients with the *ABCG2**2/*2 genotype or with *SLCO1B1* genotypes predicting poor OATP1B1 function should avoid high doses of rosuvastatin, as their rosuvastatin exposure may be more than doubled.

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COMPETING INTERESTS

The authors declare no conflicts of interest.

CLINICAL TRIAL REGISTRATION

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CONTRIBUTORS

M.L. and M.Ni. wrote the manuscript; S. T., A.T., J.T.B. and M.Ni. designed the research; E.K.T., S.T., M.Ne., J.V., M.P-H., T.O.L., T.T., J.T.B., A.T. and M.Ni. performed the research; M.L. and M.Ni. analysed the data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to the extent allowed by the EU General Data Protection Regulation, other applicable regulations and participant consent from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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