Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort
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Background The efficacy of statins, which are used commonly in primary and secondary prevention of cardiovascular diseases, shows a wide range of interindividual variability. Genetic variants of OATP1B1, a hepatic uptake transporter, can modify access of statins to its therapeutic target, thereby potentially altering drug efficacy. We studied the impact of genetic variants of OATP1B1 on the lipid-lowering efficacy of statins in a population-based setting.

Materials and methods The basis of the analysis was the Study of Health in Pomerania, a cohort of 2732 men and women aged 20–81 years. Included in the statistical analysis to evaluate the impact of OATP1B1 on therapeutic efficacy of statins were 214 individuals diagnosed with dyslipidaemia during initial recruitment and receiving statins during the 5-year follow-up.

Results Analysing the impact of the OATP1B1 genotype, we observed a trend for lower statin-induced total cholesterol reduction in carriers of the SLCO1B1 512C variant. Restricting the analysis to patients receiving simvastatin, pravastatin, lovastatin and fluvastatin indicated a statistically significant association of the OATP1B1 genotype on lipid parameters at the 5-year follow-up. No such effect was observed for atorvastatin. Calculation of achievement of treatment goals according to the NCEP-ATPIII guidelines showed a lower rate of successful treatment when harbouring the mutant allele for patients taking simvastatin (46.7 vs. 73.9%). A similar trend was observed for pravastatin (34.4 vs. 70.4%).

Conclusion Genetic variants of OATP1B1 leading to impaired hepatic uptake of statins translated into reduced drug efficacy in a population-based cohort.

Keywords: drug efficacy, hypercholesterolaemia, OATP1B1, statins

Introduction One class of drugs used commonly in the primary and secondary prevention of atherosclerosis are statins. Inhibition of the hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) blocks endogenous cholesterol synthesis and results in decreased cholesterol levels, an effect driven mainly by upregulation of hepatic cholesterol-metabolizing enzymes facilitating the hepatocellular uptake of the lipid-lowering effects of statins, however, show interindividual variability [1–3].

Thus, despite the widespread use of these drugs, prediction of statin action in the individual patient remains a challenge. Several studies analysing the influence of genetic variants on the individual variability of statin efficacy have focused on candidate genes obviously involved in cholesterol metabolism and disease progression. These studies have focused on genes such as the cholesterol receptors LDLR and SCARB1, the cholesterol-metabolizing enzymes HMGCR and CYP7A1, or the cholesterol transporter ABCG8 and ABCA1 [4–10].

In this report, we assessed the impact of a hepatic uptake transporter as a promising pharmacokinetic candidate gene on the efficacy of statins. It is now widely accepted that the pharmacodynamics of statins – the inhibition of the intracellular located HMGCR – depends in part on processes facilitating the hepatocellular uptake of the inhibitors. Hsiang et al. [11] reported that statins are transported by the liver-enriched transporter OATP1B1,
thereby identifying a mechanism modifying the cellular uptake of statins. In 2001, Tirona et al. [12] identified several polymorphisms localized in the coding region of the gene to be associated with impaired transport function. In particular, the frequent single nucleotide polymorphism (SNP) SLCO1B1 c.521C results in significant changes in pharmacokinetics (increased area under the curve) of several statins (pravastatin, atorvastatin, rosuvastatin and simvastatin) in healthy volunteers (summarized in the study of Niemi et al. [13]). The assumption that OATP1B transporters are important in pharmacokinetics of statins is indirectly supported by findings showing that the frequently occurring function-impairing allele SLCO1B1 c.521C is most predictive for extrahepatic adverse events (myopathy, rhabdomyolysis) of simvastatin therapy [14,15]. In detail, Link and colleagues had identified the noncoding rs4363657 polymorphism after performing a Genome-wide association scan in patients experiencing simvastatin-induced myopathy. The polymorphism identified is in almost complete linkage disequilibrium with the function-impairing haplotype. The polymorphism identified is in almost complete linkage disequilibrium with the function-impairing allele SLCO1B1 c.521C (\( r^2 = 0.97 \)). In addition, the authors report findings from the HPS study, where LDL reductions were 1.28 ± 0.25% smaller per copy of the SLCO1B1 c.521C allele and 0.62 ± 0.18% larger per copy of the SLCO1B1 c.388G allele. In a subsequent study, Brunham and colleagues replicated the finding, reporting an association of the rs4149056 (c.521C) variant with simvastatin-associated myopathy [odds ratio (OR) of 3.2 (95% confidence interval 0.83–11.96)]. The relevance of OATP1B1 SNPs for statin efficacy during chronic application in a general population, however, is still unclear. We therefore focused on the effect of SNPs located in the coding sequence of OATP1B1 on the therapeutic outcome of individuals treated with statins from a well-characterized general population cohort. Individuals recruited for a population-based study [Study of Health in Pomerania (SHIP)] were evaluated for the influence of impaired function alleles of OATP1B1 on the efficacy of prescribed statins.

Taken together, we describe reduced efficacy of statin treatment determined by the LDL-cholesterol-lowering effects in individuals carrying functionally impaired variants of OATP1B1. In addition, the fraction of individuals reaching target levels was significantly reduced in this subgroup. Importantly, although most of the statins showed a similar trend in our population, no modulation of efficacy by the genotype was detected in individuals treated with atorvastatin.

**Materials and methods**

**Study population**

The presented data were derived from the population-based SHIP. The study design and recruitment of the study have been described previously in more detail [16]. In brief, a sample was drawn from the population aged 20–79 years of West Pomerania, a north-eastern coastal region of Germany. From the 7006 initially sampled individuals, 6265 were eligible for the study and 4308 participated (response 68.9%). Baseline examinations (SHIP-0) were performed between 1997 and 2001. Between 2002 and 2006, all participants were invited to a follow-up examination (SHIP-1) and 3300 individuals (1589 men), corresponding to a response rate of 83.5% among living and eligible participants, participated. In the present study, we included individuals who participated in the follow-up examination (N=3300) and excluded participants with missing values at baseline or in the follow-up assessment for the polymorphisms (\( n = 214 \)) or for clinical data such as high-density lipoprotein (HDL) (\( n = 39 \)), LDL (\( n = 53 \)), total cholesterol (TC) (\( n = 30 \)), triglycerides (TGs) (\( n = 30 \)), HbA1c (\( n = 30 \)) or high-sensitive C-reactive protein (hs-CRP) values (\( n = 216 \)), respectively. In addition, we excluded individuals taking glucocorticoids at baseline or at the 5-year follow-up (\( n = 84 \)) or those with lack of information on dosing of statins at follow-up (\( n = 18 \)). Overall, we excluded a total of 495 individuals. This number is smaller than the sum of exclusions as there was an overlap. The initial analytical sample included a total of 2805 participants; of these, only 214 individuals started a statin therapy during the 5-year follow-up. All participants provided written informed consent. The study was approved by the local Ethics Committee of the University of Greifswald.

**Data collection**

All participants underwent an extensive standardized medical examination including the collection of blood samples. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the participant standing comfortably with weight distributed evenly on both feet. The BMI was calculated.

**CHD risk assessment**

The coronary heart disease (CHD) risk assessment was performed using the Framingham Heart Score [17]. To determine the individuals’ Framingham Heart Score, data on age, sex, TC, cigarette smoking, measured HDL, family history of premature CHD, CHD in female first-degree relative below 65 years, systolic blood pressure and antihypertensives (on the basis of the result of the questionnaire; ATC code C02) were included as described previously [17]. On the basis of the scores calculated, treatment goals were determined according to ATPIII [18]. In detail, the above-mentioned CHD risk factors of age, smoking, systolic blood pressure and HDL levels were assigned Framingham score points. Those points are used to estimate a 10-year risk in men and women. In the treatment guidelines ATPIII the 10-year risk has been assigned to different categories, where individuals...
with CHD or CHD risk equivalents (10-year risk > 20%) should reach an LDL-treatment goal below 100 mg/dl, whereas those with more than two risk factors (10-year risk < 20%) should reach levels below 130 mg/dl. Individuals with only 0–1 risk factors (10-year risk < 10%) should reach a treatment goal below 160 mg/dl. The 10-year risk was estimated for each individual separately; then, the recommended LDL-treatment goal was compared with the estimated cardiovascular disease risk in SHIP-1. Those not reaching their treatment goal were labelled the ‘failure’ group.

Medical examination and clinical chemical measurements
A nonfasting venous blood sample was obtained from all study participants between 07:00 a.m. and 04:00 p.m. while sitting. Serum aliquots were stored at −80°C. At baseline, TC and HDL-cholesterol concentrations were measured photometrically (Hitachi 704; Roche Diagnostics, Mannheim, Germany), whereas follow-up HDL concentrations were quantified by lipid electrophoresis (Helena SAS-3 system; Helena 7 BioSciences Europe, Tyne and Wear, UK). To ensure comparability in the longitudinal HDL analyses, we used baseline HDL concentrations as the reference and calculated corrected follow-up HDL-cholesterol concentrations on the basis of a previously published conversion formula: Corrected HDL = −80 + (1.158 × uncorrected HDL) [19]. Doing so, we found that the average HDL-cholesterol concentrations produced by the two methods were almost identical, suggesting that the differences in HDL-cholesterol will be small within the range of practical relevance. Serum LDL-cholesterol was measured by applying a precipitation procedure using dextran sulphate (Immuno, Heidelberg, Germany) on an Epos 5060 (Eppendorf, Hamburg, Germany). TG and glucose concentrations were determined enzymatically using reagents from Roche Diagnostics (Hitachi 717; Roche Diagnostics). Glycated haemoglobin (HbA1c) concentrations were determined by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). hs-CRP was determined immunologically on a Behring Nephelometer II with commercially available reagents from Dade Behring (Eschborn, Germany). All assays were performed according to the manufacturers’ recommendations by skilled technical personnel. In addition, the laboratory participates in official quarterly German external proficiency testing programmes. Dyslipoproteinaemia in SHIP-0 in individuals without statin treatment (ATC code C10AA01–08) was determined on the basis of the blood work; the limits were as follows: TG levels ≥160 mg/dl (equivalent to ≥1.8 mmol/l), TC ≥190 mg/dl (or >5.0 mmol/l), LDL-cholesterol ≥150 mg/dl (or >3.88 mmol/l), HDL-cholesterol <40 mg/dl (or <0.9 mmol/l) in men and HDL-cholesterol <50 mg/dl (or <1.1 mmol/l) in women.

Genotyping
All individuals included in the study were genotyped for the frequently occurring nonsynonymous polymorphisms SLC01B1 c.521T > C and SLC01B1 c.388A > G [12,13]. Assessment for the c.SLC01B1 388A > G was performed using a predeveloped TaqMan SNP detection assay from Applied Biosystems (Darmstadt, Germany). Briefly, reactions were carried out in a volume of 10 μl containing 5 μl Genotyping Master Mix (Applied Biosystems) 1 μl genomic DNA and 0.5 μl of the Primer Probe-Mix. Fluorescence was assessed using the Fast Real-Time PCR system 7900 HT (Applied Biosystems) and the Sequence Detection Software SDS 2.3 (Applied Biosystems). The rs4149056 (c.SLC01B1 521T > C) polymorphism was detected in a genome-wide SNP scan performed using the Affymetrix Human SNP Array 6.0 (Affymetrix Inc., Santa Clara, California, USA) (SNP_A-860113) [20]. Data on SNP_A-860113 were extracted and used for statistical analysis.

Statistical analysis
Categorical data were expressed as percentages; continuous data were expressed as arithmetic means (SDs). Geometric means were reported for HbA1c and hs-CRP as they followed an approximately log-normal distribution. Linear regression models were used for continuous data. ORs for incident statin therapy, adjusted for age and sex, were derived from logistic regression models. The association between SNPs and baseline lipid parameters was measured using linear regression adjusted for age and sex. The association between SNPs and change in lipid parameters was investigated using linear regression models that were adjusted for statin dose and baseline value of the lipid parameter comparing the group of individuals harbouring the wild type with the group of individuals harbouring at least one genetic variant allele. For subgroups combining individuals treated with different statins, the simvastatin equipotential dose was used instead of the actual statin dose. The equipotent doses have been calculated as described by Helfand et al. [21]. Furthermore, the χ²-test was used to test the association of categorical variables. Similarly, we related genetic variants with achievement of ATPIII treatment goals using binary logistic regression models that were adjusted for statin dose. The statin doses used for statistical analysis were transformed into simvastatin equivalent doses as described elsewhere [21]. P-values less than 0.05 were considered statistically significant. All statistical calculations were carried out using Stata 12.1 (Stata Corp., College Station, Texas, USA).

Results
Dyslipoproteinaemia in untreated individuals in SHIP-0
Although evaluation of lipid parameters (TG, TC and LDL-cholesterol) obtained during baseline examinations (N=2805) showed a total of 2048 individuals (81.51%) of the SHIP-0 population, excluding those receiving
statins during SHIP-0 (N = 179) to have dyslipoproteinemia according to the definition by the National Cholesterol Education Program ATPIII Guidelines, only 214 (10.45%) of these individuals received statins in SHIP-1. Among those with dyslipoproteinemia diagnosed by their blood work during the first recruitment, male participants, despite similar ages and BMIs, had higher HbA1c levels and reduced levels of hs-CRP (Supplemental Table 1, Supplemental digital content 1, http://links.lww.com/FPC/A783). The subpopulation of individuals with dyslipoproteinemia was further divided into several subgroups according to their observed lipid profile. Those subgroups summarized patients with isolated hypertriglyceridaemia (only TG elevated), isolated hypercholesterolaemia (LDL-cholesterol or LDL-cholesterol and TC elevated), pandyslipoproteinemia (TG and LDL-cholesterol and TC elevated) and isolated hypo-HDL-aemia (only HDL-cholesterol reduced). As shown in Fig. 1, in this population, female participants appeared more likely to have isolated hypercholesterolaemia, whereas male participants appeared more likely to have pandyslipoproteinemia with elevation of TGs and cholesterol. There is one important limitation in the above-mentioned analysis, which needs to be highlighted at this point. The quantification of lipid parameters was not performed in a standardized fasting state. However, by using the nonfasting blood values, we underestimated the prevalence of hypercholesterolaemia [26% overall, 31% for individuals fasting (= not eating) for at least 7 h], whereas hypertriglyceridaemia was overestimated (40% overall vs. 29% for individuals fasting for at least 7 h). This yields a biased estimation of dyslipoproteinemia.

Assessment of the OATP1B1 genotype and lipid parameters in treatment-naive individuals in SHIP-0

It had been suggested before that genetic variants of OATP1B1 are associated with increased endogenous cholesterol synthesis [22]. We determined the influence of OATP1B1 variants on nonfasting lipid parameters in treatment-naive individuals in SHIP-0 (Fig. 1, inset). These individuals had been assessed for the 388A > G variant did not indicate any association of pathological lipid profiles with the genotype of the hepatic uptake transporter.

Lipid parameters in patients diagnosed with dyslipoproteinemia in SHIP-0 and treated with statins in SHIP-1

As mentioned before, a total of 214 individuals were summarized in the statin therapy group for statistical analysis (Fig. 2, inset). These individuals had been diagnosed with dyslipoproteinemia in SHIP-0 on the basis of the determination of lipid parameters and received statin therapy until the re-examination in SHIP-1. Importantly, the c.SLCO1B1 521T > C variants did not influence the levels of LDL-cholesterol (ANOVA P = 0.871, Fig. 2a) or of TC (P = 0.861, Fig. 2b) at the baseline examination. We observed, however, a trend towards lower levels of
LDL-cholesterol in heterozygote carriers of the SLCO1B1 c.388A>G polymorphism ($P=0.09$, Fig. 2c). Similar results were obtained for the TC plasma levels at baseline in individuals harbouring the SLCO1B1 c.388AG genotype ($P=0.033$, Fig. 2d). However, it seems noteworthy that 5% lower TC levels as observed in
individuals are assumed to be of limited clinical significance. Second, there is no gene–dose effect, suggesting that this result is not directly associated with the SLCO1B1 genotype. The impact of the previously reported OATP1B1 haplotypes including the SLCO1B1*11b (c.388G, c.521T), SLCO1B1*15 (388G, 521C) and SLCO1B1*5 (388A, 521C) variants was determined. Individuals harbouring at least one mutation in positions 388 and 521, respectively, were summarized in the SLCO1B1*15 group (*63), whereas SLCO1B1*11b (n=6) represents individuals carrying at least one mutation at position 388 and a homozygous wild-type allele in position 521. Thus, SLCO1B1*5 (n=6) summarizes individuals carrying at least one mutated allele in position 521 and a homozygous wild-type allele at 388. The baseline LDL-cholesterol levels detected were statistically significantly lower in individuals harbouring the SLCO1B1*11b variant compared with those carrying the SLCO1B1*1a genotype (Table 1). In the following, the statistical analyses have to be adjusted for baseline levels.

Association of OATP1B1 polymorphisms and changes in lipid parameters

Interestingly, dyslipoproteinemia in SHIP-0 led to an initiation of antilipidaemic drug therapy in the 5-year follow-up period in only 10.5% of the cases. In SHIP-1, 8.7 or 14.0% of the individuals had isolated hypercholesterolaemia or pandyslipoproteinemia, respectively, and therefore indications for statin therapy were treated. Despite this low figure of statin-treated patients, high LDL-cholesterol at baseline was related to initiating a statin therapy in the 5-year follow-up period [OR for incident statin therapy = 3.04 (1.90; 4.85)]. In contrast, elevated TG, TC and lowered HDL-cholesterol levels were not significantly associated with statin use.

Testing the influence of SNPs on the efficacy of statins in general, by comparing the per cent change in LDL-cholesterol and TC levels, indicated a tendency towards an impaired efficacy of statins. Similar results were obtained on testing the influence of the SLCO1B1 c.388G > A genotype on LDL-lowering and TC-lowering efficacy of particular statins. However, it appears that individuals harbouring the c.521C allele showed a tendency towards an impaired efficacy of statins, whereas a trend towards higher efficacy of atorvastatin was observed in individuals receiving this particular statin. Importantly, there was no difference in dosing. It appears that the efficacy of atorvastatin is different from that of other statins. Assessment of all other statins together showed a significant effect of the genotype on statin efficacy (compare Tables 2 and 3). For further analyses, patients treated with simvastatin, pravastatin and atorvastatin are considered separately.

Table 1: Haplotype analysis on baseline levels of lipid parameters in patients diagnosed with dyslipoproteinemia according to the definition by the American Society of Cardiology that started treatment with statins until the recruitment in SHIP-1 (data were analysed using a linear regression model)

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>n</th>
<th>Triglycerides (mmol/l)</th>
<th>P-value</th>
<th>LDL-cholesterol (mmol/l)</th>
<th>P-value</th>
<th>Total cholesterol (mmol/l)</th>
<th>P-value</th>
<th>HDL/ LDL-ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLCO1B1*11a</td>
<td>64</td>
<td>2.06±0.17</td>
<td>–</td>
<td>4.89±0.14</td>
<td>–</td>
<td>7.08±0.15</td>
<td>–</td>
<td>0.297±0.012</td>
<td>–</td>
</tr>
<tr>
<td>SLCO1B1*11b</td>
<td>84</td>
<td>2.31±0.14</td>
<td>0.264</td>
<td>4.44±0.12</td>
<td>0.023</td>
<td>6.65±0.13</td>
<td>0.043</td>
<td>0.316±0.011</td>
<td>0.283</td>
</tr>
<tr>
<td>SLCO1B1*15</td>
<td>56</td>
<td>2.25±0.17</td>
<td>0.442</td>
<td>4.68±0.14</td>
<td>0.319</td>
<td>6.92±0.16</td>
<td>0.477</td>
<td>0.307±0.013</td>
<td>0.619</td>
</tr>
<tr>
<td>SLCO1B1*5</td>
<td>6</td>
<td>1.55±0.55</td>
<td>0.382</td>
<td>4.12±0.46</td>
<td>0.119</td>
<td>6.54±0.51</td>
<td>0.120</td>
<td>0.334±0.041</td>
<td>0.410</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SHIP, Study of Health in Pomerania.

SLCO1B1 genotype on meeting the target LDL levels

Following the recommendations of the NCEP-ATPIII guidelines [18], statin treatment goals depend on the risk of CHD, which is determined in the Framingham CHD risk assessment. Inclusion of this individual risk in the analysis on the impact of OATP1B1 variants on the statin efficacy showed that patients treated with simvastatin or pravastatin and harbouring the SLCO1B1 521C allele were less likely to achieve the treatment goal at the 5-year follow-up (Fig. 4). This was statistically significant for individuals harbouring the 521C allele and receiving simvastatin in particular (χ²-test; P=0.02). There was no such effect on atorvastatin efficacy (% of individuals reaching the treatment goal c.SLCO1B1 521TT 69.9% vs.
Impact of \textit{SLCO1B1} missense mutations on the efficacy of statins determined by the % change in LDL-cholesterol (a, c) and total cholesterol (b, d). Data are presented as mean ± SD. Statistical analysis was carried out using a linear regression model adjusted for baseline levels and simvastatin equipotent doses; \textit{SLCO1B1} c.521TT (n=148) and c.521TC and CC (n=66); \textit{SLCO1B1} c.388AA (n=70) and c.388AG and GG (n=144). LDL, low-density lipoprotein; SHIP, Study of Health in Pomerania; TC, total cholesterol. *P<0.05.
Change in total cholesterol (%)

LDL, low-density lipoprotein; TC, total cholesterol.

was used.

several studies [5,24]

lowering response to statin therapy has been the focus of

The genetic contribution towards variation in the lipid-

c.

388 genotype.

Similarly, no effect on reaching treatment goals was

observed when testing the association with the SLCO1B1

388 genotype.

Table 2 Association of the SLCO1B1 521T > C and mean change in LDL cholesterol or TC for particular statins

<table>
<thead>
<tr>
<th>c.SLCO1B1 521TT</th>
<th>c.SLCO1B1 521TC and CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean change</td>
</tr>
<tr>
<td>ΔLDL cholesterol (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 77</td>
<td>-1.78 ± 0.07</td>
</tr>
</tbody>
</table>
| Lovastatin 2 | 0.50 | 2 | -0.81 | -
| Pravastatin 28 | -1.48 ± 0.12 | 8 | -0.87 ± 0.19 | 0.011 |
| Fluvastatin 14 | -1.28 ± 0.20 | 8 | -0.82 ± 0.28 | 0.243 |
| All abovea | 121 | -1.66 ± 0.06 | 52 | -1.33 ± 0.09 | 0.010 |
| Atorvastatin 27 | -1.88 ± 0.13 | 14 | -2.28 ± 0.19 | 0.104 |
| ΔTotal cholesterol (mmol/l) |
| Simvastatin 77 | -2.13 ± 0.08 | 30 | -1.87 ± 0.13 | 0.119 |
| Lovastatin 2 | -1.29 | 2 | -1.08 | -
| Pravastatin 28 | -1.57 ± 0.20 | 12 | -1.00 ± 0.30 | 0.134 |
| Fluvastatin 14 | -1.28 ± 0.24 | 8 | -1.09 ± 0.33 | 0.680 |
| All abovea | 121 | -1.66 ± 0.08 | 52 | -1.52 ± 0.12 | 0.013 |
| Atorvastatin 27 | -2.19 ± 0.17 | 14 | -2.36 ± 0.24 | 0.580 |

Change in LDL cholesterol (%) |
| Simvastatin 77 | -370 ± 1.56 | 30 | -33.6 ± 2.5 | 0.249 |
| Lovastatin 2 | -16.07 | 2 | -18.46 | -
| Pravastatin 28 | -31.6 ± 3.6 | 12 | -15.6 ± 5.5 | 0.022 |
| Fluvastatin 14 | -26.7 ± 4.4 | 8 | -18.2 ± 6.5 | 0.324 |
| All abovea | 121 | -34.1 ± 1.4 | 52 | -26.6 ± 2.2 | 0.077 |
| Atorvastatin 27 | -36.3 ± 2.8 | 14 | -43.7 ± 3.9 | 0.134 |

Change in total cholesterol (%) |
| Simvastatin 77 | -30.0 ± 1.3 | 30 | -26.4 ± 2.0 | 0.148 |
| Lovastatin 2 | -22.6 | 2 | -17.0 | -
| Pravastatin 28 | -22.4 ± 3.8 | 12 | -10.9 ± 5.9 | 0.116 |
| Fluvastatin 14 | -18.3 ± 3.5 | 8 | -16.0 ± 4.8 | 0.730 |
| All abovea | 121 | -26.8 ± 1.3 | 52 | -20.7 ± 2.0 | 0.012 |
| Atorvastatin 27 | -30.2 ± 2.2 | 14 | -32.2 ± 3.1 | 0.612 |

Statin dose (mg) |
| Simvastatin 77 | 23.1 ± 1.3 | 30 | 23.6 ± 2.1 | 0.826 |
| Lovastatin 2 | 15.7 | 2 | 14.2 | -
| Pravastatin 28 | 19.7 ± 2.2 | 12 | 24.8 ± 3.4 | 0.252 |
| Fluvastatin 14 | 65.1 ± 5.6 | 8 | 40.9 ± 7.8 | 0.022 |
| All abovea | 121 | 54.0 ± 6.8 | 52 | 52.6 ± 10.4 | 0.911 |
| Atorvastatin 27 | 178 ± 1.9 | 14 | 166 ± 2.6 | 0.717 |

Mean changes were derived from linear regression models adjusted for statin dose and baseline values.

LDL, low-density lipoprotein; TC, total cholesterol.

aFor analysis of the summarized statin group, the simvastatin equipotent dose was used.

Discussion

The genetic contribution towards variation in the lipid-

lowering response to statin therapy has been the focus of several studies [5,24-27]. Even though hepatic uptake transporters, particularly OATP1B1, have been studied extensively for their implication in hepatocellular accumulation of substrate drugs showing a significant influence of function-impaired polymorphisms on pharmacokinetic parameters, studies focusing on the role of those transporters in governing pharmacodynamics are still limited. In the present report, we used a population-based cohort study to evaluate the impact of function-impaired polymorphisms on the real-life outcome of statin therapy. In detail, we report that OATP1B1, particularly the 521T > C polymorphism, results in a trend towards lower drug efficacy as indicated by the changes in both LDL and TC levels (Fig. 3). In accordance with the assumption of lower efficacy because of limited hepatic uptake were findings on OATP1B1 functioning as a determinant of successful statin therapy assessed to determine the likelihood of achieving treatment goals according to the NCEP-ATPIII guidelines (Fig. 4). As mentioned before, statin therapy is accepted widely as an important strategy to reduce cardiovascular incidences; assuming that the OATP1B1 genotype is predictive for the efficacy of this treatment would suggest that genotyping before starting treatment could be a useful tool to stratify patients at risk.

Surprisingly, our data indicate that patients treated with atorvastatin, even if characterized as a substrate of OATP1B1 [28,29], did not show a predictive value of the SLCO1B1 genotype on drug efficacy or treatment outcome. This is in accordance with the findings obtained by Thompson et al. [6], who carried out a genome-wide association study that sought markers predictive for LDL-cholesterol reduction in a population summarizing
genetic information of 5745 patients treated with atorvastatin. Testing candidate gene polymorphisms in another cohort, they provided evidence that OATP1B1 polymorphisms might be associated with an increase in HDL in patients treated with fluvastatin, whereas no association was observed in patients treated with atorvastatin [30]. Similarly, Fu et al. [31] reported no significant effect on atorvastatin efficacy in a Chinese population. In agreement with this are findings showing that genetic variants of OATP1B1 are not predictive for atorvastatin-associated myopathic side effects [15]. It should be noted at this point that in healthy volunteers, the OATP1B1 polymorphisms exerted a more pronounced effect on pharmacokinetic parameters of the atorvastatin acid levels compared with the less lipophilic rosuvastatin [32]. In addition, Lau et al. [33] suggested
that even if elimination of atorvastatin is governed by multiple mechanisms including CYP enzymes and efflux-mediating ABC transporters, the hepatic uptake transporter might be the limiting factor in pharmacokinetics. Recently, a genetic variant of the efflux transporter ABCG2 has been identified to be associated with the LDL-reducing efficacy of rosuvastatin performing a Genome-wide association scan [34]. In general, despite being summarized in one compound class, statins differ markedly in their pharmacokinetics. Indeed, the more lipophilic compounds such as the simvastatin, atorvastatin and lovastatin studied here are mainly metabolized by cytochrome P450 (CYP) 3A, whereas pravastatin is excreted mostly unchanged. In addition, statins differ in their affinity (determined as $K_m$ value in vitro) to the OATP1B1 transporter, with the following values determined in vitro for the particular statin 12.4 μmol/l for atorvastatin [11,28,33], 1.4–3.5 μmol/l for fluvastatin [35,36] and 14–34 μmol/l for the less lipophilic pravastatin [11,37,38].

For pravastatin, several studies have focused on the impact of the genetic makeup of the uptake transporter on the efficacy. Tachibana-Iimori et al. [39] explored retrospectively the efficacy of atorvastatin, pravastatin and simvastatin, showing attenuated response of statins in terms of TC reduction. Similarly, Zhang et al. [40] found an effect of the genotype after 30 days of treatment with pravastatin (20 mg/day). In contrast, Igel et al. [41] could not find more than a weak trend after 21 days of treatment with 40 mg pravastatin. Similarly, a lower LDL-cholesterol response (~1.28% per allele) has been reported for simvastatin by the SEARCH collaborative group [14]. It has been suggested previously that the $SLCO1B1$ genotype is only predictive of a slower response to pravastatin treatment as genotype-associated reduction in TC was only observed in the assessment after 8 weeks, but not after a 1-year treatment [42].

Furthermore, a population-based survey showed an influence of genetic variants in the efflux transporter ABCB1 genotype on simvastatin efficacy in men by showing that previously identified SNPs are associated with larger reduction of lipid parameters than carriers of the wild-type haplotype [43]. Similarly, Tomlinson et al. [44] reported a significant effect of genetic variants of the ABCG2 transporter in a patient cohort treated with rosuvastatin. In summary, the present work confirms our hypothesis of intrahepatic drug effects as assessed by reaching treatment goals being dependent on the genetic makeup of hepatocellular uptake transport. However, one limitation of this study is that the duration of treatment was not assessed. This should be included in future population-based cohorts if pharmacogenomics analyses have to be carried out. In addition, if accounting for multiple testing as performed in this particular study to cover various aspects of the relationship between genotype and drug efficacy, the statistical significance of the findings is no longer confirmed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**


Identification of a liver-specific human organic anion transporting polypeptide


