Function-impairing polymorphisms of the hepatic uptake transporter *SLCO1B1* modify the therapeutic efficacy of statins in a population-based cohort

Henriette E. Meyer zu Schwabedissen[a,b], Martin Albers[c], Sebastian E. Baumeister[c], Christian Rimmbach[a], Matthias Nauck[d], Henri Wallaschofski[d], Werner Siegmund[b], Henry Völzke[c] and Heyo K. Kroemer[b]

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.**

Pharmacogenetics and Genomics 2015, **25**:8–18

Keywords: drug efficacy, hypercholesterolaemia, OATP1B1, statins

[a]Biopharmacy Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, [b]Institute of Pharmacology, [c]Institute of Community Medicine and [d]Institute of Clinical Chemistry and Laboratory Medicine, Ernst Moritz Arndt University of Greifswald, Greifswald, Germany

Correspondence to Henriette E. Meyer zu Schwabedissen, MD, Biopharmacy Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland
Tel: +41 61 2671495; fax: +41 61 2671498;
e-mail: h.meyerzuschwabedissen@unibas.ch

Received 27 June 2013 **Accepted** 2 October 2014

Introduction

One class of drugs used commonly in the primary and secondary prevention of atherosclerosis are statins. Inhibition of the hepatic 3-hydroxymethyl-3-glutaryl coenzyme A reductase (HMGCR) blocks endogenous cholesterol synthesis and results in decreased cholesterol levels, an effect driven mainly by upregulation of hepatocellular low-density lipoprotein (LDL) receptors and internalization of cholesterol-rich lipoproteins. With their efficacy documented in a large number of clinical trials, statins are prescribed chronically for millions of patients. 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,

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (*www.pharmacogeneticsandgenomics.com*).

1744-6872 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/FPC.0000000000000098

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 allele *SLCO1B1* c.521C ($r^2 = 0.97$). In addition, the authors report findings from the HPS study, where LDL reductions were $1.28 \pm 0.25\%$ smaller per copy of the *SLCO1B1* c.521C allele and $0.62 \pm 0.18\%$ 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 *SLCO1B1* c.521T > C and SLCO1B1 c.388A > G [12,13]. Assessment for the c.SLCO1B1 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.*SLCO1B1* 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 equipotent dose is used instead of the actual statin dose. The equipotent doses have been calculated as described by Helfand *et al.* [21]. Furthermore, the χ^2-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).

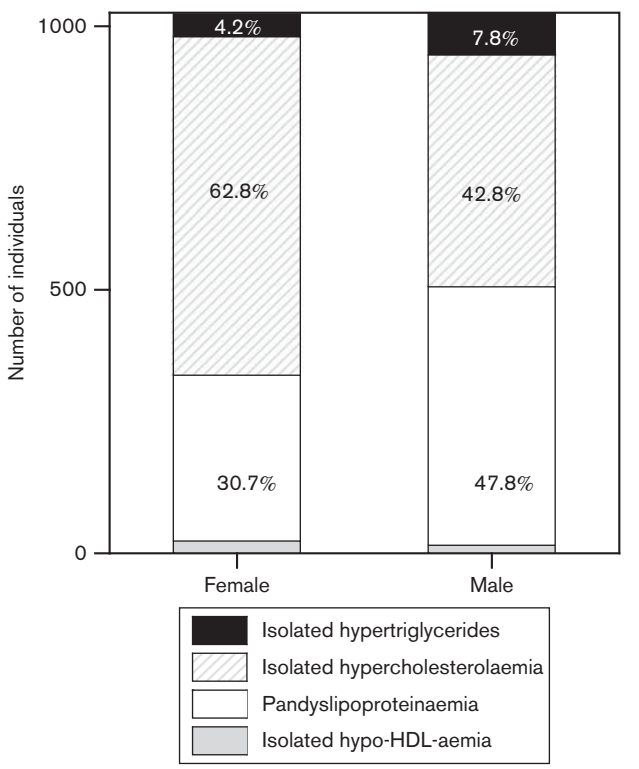
Results

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 dyslipoproteinaemia 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 dyslipoproteinaemia 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 dyslipoproteinaemia 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), pandyslipoproteinaemia (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 pandyslipoproteinaemia 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 dyslipoproteinaemia.

Fig. 1



After assessment of lipid parameters, female and male patients with dyslipoproteinaemia were assigned to subgroups with isolated hypertriglyceridaemia, isolated hypercholesterolaemia, pandyslipoproteinaemia and isolated hypo-HDL-aemia. Data are presented as number of individuals on the basis of the proportion observed in the dyslipoproteinaemic subpopulation. Multinomial regression analysis shows that the proportion is statistically significantly different. HDL, high-density lipoprotein.

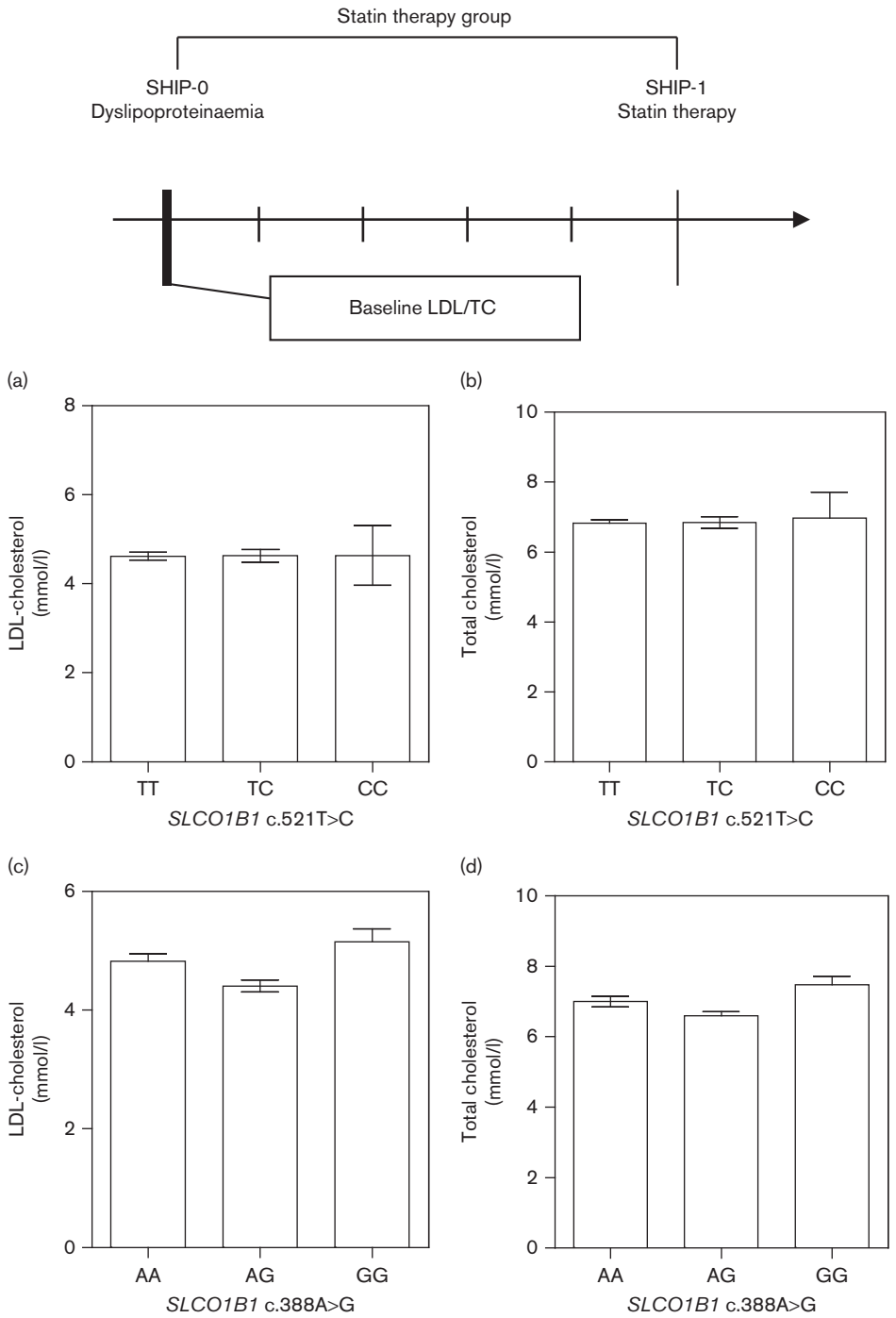
Association of the OATP1B1 genotype and lipid parameters in treatment-naïve individuals in SHIP-0

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 the subpopulation with dyslipoproteinaemia according to the ATPIII guidelines [18]. Importantly, there was no difference in the c.521C allele frequency (0.17) in this subgroup compared with previously published frequencies in a White population (0.14) [23] or the frequency in the rest of the SHIP population. Similarly, the frequency of the 388G allele was comparable to those reported previously (0.39 compared with published 0.30) [23]. At baseline, there was no association of the *SLCO1B1* c.521T > C genotype with LDL or TC plasma levels, respectively, either in patients with isolated hypercholesterolaemia (mean ± SD LDL-cholesterol, *SLCO1B1* c.521TT 3.97 ± 0.03, $n=795$; TC 3.90 ± 0.03, $n=340$; CC 3.85 ± 0.13, $n=26$, $P=0.514$; mean TC c. SLCO1B1 521TT 6.12 ± 0.03, TC 6.05 ± 0.04, CC 5.94 ± 0.14, $P=0.453$) or in patients with pandyslipoproteinaemia [mean ± SD LDL-cholesterol, *SLCO1B1* c.521TT 4.08 ± 0.03, $n=614$; TC 4.17 ± 0.06, $n=243$; CC 4.20 ± 0.22, $n=23$ analysis of variance (ANOVA) $P=0.457$; mean ± SD TC c.*SLCO1B1* 521TT 6.47 ± 0.04; TC 6.65 ± 0.06; CC 6.66 ± 0.21, $P=0.113$]. Similarly, assessment 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 dyslipoproteinaemia 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 dyslipoproteinaemia 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 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

Fig. 2



Baseline LDL and TC levels in individuals genotyped for *SLCO1B1* c.521T > C (a, b) or *SLCO1B1* c.388A > G (c, d); these patients were diagnosed with dyslipoproteinaemia in SHIP-0 and were treated with statins within the 5-year follow-up (schematic). Data are presented as mean ± SD. Statistical analysis was carried out using a linear regression model adjusted for age and sex. *SLCO1B1* c.521TT ($n = 148$), c.521TC ($n = 63$), c.521CC ($n = 3$). *SLCO1B1* c.388AA ($n = 70$), c.388AG ($n = 118$), c.388GG ($n = 26$). LDL, low-density lipoprotein; SHIP, Study of Health in Pomerania; TC, total cholesterol.

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 c.*SLCO1B1* 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**1b (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 ($n=63$), whereas *SLCO1B1**1b ($n=86$) 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*1b* 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, dyslipoproteinaemia 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 pandyslipoproteinaemia, 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 lower efficacy of statins for LDL-cholesterol (ANOVA $P=0.082$, Fig. 3a) and TC (ANOVA $P=0.035$, Fig. 3b) plasma level reduction in individuals harbouring the 521C variant, respectively (Fig. 3). Similar results were obtained for the *SLCO1B1* c.388A > G variant, where a tendency for reduced LDL-lowering (ANOVA $P=0.033$, Fig. 3c) and TC-lowering (ANOVA $P=0.252$, Fig. 3d) efficacy associated with the *SLCO1B1* c.388G allele was observed. The statistical analysis was adjusted for baseline lipid levels and statin doses; for this, the simvastatin equipotent doses were calculated as described previously by Helfand *et al.* [21].

However, even if statins are well-known substrates of the hepatic OATP1B1 transporter, individual statins differ in their affinity to this particular uptake transporter. To elucidate the impact of OATP1B1 on individual statins, the statin therapy group was stratified according to the compound used in therapy. Most of the individuals in the population studied here were treated with simvastatin (50.9%, $n=110$), followed by pravastatin (18.5%, $n=40$) and atorvastatin (18.0%, $n=39$) (compare Tables 2 and 3). As shown in Table 2, there was no statistically significant effect of the *SLCO1B1* c.521T > C genotype on LDL-lowering and TC-lowering efficacy of particular statins. Similar results were obtained on testing the influence of the *SLCO1B1* c.388G > A genotype on LDL-lowering and TC-lowering efficacy. 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.

SLCO1B1 genotype on meeting the target LDL levels

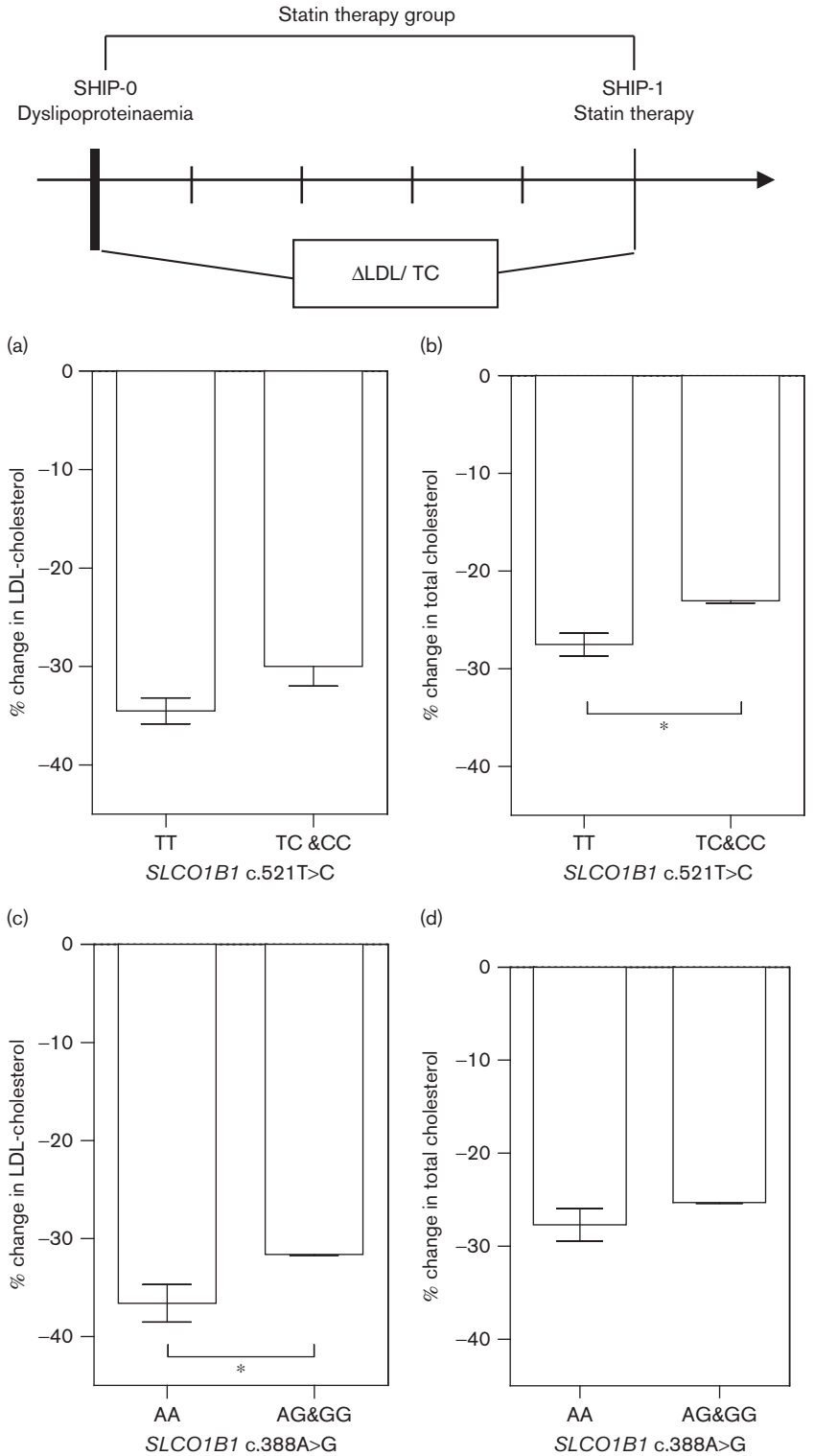
Following the recommendations of the NCEP-ATPIII guidelines [18], statin treatment goals depend on the risk of CHD, which is determined in the Framingham CHD risk assessment. Inclusion of this individual risk in the analysis on the impact of OATP1B1 variants on the statin efficacy showed that patients 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 (χ^2-test; $P=0.02$). There was no such effect on atorvastatin efficacy (% of individuals reaching the treatment goal c.*SLCO1B1* 521TT 69.9% vs.

Table 1 Haplotype analysis on baseline levels of lipid parameters in patients diagnosed with dyslipoproteinaemia 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)

Haplotypes	*n*	Triglycerides (mmol/l)	*P*-value	LDL-cholesterol (mmol/l)	*P*-value	Total cholesterol (mmol/l)	*P*-value	HDL/LDL-ratio	*P*-value
SLCO1B1*1a	64	2.06 ± 0.17	–	4.89 ± 0.14	–	7.08 ± 0.15	–	0.297 ± 0.012	–
SLCO1B1*1b	84	2.31 ± 0.14	0.264	4.44 ± 0.12	0.023	6.65 ± 0.13	0.043	0.316 ± 0.011	0.283
SLCO1B1*15	60	2.25 ± 0.17	0.442	4.68 ± 0.14	0.319	6.92 ± 0.16	0.477	0.307 ± 0.013	0.619
SLCO1B1*5	6	1.55 ± 0.55	0.382	4.12 ± 0.46	0.119	6.24 ± 0.51	0.120	0.334 ± 0.041	0.410

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

Fig. 3



Impact of *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; *SLCO1B1* c.521TT ($n = 148$) and c.521TC and CC ($n = 66$); *SLCO1B1* c.388AA ($n = 70$) and c388AG and GG ($n = 144$). LDL, low-density lipoprotein; SHIP, Study of Health in Pomerania; TC, total cholesterol. *$P<0.05$.

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

	c.*SLCO1B1* 521TT		c.*SLCO1B1* 521TC and CC		
	n	Mean change	*n*	Mean change	*P*-value
ΔLDL cholesterol (mmol/l)					
Simvastatin	77	−1.78 ± 0.07	30	−1.64 ± 0.11	0.295
Lovastatin	2	−0.50	2	−0.81	–
Pravastatin	28	−1.48 ± 0.12	12	−0.87 ± 0.19	0.011
Fluvastatin	14	−1.28 ± 0.20	8	−0.82 ± 0.28	0.243
All above[a]	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 above[a]	121	−1.88 ± 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	−37.0 ± 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 ± 6.2	0.324
All above[a]	121	−34.1 ± 1.4	52	−26.8 ± 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 above[a]	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	24.6 ± 3.4	0.252
Fluvastatin	14	65.1 ± 5.6	8	40.9 ± 7.6	0.022
All above[a]	121	54.0 ± 6.8	52	52.6 ± 10.4	0.911
Atorvastatin	27	17.8 ± 1.9	14	16.6 ± 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.
[a]For analysis of the summarized statin group, the simvastatin equipotent dose was used.

Table 3 Association of the SLCO1B1 388A > G and mean change in LDL cholesterol or TC for particular statins

	c.*SLCO1B1* 388AA		c.*SLCO1B1* 388AG and GG		
	n	Mean change	*n*	Mean change	*P*-value
ΔLDL cholesterol (mmol/l)					
Simvastatin	41	−1.78 ± 0.09	66	−1.71 ± 0.07	0.539
Lovastatin	0	–	4	−0.65 ± 0.15	–
Pravastatin	10	−1.59 ± 0.22	30	−1.20 ± 0.12	0.129
Fluvastatin	5	−1.21 ± 0.34	17	1.08 ± 0.17	0.747
All above[a]	56	−1.68 ± 0.09	117	−1.46 ± 0.06	0.044
Atorvastatin	14	−2.17 ± 0.19	27	−1.94 ± 0.14	0.346
ΔTotal cholesterol (mmol/l)					
Simvastatin	41	−2.09 ± 0.11	66	−2.03 ± 0.09	0.690
Lovastatin	0	–	4	−1.19 ± 0.09	–
Pravastatin	10	−1.23 ± 0.34	30	−1.45 ± 0.19	0.579
Fluvastatin	5	−1.00 ± 0.39	17	−1.27 ± 0.20	0.566
All above[a]	56	−1.85 ± 0.11	117	−1.74 ± 0.08	0.449
Atorvastatin	14	−2.49 ± 0.23	27	−2.12 ± 0.16	0.207
Change in LDL cholesterol (%)					
Simvastatin	41	−36.3 ± 2.1	66	−35.9 ± 1.7	0.870
Lovastatin	0	–	4	−17.26 ± 1.1	–
Pravastatin	10	−33.9 ± 6.4	30	−24.5 ± 3.6	0.213
Fluvastatin	5	−27.7 ± 7.5	17	−22.4 ± 3.8	0.550
All above[a]	56	−35.0 ± 2.2	117	−30.4 ± 1.5	0.092
Atorvastatin	14	−43.6 ± 3.9	27	−36.3 ± 2.8	0.141
Change in total cholesterol (%)					
Simvastatin	41	−28.8 ± 1.8	66	−29.1 ± 1.4	0.913
Lovastatin	0	–	4	−19.8 ± 2.5	–
Pravastatin	10	−16.7 ± 6.7	30	−19.7 ± 3.8	0.707
Fluvastatin	5	−16.0 ± 5.7	17	−17.9 ± 3.0	0.790
All above[a]	56	−25.9 ± 2.0	117	−24.5 ± 1.3	0.587
Atorvastatin	14	−35.6 ± 3.0	27	−28.4 ± 2.1	0.064
Statin dose (mg)					
Simvastatin	41	23.8 ± 1.8	66	22.8 ± 1.4	0.673
Lovastatin	0	–	4	15.0	–
Pravastatin	10	17.8 ± 3.8	30	22.3 ± 2.2	0.313
Fluvastatin	5	72.1 ± 9.9	17	51.7 ± 5.3	0.087
All above[a]	56	49.4 ± 10.0	117	55.5 ± 6.9	0.622
Atorvastatin	14	17.1 ± 2.6	27	17.5 ± 1.9	0.890

Mean changes were derived from linear regression models adjusted for statin dose and baseline values.
LDL, low-density lipoprotein; TC, total cholesterol.
[a]For analysis of the summarized statin group, the simvastatin equipotent dose was used.

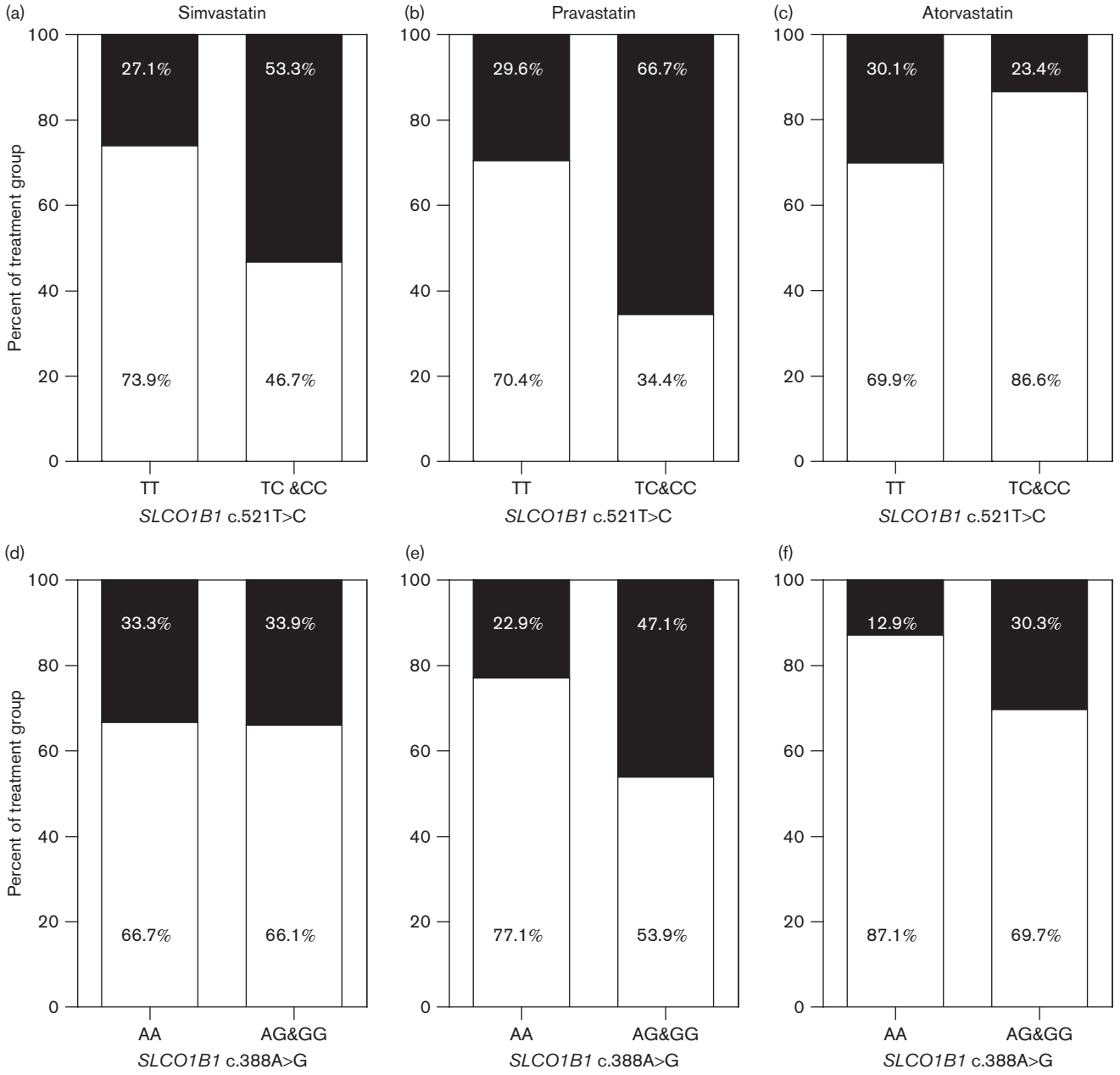
c.*SLCO1B1* 521TC and CC 86.6%, χ^2-test; $P = 0.212$). Similarly, no effect on reaching treatment goals was observed when testing the association with the *SLCO1B1* 388 genotype.

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-impairing 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-impairing 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

Fig. 4



Effect of the c.*SLCO1B1* 521T > C and 388A > G polymorphisms on the likelihood of reaching the treatment goal with simvastatin (a, d) pravastatin (b, e) and atorvastatin (c, f) according to the individual CHD risk assessment. The risk of CHD was assessed as recommended by the NCEP-ATPIII guidelines for each individual included in this analysis. *Black* did not reach treatment goal, *white* did reach treatment goal. Statistical analysis was carried out using binary logistic regression models that were adjusted for statin dose. CHD, coronary heart disease.

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.

Acknowledgements

This work is also part of the research project 'Greifswald Approach to Individualized Medicine (GANI_MED)'. The contributions to data collection made by field workers, study physicians, ultrasound technicians, interviewers and computer assistants are gratefully acknowledged.

SHIP is part of the Community Medicine Net (*http://medizin.uni-greifswald.de/icm*) of the University of Greifswald funded by grants from the German Federal Ministry of Education and Research (BMBF, grant 01ZZ96030, 01ZZ0701). This work was supported by the GANI_MED-project (Greifswald Approach to INdIvidualized MEDicine), funded by the Federal Ministry of Science and Technology, Berlin, Germany (03IS2061A).

Conflicts of interest

There are no conflicts of interest.

References

1 Bucher HC, Griffith LE, Guyatt GH. Systematic review on the risk and benefit of different cholesterol-lowering interventions. *Arterioscler Thromb Vasc Biol* 1999; **19**:187–195.
2 Krauss RM, Mangravite LM, Smith JD, Medina MW, Wang D, Guo X, *et al.* Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation* 2008; **117**:1537–1544.
3 Simon JA, Lin F, Hulley SB, Blanche PJ, Waters D, Shiboski S, *et al.* Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: the Cholesterol and Pharmacogenetics (CAP) Study. *Am J Cardiol* 2006; **97**:843–850.
4 Versmissen J, Oosterveer DM, Yazdanpanah M, Mulder M, Dehghan A, Defesche JC, *et al.* A frequent variant in the ABCA1 gene is associated with increased coronary heart disease risk and a better response to statin treatment in familial hypercholesterolemia patients. *Eur Heart J* 2011; **32**:469–475.
5 Mangravite LM, Medina MW, Cui J, Pressman S, Smith JD, Rieder MJ, *et al.* Combined influence of LDLR and HMGCR sequence variation on lipid-lowering response to simvastatin. *Arterioscler Thromb Vasc Biol* 2010; **30**:1485–1492.
6 Thompson JF, Hyde CL, Wood LS, Paciga SA, Hinds DA, Cox DR, *et al.* Comprehensive whole-genome and candidate gene analysis for response to statin therapy in the Treating to New Targets (TNT) cohort. *Circ Cardiovasc Genet* 2009; **2**:173–181.
7 Cerda A, Genvigir FD, Arazi SS, Hirata MH, Dorea EL, Bernik MM, *et al.* Influence of SCARB1 polymorphisms on serum lipids of hypercholesterolemic individuals treated with atorvastatin. *Clin Chim Acta* 2010; **411 (9–10)**:631–637.
8 Kajinami K, Brousseau ME, Ordovas JM, Schaefer EJ. A promoter polymorphism in cholesterol 7alpha-hydroxylase interacts with apolipoprotein E genotype in the LDL-lowering response to atorvastatin. *Atherosclerosis* 2005; **180**:407–415.
9 Kajinami K, Brousseau ME, Ordovas JM, Schaefer EJ. Interactions between common genetic polymorphisms in ABCG5/G8 and CYP7A1 on LDL cholesterol-lowering response to atorvastatin. *Atherosclerosis* 2004; **175**:287–293.
10 Srivastava A, Garg N, Srivastava K, Mittal B. Effect of genetic variant (rs11887534) in ABCG8 gene in coronary artery disease and response to atorvastatin therapy. *Dis Markers* 2010; **28**:307–313.
11 Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, Yang WP, *et al.* A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide

and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J Biol Chem* 1999; **274**:37161–37168.
12 Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *J Biol Chem* 2001; **276**:35669–35675.
13 Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* 2011; **63**:157–181.
14 Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, *et al*. SLCO1B1 variants and statin-induced myopathy – a genomewide study. *N Engl J Med* 2008; **359**:789–799.
15 Brunham LR, Lansberg PJ, Zhang L, Miao F, Carter C, Hovingh GK, *et al*. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J* 2012; **12**:233–237.
16 Volzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, *et al*. Cohort profile: the Study of Health in Pomerania. *Int J Epidemiol* 2011; **40**:294–307.
17 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97**:1837–1847.
18 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285**:2486–2497.
19 Nauck M, Winkler K, Marz W, Wieland H. Quantitative determination of high-, low-, and very-low-density lipoproteins and lipoprotein(a) by agarose gel electrophoresis and enzymatic cholesterol staining. *Clin Chem* 1995; **41 (Pt 1)**:1761–1767.
20 Teumer A, Rawal R, Homuth G, Ernst F, Heier M, Evert M, *et al*. Genome-wide association study identifies four genetic loci associated with thyroid volume and goiter risk. *Am J Hum Genet* 2011; **88**:664–673.
21 Helfand M, Carson S, Kelley C. *Drug class review on HMG-CoA reductase inhibitors (statins): final report*. Portland, OR; 2006.
22 Pasanen MK, Miettinen TA, Gylling H, Neuvonen PJ, Niemi M. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. *Pharmacogenet Genomics* 2008; **18**:921–926.
23 Meyer zu Schwabedissen HE, Kim RB. Hepatic OATP1B transporters and nuclear receptors PXR and CAR: interplay, regulation of drug disposition genes, and single nucleotide polymorphisms. *Mol Pharm* 2009; **6**:1644–1661.
24 Barber MJ, Mangravite LM, Hyde CL, Chasman DI, Smith JD, McCarty CA, *et al*. Genome-wide association of lipid-lowering response to statins in combined study populations. *PLoS One* 2010; **5**:e9763.
25 Mangravite LM, Wilke RA, Zhang J, Krauss RM. Pharmacogenomics of statin response. *Curr Opin Mol Ther* 2008; **10**:555–561.
26 Takahashi T, Takahashi K, Yamashina M, Maesawa C, Kajiwara T, Taneichi H, *et al*. Association of the TNF-{alpha}-C-857T polymorphism with resistance to the cholesterol-lowering effect of HMG-CoA reductase inhibitors in type 2 diabetic subjects. *Diabetes Care* 2010; **33**:463–466.
27 Medina MW. The relationship between HMGCR genetic variation, alternative splicing, and statin efficacy. *Discov Med* 2010; **9**:495–499.
28 Kameyama Y, Yamashita K, Kobayashi K, Hosokawa M, Chiba K. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15 + C1007G, by using transient expression systems of HeLa and HEK293 cells. *Pharmacogenet Genomics* 2005; **15**:513–522.
29 Lau YY, Huang Y, Frassetto L, Benet LZ. Effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. *Clin Pharmacol Ther* 2007; **81**:194–204.
30 Thompson JF, Man M, Johnson KJ, Wood LS, Lira ME, Lloyd DB, *et al*. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. *Pharmacogenomics J* 2005; **5**:352–358.
31 Fu Q, Li YP, Gao Y, Yang SH, Lu PQ, Jia M, *et al*. Lack of association between SLCO1B1 polymorphism and the lipid-lowering effects of atorvastatin and simvastatin in Chinese individuals. *Eur J Clin Pharmacol* 2013; **69**:1269–1274.
32 Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther* 2007; **82**:726–733.
33 Lau YY, Okochi H, Huang Y, Benet LZ. Multiple transporters affect the disposition of atorvastatin and its two active hydroxy metabolites: application of in vitro and ex situ systems. *J Pharmacol Exp Ther* 2006; **316**:762–771.
34 Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circ Cardiovasc Genet* 2012; **5**:257–264.
35 Kopplow K, Letschert K, Konig J, Walter B, Keppler D. Human hepatobiliary transport of organic anions analyzed by quadruple-transfected cells. *Mol Pharmacol* 2005; **68**:1031–1038.
36 Noe J, Portmann R, Brun ME, Funk C. Substrate-dependent drug–drug interactions between gemfibrozil, fluvastatin and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. *Drug Metab Dispos* 2007; **35**:1308–1314.
37 Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, Ikeda T, *et al*. Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human hepatocytes. *J Pharmacol Exp Ther* 2001; **297**:861–867.
38 Sasaki M, Suzuki H, Ito K, Abe T, Sugiyama Y. Transcellular transport of organic anions across a double-transfected Madin-Darby canine kidney II cell monolayer expressing both human organic anion-transporting polypeptide (OATP2/SLC21A6) and Multidrug resistance-associated protein 2 (MRP2/ABCC2). *J Biol Chem* 2002; **277**:6497–6503.
39 Tachibana-Iimori R, Tabara Y, Kusuhara H, Kohara K, Kawamoto R, Nakura J, *et al*. Effect of genetic polymorphism of OATP-C (SLCO1B1) on lipid-lowering response to HMG-CoA reductase inhibitors. *Drug Metab Pharmacokinet* 2004; **19**:375–380.
40 Zhang W, Chen BL, Ozdemir V, He YJ, Zhou G, Peng DD, *et al*. SLCO1B1 521T→C functional genetic polymorphism and lipid-lowering efficacy of multiple-dose pravastatin in Chinese coronary heart disease patients. *Br J Clin Pharmacol* 2007; **64**:346–352.
41 Igel M, Arnold KA, Niemi M, Hofmann U, Schwab M, Lutjohann D, *et al*. Impact of the SLCO1B1 polymorphism on the pharmacokinetics and lipid-lowering efficacy of multiple-dose pravastatin. *Clin Pharmacol Ther* 2006; **79**:419–426.
42 Takane H, Miyata M, Burioka N, Shigemasa C, Shimizu E, Otsubo K, *et al*. Pharmacogenetic determinants of variability in lipid-lowering response to pravastatin therapy. *J Hum Genet* 2006; **51**:822–826.
43 Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Common genetic variation in the ABCB1 gene is associated with the cholesterol-lowering effect of simvastatin in males. *Pharmacogenomics* 2009; **10**:1743–1751.
44 Tomlinson B, Hu M, Lee VW, Lui SS, Chu TT, Poon EW, *et al*. ABCG2 polymorphism is associated with the low-density lipoprotein cholesterol response to rosuvastatin. *Clin Pharmacol Ther* 2010; **87**:558–562.