Published in final edited form as:

Pharmacogenomics. 2015 ; 16(5): 449–458. doi:10.2217/pgs.15.2.

***SLCO1B1* genetic variants, long-term low-density lipoprotein cholesterol levels and clinical events in patients following cardiac catheterization**

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Abstract

Aim—*SLCO1B1* variants are associated with intermediate outcomes that may increase risk of death/myocardial infarction (MI) in statin-treated patients.

Patients & methods—In high-risk Caucasians undergoing cardiac catheterization, we tested the association between rs4149056/625T>C and rs2306283/492A>G with low-density lipoprotein cholesterol (LDL-c) over 3 years (n = 1402) and death/MI over 6 years (n = 2994), accounting for statin use or type during follow-up.

Results—Carriers of the rs4149056 C allele had 6.2 ± 1.7 mg/dl higher LDL-c per C allele ($p < 0.001$) but were not at higher risk for death/MI ($p = 0.9$). We found no associations between rs2306283 and LDL-c or death/MI ($p > 0.6$).

Conclusion—Functional *SLCO1B1* variants are not associated with death/MI in patients commonly treated with statins, despite higher LDL-c in carriers of the rs4149056 C allele.

Keywords

cardiovascular events; low-density lipoprotein cholesterol; myocardial infarction; pharmacogenetics; rs4149056; rs2306283; *SLCO1B1*; statin

Statins are widely prescribed medications that prevent major coronary artery disease (CAD) events such as myocardial infarction (MI) primarily through the reduction of low-density

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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lipoprotein cholesterol (LDL-c) [1]. Despite the well-established benefits of statins, current management remains sub-optimal with a substantial portion of patients failing to achieve significant LDL-c lowering in clinical practice [2,3]. A major barrier to long-term LDL-c lowering is statin adherence [4]. In patients with CAD, up to 50% were nonadherent to statins after 1 year [5,6]. One main reason for nonadherence is the development of statin-induced musculoskeletal side effects [7]. In randomized clinical trials, the incidence of statin-induced myopathy has been reported as 1–5% [8,9] whereas observational studies suggest the frequency of statin myopathy to be 9–20% [10–13]. The reason for this discrepancy is not fully explained but can be attributed, in part, to more stringent screening in clinical trials that exclude patients with renal/hepatic insufficiency, history of prior intolerance or musculo skeletal complaints, as well as the use of ‘run-in’ phases. Furthermore, randomized control trials often only focused on rhabdomyolysis, the most severe form of myopathy or large elevations in creatine kinase, rather than other common side effects, which include myalgia with or without CK elevations [9,13,14].

Genetic variation in *SLCO1B1* has been well described; the two most common functional variants in *SLCO1B1* are rs4149056 and rs2306283. The C allele at rs4149056 (referred to as the *5 variant) causes a V174A substitution in the hepatic transporter protein OATP1B1 and is a risk factor for statin-induced side effects and premature drug discontinuation [15–17]. The *5 variant interferes with localization of the hepatic drug transporter to the plasma membrane, resulting in elevated systemic concentration of statins [18,19]. The effect of the *5 variant on statin clearance appears to be statin-specific, where simvastatin and atorvastatin are most affected, followed by fluvastatin, pravastatin and rosuvastatin [20]. The risk of myopathy conferred by *5 mirrors this pharmacokinetic data, with the greatest effects on simvastatin and atorvastatin and the least on pravastatin and rosuvastatin [16,21,22]. By interfering with statin transport into the hepatocyte, the *5 variant is associated with mild reductions in LDL-c lowering (1–3%) in short-term statin exposure studies (1 year) [15,16,22–26]. In contrast to the *5 variant, which reduces OATP1B1 function, the G allele at rs2306283 (referred to as the *1B variant) causes an N130D substitution that may increase OATP1B1 function [27]. As a consequence, the G allele reduces systemic statin concentrations [28] as well as the risk for statin-induced side effects [29] but does not result in differences in LDL-c lowering [26].

Because genetic variants in *SLCO1B1* are associated with intermediate outcomes (i.e., hepatic exposure, systemic concentrations, side effects, and utilization) of statin therapy, we hypothesized that *SLCO1B1* variants would be associated with clinical outcomes that are known to be affected by statin therapy: death, MI and LDL-c in a real-world population with cardiovascular disease with indications for statins. Further, we hypothesized that the effects of genetic variants would be statin-specific, based on the known statin-specific pharmacokinetic and side-effect data.

Patients & methods

Study population

The study population was selected from patients enrolled in the Duke Catheterization Genetics (CATHGEN) biorepository: a registry of clinical data, longitudinal yearly follow-

up data and blood samples collected from 9334 subjects who presented to Duke University Medical Center (DUMC) for cardiac catheterization from 2001 to 2010. Details of CATHGEN have been previously published [30]. We identified 3409 Caucasians who had available genotype data for rs2306283 and rs4149056 (Figure 1). All subjects consented to participation in CATHGEN. This study and CATHGEN were approved by the Duke University Institutional Review Board.

Genotyping

Genotyping for 3409 Caucasians was performed on two platforms: 1919 individuals using the Affymetrix Axiom chip as part of a previous study in nondiabetic CATHGEN patients [31] and 2300 using the Illumina Human Omni1-Quad Bead Chip. Two individuals failed quality control (call rate > 99% for both platforms) and four individuals were excluded because they were genotyped on both platforms but had discordant genotypes, resulting in 3403 unique individuals (Figure 1). Hardy–Weinberg Equilibrium for rs4149056 and rs2306283 was checked using PLINK, Version 1.07 [32,33]. Genotypes were coded to test an additive model, based on prior observations supporting this relationship [34], defined as 0, 1, or 2 copies of the minor allele. Haplotypes (*1a, *1b, *5 and *15) were constructed from the two genotypes such that the *1a haplotype was designated the reference (i.e., N130, V174).

Study definitions

Baseline characteristics—Baseline variables collected at the time of catheterization included age, sex, BMI, hypertension, diabetes, hyperlipidemia, CAD, smoking, left ventricular ejection fraction and LDL-c. CAD was defined as the presence of any of the following: CAD index ≥ 32 (a summary of angiographic data [35]) or ≥ 1 epicardial coronary artery with $\geq 75\%$ stenosis on cardiac catheterization including the CATHGEN enrollment catheterization, history of previous MI, previous coronary artery bypass graft, or interventional cardiac catheterization procedure (i.e., coronary angioplasty and/or stenting).

Medication data—Admission and discharge medications at the time of catheterization were collected through chart review as part of CATHGEN. Medication data with a report date of ≤ 60 days prior to catheterization were considered to be at baseline. As part of CATHGEN, subjects provided a list of their medications annually following index enrollment cardiac catheterization. Of the 3403 individuals with genotyping data that passed quality control, 409 did not have subject-reported medication data, resulting in 2994 individuals (Figure 1) for analysis. The first 3 years of medication data were utilized for the association with LDL-c. If multiple medication reports for a period were available, the measurement with the latest report date within the interval was used.

Subject-reported statin utilization at the end of each interval (i.e., baseline, baseline to 1 year, 1–2 years, 2–3 years) was coded as a dichotomous variable, regardless of statin type. For statin-specific effects, a separate four-level variable was created for statin type and coded as: ‘simvastatin’, ‘atorvastatin’, ‘other statin’ (containing all remaining statin types) and ‘no statin’ for each interval. Individuals who changed statin type from one interval to another were included in the analyses through the use of a mixed-effect model (see below),

thus allowing for all available data during follow-up to be included. The resulting dataset captured subject-reported statin utilization and categorized individuals as taking or not taking a statin for any given interval.

Cardiovascular event data—All 2994 individuals with subject-reported medication data had complete follow-up data for the occurrence of first MI or death in the period after catheterization (Figure 1).

Laboratory data—LDL-c levels at four time points: baseline (60 days prior to catheterization), and 1, 2 and 3 years following cardiac catheterization were analyzed. LDL-c levels were obtained using Duke Enterprise Data Unified Content Explorer (DEDUCE), a web-based query tool [36] that allows extraction of laboratory data from DUMC patients. If multiple LDL-c levels for an interval were available, the measurement with the most recent report date within that interval was used. LDL-c levels were primarily calculated from the Friedewald equation [37] and were not used if triglyceride levels were >400 mg/dl. Of the 2994 individuals with available genotype and medication data, only those with both medication and LDL-c data available for at least one time point over the 3-year follow-up period were included for analysis, resulting in 1402 unique individuals (Figure 1).

Statistical analysis

Survival analyses—To assess the effect of genotype/haplotype on a composite outcome of incident death/MI following catheterization, an extended Cox model was performed, where statin utilization was modeled as a time-dependent covariate. The date of catheterization was considered as time zero. For the first interval (i.e., from catheterization to first survey) we defined statin usage based on available medication data within 30 days of the catheterization date. For each subject-reported medication survey following catheterization, the interval was defined as the time between that survey and the next survey. Individuals who missed at least one annual survey received 16 months of credit for their previous medication report, chosen because 95% of the time elapsed between surveys fell within this time range (data not shown). Multivariable analyses, adjusting for age, BMI, diabetes, hyperlipidemia, CAD and smoking, were performed and interaction terms were introduced.

LDL-c analyses—To assess for effects of genotype/haplotype on LDL-c, linear mixed models were used to account for the repeated measures within an individual and to control for the effects of subject-reported statin utilization and statin type over time as well as multivariable analysis adjusting for known predictors of statin-mediated LDL-c lowering: age, BMI, diabetes, hyperlipidemia, CAD and smoking [38,39]. Interaction terms were introduced to assess homogeneity of genotype effects on LDL-c by statin type.

SAS statistical software, Version 9.3 (SAS Institutes, Cary, NC, USA) was used for mixed models analyses. All other analyses were performed using R statistical software [40].

Results

Table 1 summarizes baseline characteristics for the 2994 Caucasian individuals in the study with available genotype and medication data. The study population was ~60% male and broadly representative of a population with established cardiovascular disease. Allele frequencies were consistent with those previously reported and did not differ between genotyping platforms (data not shown). No deviations from Hardy–Weinberg Equilibrium were observed.

Association of genetic variants with long-term clinical events

There were 169 MI and 374 death events, combining for an event rate of 18% over a median follow-up of 5.6 ± 2.4 years. In unadjusted extended Cox models, neither rs2306283 (HR 0.99; 95% CI [0.88–1.12], $p = 0.94$) nor rs4149056 (HR 0.99; 95% CI [0.84–1.17]; $p = 0.93$) was associated with the composite outcome of death/MI. As expected, statin usage was independently associated with better long-term survival (HR 0.68; 95% CI [0.57–0.81]; $p < 0.001$). There was no evidence of interactions between either rs2306283 or rs4149056 and statin type ($p > 0.12$). Multivariable and haplotype analyses were consistent with findings in univariate analysis (data not shown).

Association of genetic variants with LDL-c levels

In models that accounted for statin use, rs4149056 genotype ($p = 0.0003$) was associated with LDL-c levels during follow-up. Carriers of the C allele for rs4149056 had an estimated 6.2 ± 1.7 mg/dl higher LDL-c level per C allele (Figure 2). We did not find an interaction between rs4149056 and statin type (Figure 3, $p = 0.38$). Multivariable and haplotype analyses revealed consistent findings as the univariate models using rs4149056 alone (data not shown). We did not find an association between rs2306283 and LDL-c levels (Figure 4, $p = 0.68$) or an interaction between rs2306283 and statin type (Figure 5, $p = 0.40$).

Discussion

Association of genetic variants with long-term clinical events

Genetic variation in *SLCO1B1* has been well described, and two common, functional genetic variants (rs2306283 and rs4149056) lead to differences in hepatic uptake, statin clearance, different risks for statin-induced side effects, premature drug discontinuation and reduced hepatic uptake [15–19,29]. Since statins are long-term medications and prior studies were primarily short-term clinical trials [15,16,22–25] that could not examine any effects on clinical outcomes, we examined the impact of these common, functional variants on cardiovascular outcomes in a cohort representative of patients with complex cardiovascular disease in a ‘real-world’ clinical setting. We hypothesized that the combined effects of *SLCO1B1* variants on intermediate outcomes would result in differences in long-term risk for death/MI following cardiac catheterization – two outcomes known to be prevented by statin use. Although statin use was strongly associated with a decreased risk for death/MI in our cohort and lower LDL-c, thus establishing the validity of statin exposure data, we found no association between either rs2306283 or rs4149056 and death/MI, despite the higher LDL-c levels in carriers of the C allele for rs4149056. Our results appear to be consistent

with that seen by Akao *et al.*, who found no association between rs4149056 or rs2306283 and coronary heart disease (CHD) events in a placebo-controlled trial of 40 mg/day pravastatin in elderly men and women [26].

Clinical trials have shown a log-linear relationship between LDL-c and relative risk for CHD where the relative risk for CHD is reduced by 1% for every 1% reduction in LDL-c [1,41]. For rs4149056, we observed ~5% higher LDL-c per C allele over 3 years, which should have translated to a predicted 5% increase in clinical events per C allele. In a *post-hoc* power analysis, we had adequate statistical power to detect a 10% or greater difference in risk between carriers and non-carriers. Therefore, although we did not have sufficient power to detect a 5% higher risk, our sample size was large enough to exclude an increased risk of death/MI of greater than 10% between carriers and non carriers. To further explore the lack of association between genetic variants and cardiac events, we performed exploratory analysis testing for an association between the *5 allele and high-density lipoprotein cholesterol (HDL-c) levels. However, we did not find evidence of an association between rs4149056 and HDL-c ($p = 0.70$) to support a protective mechanism through elevations in HDL-c.

Compared to a prior study by Peters *et al.* [42] in which the authors identified a potential interaction between the *15/*15 haplotype and statin use on MI, we did not find any evidence for any differential effects (haplotype by statin use interaction in the current study, p -value = 0.78). In comparison to the study by Peters *et al.*, which was a retrospective case-control study of patients with hyperlipidemia that survived MI, our study population was a larger cohort of high-risk patients with cardiovascular disease who were prospectively followed for death/MI. Therefore, our study design eliminated the potential biases introduced through a case-control study of MI survivors and thus resolves any uncertainty regarding the association of genetic variation in *SLCO1B1* and cardiovascular events in patients taking statins.

Association of genetic variants with LDL-c levels

We hypothesized that the combined effects of altered hepatic uptake of statins and risk of drug discontinuation as a result of side effects would lead to different LDL-c levels in carriers versus noncarriers. We found that carriers of the C allele for rs4149056 had, on average, a ~5% higher LDL-c per C allele over 3 years. At baseline at the time of cardiac catheterization, there were no significant differences in LDL-c between carriers and noncarriers ($p = 0.93$), which was expected since genetic variants in *SLCO1B1* do not affect native, pre-statin LDL-c levels [43,44]. The direction of association between the *5 variant and higher LDL-c in this patient-based cohort with cardiovascular disease was consistent with prior clinical trial data and short-term statin exposure studies, in which a 1–3% higher LDL-c per allele was observed [15,16,22–26]. Moreover, the association with LDL-c appeared to be consistent across statin types. Therefore, in a clinically relevant, high-risk cardiovascular cohort, the *SLCO1B1**5 variant is associated with higher LDL-c.

Limitations

The largest limitations to our study were the lack of day-to-day statin adherence data and statin dose information. Indirect surrogates for adherence, such as patient questionnaires used in our study, can be biased by poor patient recall, inconsistent reporting, and may result in an inaccurate estimation of medication adherence [45]. Despite these known limitations, we chose to include self-reported statin utilization data in our statistical models, though we acknowledge that these data cannot substitute for the day-to-day variability in statin adherence. Nevertheless, subject-reported statin use in our cohort was strongly associated with lower LDL-c and lower risk for death/MI, and thus was an adequate surrogate for long-term statin utilization. Although alternative metrics for true statin adherence have been proposed, no other adherence metrics were available to us in this retrospective data.

Another limitation of this study was that only individuals who were seen for clinical follow-up at DUMC were included in the LDL-c analysis. These patients likely received closer monitoring and higher statin doses, which may have resulted in an overestimated effect size. Using only LDL-c levels from DUMC also increased the amount of missing data in the mixed-model analyses and could have introduced bias. However, we tested for and found no association between missing data and the *5 variant ($p = 0.6$).

In addition, the rs2306283 and rs4149056 variants may not have entirely captured OATP1B1 transporter activity and the sole use of these variants alone may have misclassified individuals. Rare variants would, in part, have overcome this limitation, as evidenced by a recent study on methotrexate clearance, where these variants accounted for 17.8% of *SLCO1B1*'s effects [46]. In addition, alternate biomarkers for OATP1B1 activity (e.g., bilirubin, bile acids) may further allow for more accurate phenotyping in clinical cohort studies. However, such additional granularity is unlikely to have meaningfully changed our conclusions since the upper limit of the 95% CI for the hazard ratio for death/MI in those who carried of two copies of the *5 variant (i.e., null predicted OATP1B1 function) was only 1.9 and lower than what many would agree is a clinically actionable increased risk.

Conclusion

Two common, functional genetic variants in *SLCO1B1* were not associated with long-term clinical outcomes in patients at high risk for cardiovascular disease that are commonly treated with statins, despite an association between the *SLCO1B1**5 allele and higher LDL-c levels in this cohort.

Future perspective

The data presented in our study illustrate that despite a higher LDL-c observed in *5 carriers, these individuals did not experience an increased risk of long-term cardiovascular events. Given the lack of difference in clinical outcomes for both rs4149056 and rs2306283, this study, which involves primarily simvastatin and atorvastatin, along with another study focused on pravastatin [26], suggests a limited role for routine genetic testing for variants in *SLCO1B1* for reducing cardiovascular risk in statin-treated patients. We acknowledge the

limitations of our study design and advocate that future studies are necessary in order to further elucidate the clinical utility of these variants on cardiovascular outcomes. However, we believe that *SLCO1B1* genetic information may be useful in reducing major side effects such as rhabdomyolysis [47] as well as in improving LDL-c lowering outcomes since certain statins (e.g., rosuvastatin or fluvastatin) are well tolerated [22] and minimally handled by this transporter.

Acknowledgments

The authors acknowledge C Haynes, ZE Dowdy and M Hurdle for performing clinical data collection and maintaining this valuable resource. The authors are solely responsible for the design and conduct of the study, all analyses, and the drafting and editing of the paper and its final contents.

Financial & competing interests disclosure

This study was supported by research grants R01HL095987 (SH Shah) and RC2-HL101612 (WE Kraus). This research was also made possible in part by a Duke University Stead Research Scholarship (JH Li). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Background

- The reduced function *SLCO1B1**5 variant, defined by the minor C allele at rs4149056, impairs statin clearance, resulting in higher systemic statin exposure and increased risk for side effects.
- The effect of *SLCO1B1**5 on statin clearance and the risk of myopathy has been shown to be statin-specific.
- The gain of function variant in *SLCO1B1*, defined by the G allele at rs2306283, reduces systemic statin concentration and decreases risk of statin-induced side effects.

Patients & methods

- In a real-world population with cardiovascular disease, we investigated the association of both *SLCO1B1* variants with low-density lipoprotein cholesterol (LDL-c) and risk of death/myocardial infarction, in a statin-specific manner.

Results & conclusion

- There was no association of rs4149056 or rs2306283 with long-term cardiovascular events over a mean follow-up of 5.6 ± 2.4 years.
- Carriers of *SLCO1B1**5 were found to have an approximately 5% higher LDL-c per C allele over 3 years.
- No statin-specific effects of the two *SLCO1B1* variants on LDL-c or cardiovascular events were observed.
- The study suggests that there is a limited role of routine genetic testing for variants in *SLCO1B1* to improve clinical outcomes though future studies are necessary in order to further elucidate the clinical utility of these variants on cardiovascular outcomes.

Figure 1. Number of individuals included in the primary analyses examining the association between genotypes and death/myocardial infarction, and the association between genotypes and LDL-c levels

LDL-c: Low-density lipoprotein cholesterol; MI: Myocardial infarction.

Figure 2. Association of rs4149056 with low-density lipoprotein cholesterol levels

Displayed are means and standard errors of LDL-c levels by rs4149056 genotype. Levels of significance were obtained using linear mixed models for an additive model, adjusted for subject-reported statin utilization and time. Per C allele, there was a ~5% higher LDL-c over a 3-year follow-up period.

LDL-c: Low-density lipoprotein cholesterol.

Figure 3. Association of rs4149056 with low-density lipoprotein cholesterol, stratified by statin type

Displayed are means and standard errors of LDL-c levels by rs4149056 genotype and statin type. ‘Other statin’ was composed of 46.4% pravastatin, 30.4% rosuvastatin, 17.9% lovastatin and 5.3% fluvastatin. An interaction term assessed homogeneity of genotype effects on LDL-c by statin type. Due to the analysis, statin type subgroups contained overlapping individuals. There was no evidence for rs4149056 genotype by statin type interaction.

LDL-c: Low-density lipoprotein cholesterol.

Figure 4. Association of rs2306283 with low-density lipoprotein cholesterol levels

Displayed are means and standard errors of LDL-c levels by rs2306283 genotype. Levels of significance were obtained using linear mixed models for an additive model, adjusted for subject-reported statin utilization and time. There was no association between rs2306283 and LDL-c levels.

LDL-c: Low-density lipoprotein cholesterol.

Figure 5. Association of rs2306283 with low-density lipoprotein cholesterol, stratified by statin type

Displayed are means and standard errors of LDL-c levels by rs2306283 genotype and statin type. 'Other statin' was composed of 46.4% pravastatin, 30.4% rosuvastatin, 17.9% lovastatin and 5.3% fluvastatin. An interaction term assessed homogeneity of genotype effects on LDL-c by statin type. Due to the analysis, statin type subgroups contained overlapping individuals. There was no evidence for rs2306283 genotype by statin type interaction.

LDL-c: Low-density lipoprotein cholesterol.

Table 1

Baseline characteristics and genotype frequencies of 2994 Caucasians.

Characteristics	All (n = 2994)
Age, years (SD) [†]	60.4 (11.1)
Sex, male (%)	1841 (61.5)
BMI, kg/m ² (SD), n = 2977 [†]	29.6 (6.5)
Hypertension (%)	1923 (64.2)
Diabetes (%)	468 (15.6)
Hyperlipidemia (%)	1904 (63.6)
CAD (%), n = 2952	2033 (68.9)
Smoking (%)	1564 (52.2)
LVEF (SD), n = 2406 [†]	58.9 (12.3)
LDL-c [‡] , mg/dl (SD), n = 1282 [†]	103.9 (38.3)
rs4149056 genotype	
TT (%)	2159 (72.1)
TC (%)	767 (25.6)
CC (%)	68 (2.3)
rs2306283 genotype	
AA (%)	1070 (35.7)
AG (%)	1419 (47.4)
GG (%)	505 (16.9)

[†] Values presented as mean and standard deviation.

[‡] All LDL-c values are baseline levels taken 60 days prior to index catheterization.

CAD: Coronary artery disease; LDL-c: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction.