

The Clinical Pharmacogenetics Implementation Consortium Guideline for *SLCO1B1* and Simvastatin-Induced Myopathy: 2014 Update

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Simvastatin is among the most commonly used prescription medications for cholesterol reduction. A single coding single-nucleotide polymorphism, rs4149056T>C, in *SLCO1B1* increases systemic exposure to simvastatin and the risk of muscle toxicity. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for simvastatin based on *SLCO1B1* genotype. This article is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium guideline for *SLCO1B1* and simvastatin-induced myopathy.

This update to the 2012 guideline¹ provides information that enables the interpretation of *SLCO1B1* genotype tests so that the results can be used to guide dosing of simvastatin. Detailed guidelines for the use of simvastatin are beyond the scope of this article. Although polymorphisms in *SLCO1B1* affect multiple statins, the strength of the evidence is highest for simvastatin; therefore, we focus our recommendations accordingly.

FOCUSED LITERATURE REVIEW AND UPDATE

A systematic literature review was conducted, focusing on *SLCO1B1* gene polymorphisms and statin-related end points in humans (details in the **Supplementary Material** online).

All Clinical Pharmacogenetics Implementation Consortium guidelines are updated periodically. The dosing recommendations provided in the 2012 Clinical Pharmacogenetics

Implementation Consortium guideline for *SLCO1B1* and simvastatin-induced myopathy have not changed and are included here. However, this updated guideline also provides a brief review regarding *SLCO1B1* genotype and risk of myopathy for other statins. Furthermore, the accompanying supplementary material has been updated, including the addition of resources to facilitate incorporation of *SLCO1B1* pharmacogenetics into an electronic health record with clinical decision support.

DRUG: SIMVASTATIN

Background

In 2012, simvastatin was the most commonly prescribed generic statin formulation in the United States (<http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012>).

The most common statin-related adverse drug reaction (ADR) is skeletal muscle toxicity.² Statin-related muscle problems include myalgias (pain without evidence of muscle degradation), myopathy (pain with evidence of muscle degradation), and rhabdomyolysis (severe muscle damage with acute kidney injury). Frequency varies by definition; but, overall, statin-related myalgias are common, occurring in 1–5% of exposed subjects. In patients without arthritis, National Health and Nutrition Examination Survey data suggest a “number needed to harm” is 17 (ref. 3).

Statins have a wide therapeutic index,⁴ and severe ADRs are therefore relatively uncommon. Nonetheless, even though the

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myopathy rate is low, the high prevalence of the clinical indication (hypercholesterolemia and cardiovascular disease) creates a situation in which the absolute number of ADRs is substantial. Furthermore, in the absence of severe myopathy, many patients still opt to discontinue statin therapy due to intermediate toxicity, and statin nonadherence thus has the potential to increase the burden of cardiovascular disease on our healthcare infrastructure. It is with this perspective, a goal toward optimizing adherence, that we present the current guideline.

GENE: *SLCO1B1*

Background

The *SLCO1B1* gene locus occupies 109 kb on chromosome 12 (Chr 12p12.2). Although many single-nucleotide polymorphisms (SNPs) have been identified in *SLCO1B1*, only a few are known to have functional effects.^{5,6} The common c.521T>C variant, rs4149056, produces a p.V174A substitution and is contained within *SLCO1B1**5, *15, and *17 haplotypes. The minor C allele at this locus has been associated with decreased transport function *in vitro*^{7,8} and decreased clearance for a number of drugs *in vivo*.^{9–11} Additional *SLCO1B1* variants have been identified and are discussed in further detail in the supplementary material (**Supplementary Material** online; **Supplementary Tables S1** and **S2** online); however, the dosing recommendations in this guideline are specific for variant alleles in which there are clear data linking *SLCO1B1* genotype to simvastatin-induced myopathy (*SLCO1B1**5, *15, and *17).

SLCO1B1 (alternative names include OATP1B1, OATP-C) is the protein product of the *SLCO1B1* gene and facilitates the hepatic uptake of statins, as well as numerous endogenous compounds (e.g., bilirubin and 17-β-glucuronosyl estradiol).^{6,12} Changes in the function of this transporter (as occur during drug–drug interactions) can markedly increase the severity of statin-related muscle damage. For example, cyclosporine, a strong inhibitor of CYP3A4 and *SLCO1B1*, increases the area under the curve (AUC) for simvastatin acid by three- to eightfold.⁶

Beyond acquired inhibition, genetic variability in *SLCO1B1* also affects plasma concentration of statins. The overall pharmacokinetic profiles appear to be affected more for simvastatin than for any other drug in the class.^{13–15} Other transporters potentially influencing the distribution and tissue uptake of statins include *SLCO1B3*, *SLCO2B1*, *SLCO1A2*, and sodium-dependent taurocholate cotransporting polypeptide.^{6,12}

Genetic test interpretation

The assignment of the likely *SLCO1B1* phenotype, based on * allele diplotypes, has been summarized in **Table 1**, based on rs4149056. *SLCO1B1* alleles are often named using * allele nomenclature, representing various SNPs alone or in combination (<http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=33>) (**Supplementary Table S1** online) that are associated with low *SLCO1B1* protein expression or function (**Supplementary Table S2** online). The minor C allele at rs4149056 is contained within *SLCO1B1**5 (rs4149056 alone) as well as the *15 and *17 haplotypes and is associated with lower plasma clearance of simvastatin. The magnitude of this effect is similar for the *5, *15, and *17 haplotypes.¹¹ *SLCO1B1* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups. In general, rs4149056 is present at a minor allele frequency of between 5 and 20% in most populations (see **Supplementary Tables S3** and **S4** online). Although all *SLCO1B1* genetic tests interrogate rs4149056, other variants in this gene are also likely to be important, but their interpretation and application to statin prescribing is less clear. One of the limitations inherent in any genotype-only test is that very rare or *de novo* variants, which might have functional importance, will not generally be included.

Available genetic test options

Commercially available clinical testing options are presented within the **Supplementary Material** online and are freely available at <http://www.PharmGKB.org>. The rs4149056 SNP can be genotyped alone (e.g., PCR-based single-SNP assay) or multiplexed on a variety of array-based platforms. See the **Supplementary Material** online for details. This variant is also among the pharmacogenetic content available for participants in direct-to-consumer genomic offerings (e.g., 23andme.com).

Incidental findings

Genetic variability in *SLCO1B1* influences the hepatic uptake of other drugs (e.g., methotrexate)^{5,16} as well as important endogenous compounds (e.g., bilirubin)¹⁷ (**Supplementary Material** online).

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking *SLCO1B1* genotype with phenotypic variability (see **Supplementary Table S5** online).

Table 1 Assignment of likely *SLCO1B1* phenotype based on genotype

Phenotype	Genotype definition	Examples of diplotypes	Genotype at rs4149056
Normal function; homozygous wild type or normal (55–88% of patients ^a)	An individual carrying two normal-function alleles	*1a/*1a, *1a/*1b, *1b/*1b	TT
Intermediate function; heterozygous (11–36% of patients ^a)	An individual carrying one normal-function allele plus one decreased-function allele	*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17	TC
Low function; homozygous variant or mutant (0–6% of patients ^a)	An individual carrying two decreased-function alleles	*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17	CC

^aFrequency of the polymorphism varies by ancestral group (**Supplementary Tables S3** and **S4** online).

Application of a grading system to evidence linking genotypic variability indicates a high quality of evidence in the majority of cases. For simvastatin, the evidence linking myopathy to rs4149056 in *SLCO1B1* is of high quality, and this association has been reproduced in randomized trials and clinical practice-based cohorts. Conversely, the association of rs4149056 with myopathy has been less compelling for other statins. We therefore focus this guideline on simvastatin.

SLCO1B1 polymorphisms clearly impact the pharmacokinetics of simvastatin and, to a lesser degree, the pharmacokinetics of other statins¹³ (**Supplementary Table S6** online). Pasanen *et al.*¹¹ determined that homozygous carriers of the C allele at rs4149056 (CC genotype) had much greater exposure to the active simvastatin acid (AUC_{0–12}) than subjects homozygous for the ancestral T allele. In single-dose studies (**Supplementary Figure S1** online), the observed plasma AUCs of active simvastatin acid, pitavastatin, atorvastatin, pravastatin, and rosuvastatin have been 221%, 162–191%, 144%, 57–130%, and 62–117% higher in rs4149056 CC homozygotes than in rs4149056 TT homozygotes (**Supplementary Figure S1** online).

In 2008, the SEARCH Collaborative (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) Group conducted a case-control study of simvastatin-induced myopathy using archived DNA from a randomized trial including more than 12,000 subjects who had received either low-dose simvastatin (20 mg daily) or high-dose simvastatin (80 mg daily) post-myocardial infarction.¹⁸ During the course of the trial, 49 subjects in the high-dose arm developed myopathy (creatinine kinase (CK) > 10-fold the upper limit of normal with pain), compared with two subjects in the low-dose arm. An additional 49 subjects in the same treatment arm developed “incipient” myopathy (CK > 3-fold the upper limit of normal, and five times the patient’s baseline level). Of these combined incipient and definite myopathy cases, 85 underwent whole-genome scanning (with a platform containing 317,000 SNPs), and the results were compared with genome-wide data from 90 nonmyopathic controls (frequency matched from within the same treatment arm). A single-nucleotide variant survived statistical correction for multiple testing: a base substitution in the *SLCO1B1* gene. After genomic resequencing, the putative causative allele, rs4149056, was retested for association in a subset of definite myopathy cases from the original cohort, revealing an odds ratio (OR) for myopathy of 4.5 per copy of the minor C allele.¹⁸ Approximately 25% of the general population are carriers of this allele, and 1 of 100 patients taking high-dose simvastatin have an ADR.

The association between rs4149056 and statin-induced muscle toxicity has since been replicated in both a second independent trial and a practice-based longitudinal cohort. The Heart Protection Study enrolled more than 20,000 subjects with known vascular disease or vascular risk factors, and randomized each study participant to either 40 mg simvastatin daily or placebo.^{19,20} Twenty-four cases of myopathy (10 definite + 14 incipient) were identified from among the 10,269 participants receiving 40 mg simvastatin, and 21 of these cases later underwent retrospective genotyping for rs4149056.¹⁸ In this validation cohort, the relative risk was 2.6 per copy of the minor C allele.¹⁸

Although both the SEARCH trial and the Heart Protection Study represent randomized controlled treatment trials, the effect size for rs4149056 was lower in the Heart Protection Study (i.e., at the 40-mg dose) than in SEARCH (i.e., at the 80-mg dose), underscoring the importance of dose.

Practice-based data suggest that the association between rs4149056 and muscle toxicity is stronger for simvastatin than for other drugs within the class. The C allele at rs4149056 has recently been shown to influence the rate of medication adherence for simvastatin.²¹ In the STRENGTH study, 509 hypercholesterolemic patients were randomized to simvastatin, atorvastatin, or pravastatin, and followed for 16 weeks. The primary end point of the study was a composite of study drug discontinuation for any adverse effect, myalgia or muscle cramping, and/or elevated serum CK levels > 3-fold the upper limit of normal. The overall effect size was highest for simvastatin (OR: 2.8; 95% confidence interval (CI): 1.3–6.0) and rather modest for atorvastatin (OR: 1.6; 95% CI: 0.7–3.7). No significant association was observed for pravastatin (OR: 1.0; 95% CI: 0.4–2.6). As with the STRENGTH study, other groups have reported a modest association between rs4149056 and atorvastatin intolerance based on adverse muscle symptoms,²² but the association between rs4149056 and laboratory-confirmed myopathy has been less compelling for atorvastatin.²³

From the medical records of nearly 9,000 patients followed in an academic lipid clinic, Brunham and colleagues identified 25 laboratory-confirmed myopathy cases (frequency 0.26%).²³ All 25 cases, along with drug-exposed controls (frequency matched 2:1), were genotyped for rs4149056, revealing an OR for myopathy of 2.3 per copy of the minor C allele at rs4149056. The odds ratio was the highest, 3.2 (95% CI: 0.83–11.96), for subjects with the CC genotype exposed to simvastatin. No such relationship was observed using a similar number of atorvastatin cases (OR: 1.06; 95% CI: 0.22–4.80).²³ These observations are consistent with reported differences in clearance (**Supplementary Figure S1** online). To date, there is little evidence that rs4149056 genotype alters symptomatic intolerance or myopathy for pravastatin²¹ or rosuvastatin.²² Hence, the observed clinical association between rs4149056 and myopathy may not be a class effect; it likely depends on the relative importance of *SLCO1B1* to the clearance of the statin.

Therapeutic recommendations

In 2011 (updated in 2013), the US Food and Drug Administration added warnings to the simvastatin product label to direct providers away from initiating at the 80-mg simvastatin dose. The agency’s recommendations are further summarized in **Supplementary Table S7** online. The American College of Cardiology and the American Heart Association recently issued updated clinical practice recommendations for the treatment of elevated blood cholesterol to reduce atherosclerotic cardiovascular disease, including guidelines for which patients should receive which statin at which intensity.²⁴ Based on these new guidelines, it is anticipated that increasing numbers of patients will receive statin therapy; however, it is unclear

Table 2 Dosing recommendations for simvastatin based on SLCO1B1 phenotype

Phenotype	Implications for simvastatin	Dosing recommendations for simvastatin ^{a,b}	Classification of recommendations ^c
Normal function	Normal myopathy risk	Prescribe desired starting dose ^b and adjust doses of simvastatin based on disease-specific guidelines	Strong
Intermediate function	Intermediate myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong
Low function	High myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong

CK, creatine kinase.

^aIn all cases, the potential for drug–drug interaction should be evaluated before initiating a prescription. ^bThe US Food and Drug Administration recommends against 80 mg (unless already tolerated for 12 months). ^cSee the **Supplementary Material** online (text section titled “Levels of Evidence”) for additional details regarding the three-tiered system used to grade the quality of evidence.

as to what extent the incidence of statin-induced myopathy will also be affected. At lower simvastatin doses (e.g., 40 mg daily), it is our position that *SLCO1B1* genotype (if available) could be used to warn providers about modest increases in myopathy risk for patients with a C allele at rs4149056. In these circumstances, we recommend a lower dose of simvastatin or use an alternative statin (e.g., pravastatin or rosuvastatin), and we also highlight the potential utility of routine CK surveillance (**Table 2**). If patients with a C allele at rs4149056 do not achieve optimal LDL cholesterol-lowering efficacy with a lower dose (e.g., 20 mg) of simvastatin, we recommend that the prescribing physician consider an alternate statin based on (i) potency differences (i.e., use a lower dose of a higher potency statin such as atorvastatin, rosuvastatin, or pitavastatin); (ii) drug–drug interactions (e.g., boceprevir, clarithromycin, cyclosporine, strong CYP3A4 inhibitors); and (iii) relevant comorbidities (e.g., trauma, significant renal impairment, post–solid organ transplant, thyroid disease).

At the time of this writing, there are no data available regarding *SLCO1B1* genotype effects on simvastatin response or myopathy in pediatric patients, and no data to show that the rs4149056 SNP in *SLCO1B1* affects simvastatin’s disposition differently in children compared with adults.

Use of clinical decision support tools within electronic health records can assist clinicians in using genetic information to optimize drug therapy.^{25–27} Clinical implementation resources include workflow diagrams (**Supplementary Figures S2 and S3** online), tables that translate genotype test results into an interpreted phenotype, example text for documentation in the electronic health record and point-of-care alerts, and cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (**Supplementary Tables S8–S12** online).

Recommendations for incidental findings

Not applicable.

Other considerations

Other factors influencing simvastatin-induced myopathy. Other factors known to influence a patient’s risk for developing statin-induced muscle toxicity include increased statin dose, advanced age, small body mass index, female gender, meta-

bolic comorbidities (e.g., hypothyroidism), intense physical exercise, and Asian or African ancestry.^{2,28–31} Since polypharmacy is common in the elderly, the association with age is partly attributable to drug–drug interactions as well as to increases in chronic renal or hepatic disease.³²

Statin dose is the strongest independent predictor of myopathy risk. Myotoxicity is roughly sixfold higher in patients on high-dose than on lower-dose statin therapy.³³ Among the statins, a growing body of evidence suggests that the influence of dose may be the greatest for simvastatin.¹⁸ The molecular mechanism of statin-induced myopathy is unclear.

Role of SLCO1B1 genotype and other statin-induced myopathies. The relationship between rs4149056 and simvastatin-related muscle toxicity has been clearly established, whereas the relationship between this polymorphism and the safety of other statins is less clear. Previous studies evaluating atorvastatin safety in individuals with the rs4149056 polymorphism yielded conflicting results. A small study by Puccetti and colleagues evaluating 46 individuals with muscle intolerance compared with matched controls demonstrated a statistically significant association between rs4149056 and atorvastatin-related muscle symptoms (OR: 2.7; 95% CI: 1.3–4.9; *P* < 0.001) (ref. 22). The STRENGTH trial also demonstrated a nonsignificant increase in muscular adverse events occurring in *SLCO1B1**5 carriers taking atorvastatin.²¹ In addition, two small studies and a meta-analysis failed to detect a statistically significant association between the rs4149056 variant and myopathy in individuals taking 10–80 mg of atorvastatin.^{23,34,35} Of note, these studies were either underpowered or it was unclear whether power was met; so, the possibility of an actual association being present but undetected represents an important limitation of these three studies. Therefore, although there may be an increased risk in rs4149056 C-allele carriers using atorvastatin, the current data are inconclusive.

We were unable to identify any safety studies evaluating fluvastatin or pitavastatin use in individuals with the rs4149056 C allele, and the STRENGTH trial is the only safety study evaluating pravastatin use in this population. In the STRENGTH trial, there was no significant increase in muscular adverse events in *SLCO1B1**5 carriers taking pravastatin, although a relatively low maximum pravastatin dose was used in the study compared with

the maximum simvastatin and atorvastatin doses evaluated.²¹ With regard to rosuvastatin, in a subgroup analysis of 8,782 JUPITER trial participants, 417 subjects being treated with 20 mg daily experienced myalgia vs. 369 subjects on placebo (hazard ratio (HR): 1.13 (0.98–1.30), $P = 0.09$), but there was no statistically significant association between the incidence of myalgia for rosuvastatin vs. placebo in the presence of the rs4149056 C allele in this adequately powered analysis (HR: 0.95; 95% CI: 0.79–1.15).³⁶ Based on the results of this analysis, rosuvastatin use for an approximate dose of 20 mg daily has not been associated with an increased risk of myalgia compared with placebo in carriers of the minor allele of rs4149056 and could represent a reasonably safe alternative to simvastatin therapy in rs4149056 C-allele carriers.

Drug–drug interactions. In the context of statin monotherapy, myopathy rates are low.³⁷ The frequency of this ADR increases with coadministration of medications altering the pharmacokinetics of statins (e.g., coadministration with gemfibrozil). See the **Supplementary Material** online for more discussion.

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Based on the highly prevalent use of simvastatin, a potential benefit of preemptive *SLCO1B1* testing is a significant reduction in the incidence of simvastatin-induced myopathies and rhabdomyolysis, by identifying those at significant risk and recommending a lower simvastatin dose or an alternative statin as appropriate. In addition, genotyping may promote statin adherence and lower low-density lipoprotein cholesterol levels.

A possible risk could be an error in genotyping. Since genotypes are lifelong test results, any such error could stay in the medical record for the life of the patient. An error in genotyping could result in a decrease in simvastatin dose that was not otherwise necessary and could result in inadequate lipid-lowering therapy. However, since there are many effective, generic statins now available, it is often possible to switch statins rather than use a reduced simvastatin dose in high-risk patients, which further minimizes the potential for risk from a reduced simvastatin dose, especially in those who are homozygous for rs4149056C. Another potential risk to pre-emptive genotyping is that a patient's knowledge of a genetic profile associated with a high risk of adverse events may lead the patient to associate unrelated adverse events (i.e., nonspecific myalgias/arthralgias) to his/her statin therapy. If a patient then prematurely discontinues his/her statin and/or the physician reduces the dose, this may result in higher low-density lipoprotein cholesterol and cardiovascular risk.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

For the 40-mg simvastatin dose, the relative risk of myopathy is 2.6 per copy of the C allele at rs4149056. The risk is higher for the 80-mg simvastatin dose (myopathy OR 4.5 for the TC genotype, ~20.0 for the CC genotype). Nonetheless, simvastatin-related muscle toxicity can still occur in the absence of

rs4149056. Thus, a TT genotype does not imply the absence of another potentially deleterious variant in *SLCO1B1* or elsewhere. Further, because rs4149056C can also be inherited in combination with other *SLCO1B1* gene variants known to have protective effects, it should not be presumed that the C allele at rs4149056 confers risk with 100% certainty.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/cpt>

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CONFLICT OF INTEREST

The funding organizations played no role in the writing of these guidelines. D.V. is a consultant for RenaissanceRx and has funding through the Department of Defense supporting an ongoing clinical trial of genotype-guided statin therapy (NCT01894230). The other authors declared no conflict of interest.

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